INTEGRATING ORAL AND SYSTEMIC HEALTH: INNOVATIONS IN TRANSDISCIPLINARY SCIENCE, HEALTH CARE AND POLICY

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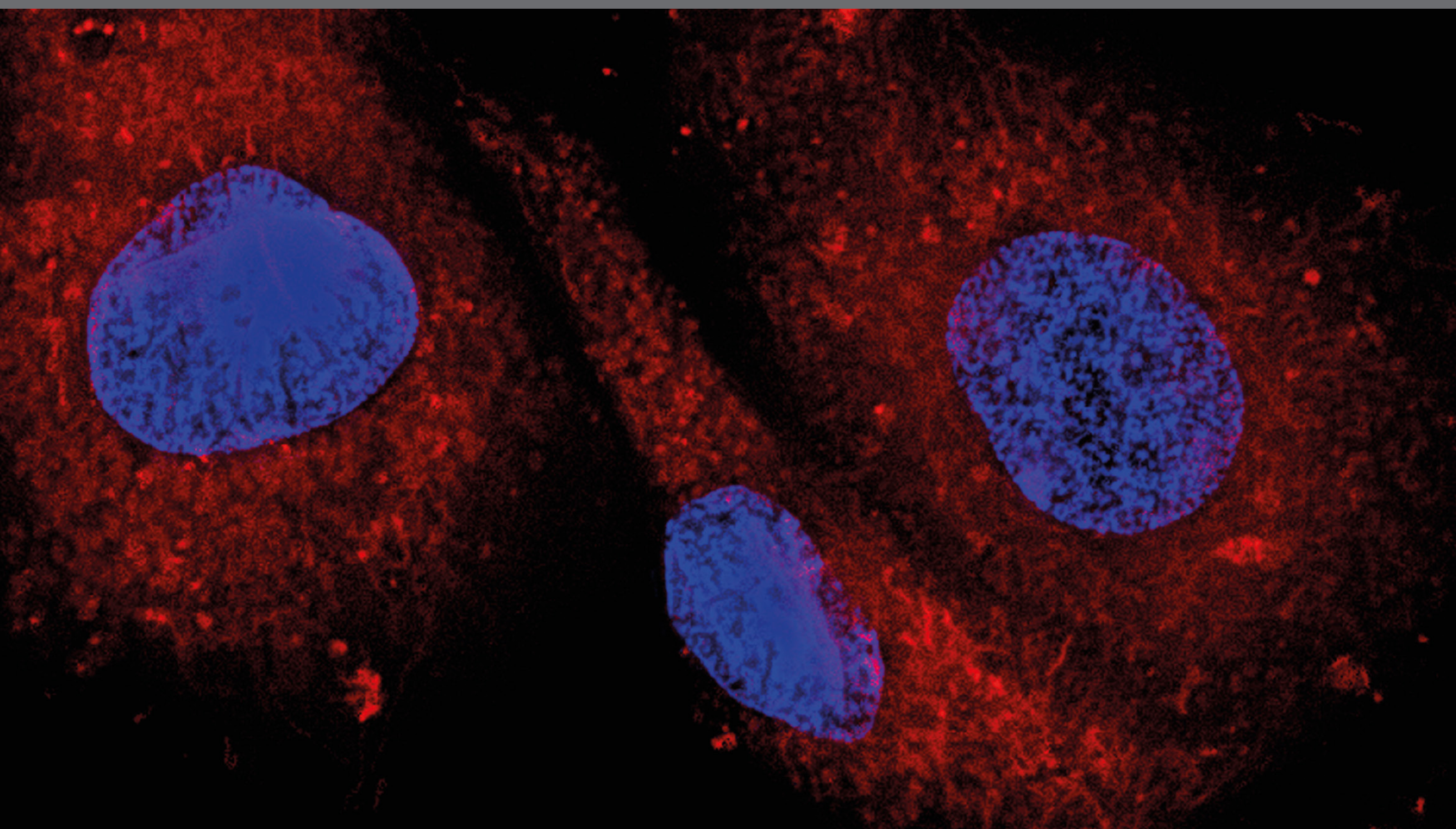

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INTEGRATING ORAL AND SYSTEMIC HEALTH: INNOVATIONS IN TRANSDISCIPLINARY SCIENCE, HEALTH CARE AND POLICY

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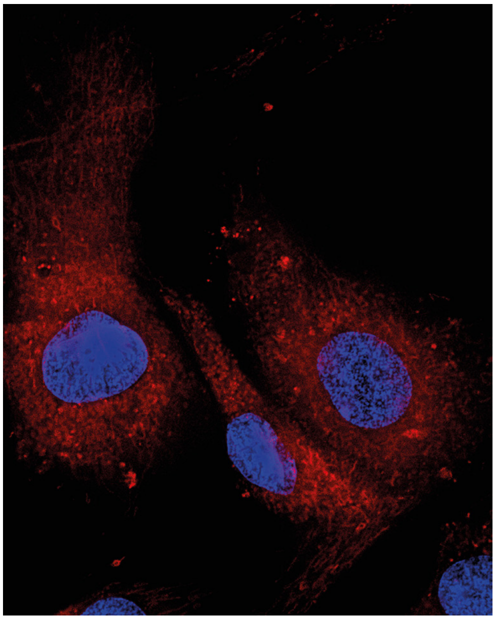

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frontiers in Dental Medicine

EDITORIAL
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Editorial: Integrating Oral and Systemic Health: Innovations in Transdisciplinary Science, Health Care and Policy

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Editorial on the Research Topic

Integrating Oral and Systemic Health: Innovations in Transdisciplinary Science, Health Care and Policy

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INTRODUCTION

Frontiers in Dental Medicine (FDEM) was launched in 2020, with a vision set forth by Field Chief Editor, Martha Somerman to advance the integration of medicine and dentistry at multiple levels, from basic science to clinical practice, to health policy decision making. My first assignment was to prepare a Field Grand Challenge (GC) and Special Research Topic (RT). I invited physician Wendy Mouradian to join me in crafting these documents since we share the same vision, and now more than ever, the urgency to remove silos across all disciplines to bring medicine and dentistry together to advance oral and overall health and well-being for all communities. We realize this can only be achieved through a combination of approaches including education, research, clinical practice, professional development, health care literacy, patient advocacy, health care systems and health policy development. The theme for both the Grand Challenge and Research Topic was therefore "*Integrating Oral and Systemic Health: Innovations in Transdisciplinary Science, Health Care and Policy*" (1).

As we were preparing these documents the world was facing a pandemic due to the SARS-CoV2 virus, which disrupted all our lives, our directions, and our priorities in numerous and unimaginable ways, some collectively and some personally. But this time period has only heightened our collective awareness of the need to overcome the divide between medicine and dentistry to improve quality of health care for all, but especially for populations suffering disproportionately from disease impacts—whether due to the coronavirus, or long-standing oral disease inequities. Further, we partnered with the Santa Fe Group (SFG), which had similarly launched an effort addressing key medical-dental integration issues, *Continuum on the Benefits of Integrating Oral Health into Healthcare,* with a series of webinars, all available for viewing on-demand, and a virtual Salon and a virtual Salon held September (https://santafegroup.org/events/). As a long-standing SFG member and oral health advocate, Dr. Mouradian was asked to lead this effort which involved numerous scientists, clinicians, policymakers, health advocates and industry partners from multiple organizations and entities.

With the release date set to be in close proximity with the Salon, we are delighted to bring you this eBook, a partnership between the SFG and Frontiers, a collection of many peer reviewed articles resulting from the Research Topic highlighting the value of integrating oral health and disease in the context of overall health. A very brief synopsis of each article included in the Research Topic is provided below and clustered into four themes for ease of reading, realizing there is much overlap between these themes. Even as this is released, we understand there are related submissions that continue to come in, evidence of the high interest these topics have attracted. Readers are invited to check Frontiers frequently for new articles of relevance.

RESEARCH/CASE REPORTS

Several manuscripts focus on the vital need to probe the dental-oral-craniofacial history and current oral health status of patients being examined to diagnose their disease in a timely manner so treatment can be implemented in an evidence-based, efficient and timely manner. This extends to animal models where often the head is dismissed. Brenchley et al. use a case report, a patient with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), to demonstrate that dental findings can aid in early diagnosis of a disease/syndrome. In another case report by Jani et al. they discuss new findings on dental abnormalities in Loeys-Dietz Syndrome Type 1, while Lee et al. use a case report to emphasize the value of dental radiographs toward informing a diagnosis, in this situation, alter root morphology and pulp calcification identified a patient with hyperphosphatemic familial tumoral calcinosis.

Osugue et al. in a preliminary case study give evidence to support a role for periodontitis as an increased risk of stent restenosis. And in a very timely article by Cardoso et al. they demonstrate the significance of periodontal disease and other oral infections as contributors to severe respiratory disease, a hall mark consequence of SARS Cov2 infection, by providing evidence of a common mechanism of action causing hyperfunction of the immune cells. In their perspective, Integrating Dental and Medical Research Improves Oral Health, Mouradian et al. give examples where integrated research has improved health care outcomes long-term and where a lag in and/or lack of integration has resulted in fragmented and inefficient health care delivery. This theme is reinforced by a perspective article, *Diabetes and Oral Health: Summary of Current Scientific Evidence for Why Transdisciplinary Collaboration Is Needed*, by Borgnakke and Poudel, which emphasizes the need to avoid siloed approaches, with a specific focus on diabetes.

TRANSDISCIPLINARY RESEARCH/HEALTH CARE TEAMS

Another cluster of manuscripts brings attention to the value of research/health care collaborations, from risk assessment, to diagnosis, to treatment planning, to improves outcomes, as well as economic benefits. The studies included: (a) "*Evaluating the Effectiveness of Medical–Dental Integration to Close Preventive and Disease Management Care Gaps*" by Mosen et al., which suggests that medical-dental integration models facilitate the delivery of preventive and disease management services, although the authors recognize that long-term health studies are needed to strengthen their findings; (b) The perspective "*Alzheimer's Disease and Oral-Systemic Health: Bidirectional Care Integration Improving Outcomes*" by Rice supplies strong evidence for the need for bidirectional health care models to improve the quality of health care for our patients; and (c) The review by Chu et al. "*Multiple Idiopathic Cervical Root Resorption (MICRR): A Challenge for a Transdisciplinary Medical-Dental Team*" uses MICRR as a model to highlight the need for transdisciplinary teams, from basic scientists to clinicians, to inform diagnosis, treatment and clinical outcomes.

DENTAL CLINICS AS PRIMARY CARE SETTINGS

The article by Glurich et al. demonstrates that dental settings, used as a means for screening for certain diseases such as diabetes, i.e., a point-of-care model, adds value for integrative models of medical/dental management and improved compliance. A further study by Qi et al. focused on urban vs. rural dental health care systems reporting barriers to care in rural settings in China. Gordon et al. consider the value of having dentists included as primary care providers and the educational modifications, specific competencies, required to train the next generation of dentists as "Oral Physicians" or "Oral Health Primary Care Providers."

EDUCATION

Several pertinent articles discuss the importance of education and communication to inform dental-medical integration models. MacNeil and Hilario in their article "*Input From Practice: Reshaping Dental Education for Integrated Patient Care*" discuss the need to reshape dental education to prepare students for a healthcare environment transitioning to integrated health care models. Mays acknowledges the fact that substantial advances in health professional educational models have been developed over the last few decades, including interprofessional education and practice, but emphasizes the need to expand these models and pay more attention to models where oral health is streamlined into overall health. Expressing a boarder view of education, Kleinman et al. focus on the need to promote oral health literacy, using a systems-oriented- approach, to foster our unified goal of achieving oral and general health integration. Dabiri et al. provide a timely review on current data, as well research needed, to inform dental practitioners of the relationship between particle dynamics, with a focus on, but not limited to, COVID-19 transmission, and safety measures used in dental settings.

We welcome your feedback as you ready through these articles and we hope you will contribute further articles on this topic, one of much significance for our community and for advancing the quality of life for all populations.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to crafting and preparing this Editorial.

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1. Mouradian W, Somerman MJ. Grand challenge: integrating oral and systemic health: innovations in transdisciplinary science, health care and policy. *Front Dent Med*. (2020) 1:599214. doi: 10.3389/fdmed.2020.599214

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frontiers in Dental Medicine

CASE REPORT
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Case Report: Dental Findings Can Aid in Early Diagnosis of APECED Syndrome

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type 1 (APS-1), is a rare genetic disorder caused most often by biallelic mutations in the *AIRE* gene. Classic clinical findings of the disease are chronic mucocutaneous candidiasis and autoimmunity that primarily targets endocrine tissues, such as hypoparathyroidism and adrenal insufficiency. Recently, however, it has been appreciated that enamel hypoplasia, together with intestinal malabsorption and a characteristic APECED rash, is a prominent early disease manifestation of APECED which can aid in the diagnosis of disease before other potentially life-threatening disease manifestations occur. To demonstrate this point, we present data from a cohort of APECED patients, ∼70% of who present with enamel dysplasia at an early age. Importantly, early life presentation with enamel dysplasia was predictive of likelihood for subsequent APECED diagnosis. Furthermore, we present a case of a patient with APECED and severe enamel defects and discuss the utility of medical-dental professional co-operation in the diagnosis and management of this complex disorder.

Keywords: APECED, APS-1, AIRE, primary immune deficiency, chronic candidiasis, enamel hypoplasia

INTRODUCTION

A growing body of evidence has suggested an association between oral manifestations and systemic disease (1, 2). Indeed, immunocompromised patients will present with various oral infection susceptibility. Often patients with numerous systemic, cutaneous and gastrointestinal inflammatory symptoms will also have clinical oral manifestations. It is therefore imperative that medical and dental professionals strengthen a collaborative understanding of common risk factors and biological findings related to oral and systemic disease. This article features clinical and diagnostic criteria and oral manifestations of Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as Autoimmune polyglandular syndrome type 1 (APS-1) to highlight the importance of a multidisciplinary approach in providing early diagnosis and comprehensive care to patients.

OVERVIEW OF APECED

APECED is an inherited monogenic disorder caused most often by biallelic mutations in *AIRE* and results in the development of multi-organ autoimmunity, chronic mucocutaneous candidiasis (CMC), and ectodermal dystrophy. AIRE is a transcription regulator highly expressed in thymic medullary epithelial cells (mTECs) where it orchestrates negative selection of auto-reactive T cells (3). These cells escape into the periphery in the AIRE-deficient patient where they are both necessary and sufficient for development of autoimmunity (4–6).

APECED affects ∼1:100,000–1:200,000 people internationally with higher prevalence in Iranian Jews, Sardinians, Finns and Slovenians (∼1:9,000–1:25,000) and lower prevalence in populations of Norwegian (1:80,000), Irish (1:130,000), French (1:500,000) and Japanese descent (1:10,000,000). In the U.S., APECED is estimated to occur in 1:100,000–1:300,000 persons (7–9).

More than 25 disease manifestations (shown in **Table 1**) have been reported through the course of disease (5, 10) amongst which CMC, hypoparathyroidism, and adrenocortical failure (Addison's disease), are three of the most highly prevalent. Together they form the "classic triad" and development of any two (a "diagnostic dyad") of these is sufficient for establishing a clinical diagnosis of APECED (6, 11). Although this classic triad is characteristic for APECED, it often occurs late in the course of the disease. Through the comprehensive evaluation of our APECED cohort at the National Institutes of Health (NIH) Clinical Center, we found 80% of patients developed an average of 3 non-classic triad manifestations before reaching a diagnostic dyad (10). Amongst these, enamel hypoplasia, intestinal malabsorption, and a characteristic APECED rash were the most prevalent early clinical manifestations. In fact, their inclusion in expanded diagnostic criteria (classic triad + adjunct triad) (**Figure 1**) would have reduced the time to diagnosis by half (**Figure 2**) (10), which has potential major implications in earlier recognition of the disease and could help improve patient outcomes.

These findings call for a multidisciplinary approach to patient evaluation with participation of multiple specialties of medicine and dentistry. Due to advances in sequencing technology, gene mutations are more frequently identified and support the theory that an inheritable factor exists in this disorder. However, identification through genetic testing is not always definitive or clinically available. There is a wide range and variability of disease manifestations and phenotypic expression of APECED (**Table 1**). Clinicians including endocrinologists, allergists, pediatricians, gastroenterologists, hematologists, ophthalmologists, pulmonologists, dermatologists, dentists and dental hygienists, can all recognize early-onset symptoms and disease manifestations and begin a differential diagnosis that may lead to early interventions helpful in establishing an APECED diagnosis and preventing life-threatening complications.

TABLE 1 | Clinical manifestations that affect patients with APECED.

Manifestations of APECED
• Chronic mucocutaneous candidiasis (CMC)
• Enamel hypoplasia
• Sjogren's-like syndrome
• Aphthous ulcers
• Urticarial eruption
• Alopecia
• Vitiligo
• Nail dystrophy
• Retinitis
• Keratoconjunctivitis
• Hypoparathyroidism
• Adrenal insufficiency (Addison's disease)
• Growth hormone deficiency
• Autoimmune gastritis
• Gastric carcinoma
• Asplenia
• Intestinal dysfunction
• Tubulointerstitial nephritis
• Autoimmune hepatitis
• Autoimmune pneumonitis
• Pernicious anemia
• Iron deficiency
• Type 1 diabetes
• Pure red cell aplasia
• Hypogonadism
• Asplenia
• Hypothyroidism

ENAMEL DEFECTS CAN BE AN EARLY SIGN OF APECED

Enamel defects may be a phenotype of hereditary conditions that involve only the enamel matrix or may be a component of a hereditary medical syndrome. Enamel is formed by ameloblasts during tooth development (12). This protective outermost layer of the tooth structure helps protect the inner dentinal and pulpal tissues from masticatory forces and continual bacterial and other pathogenic insults. Ameloblast disruptions during the development of the enamel matrix can result in hypoplastic and hypo-mineralized enamel (12). Hereditary syndromes such as Treacher Collins, which presents with craniofacial abnormalities of the zygomatic complex, jaws and palate (13, 14); Heimler syndrome, characterized by sensorineural hearing loss and nail abnormalities (15, 16); and Usher syndrome, which features sensorineural hearing loss and retinitis pigmentosa (17) have all reported enamel hypoplasia in clinical case reports.

Consistent with a previous report, but in an expanded cohort, we found enamel hypoplasia in 70% of 104 patients with APECED in our cohort. Moreover, with expansion of the diagnostic criteria for APECED (with use of the aforementioned adjunct triad), we find that CMC, APECED rash and hypoparathyroidism appear most frequently in combination with enamel hypoplasia early in life (**Table 2**). These findings may be an early predictor of those who are more likely to develop additional life-threatening manifestations of disease later in life (**Figure 2**).

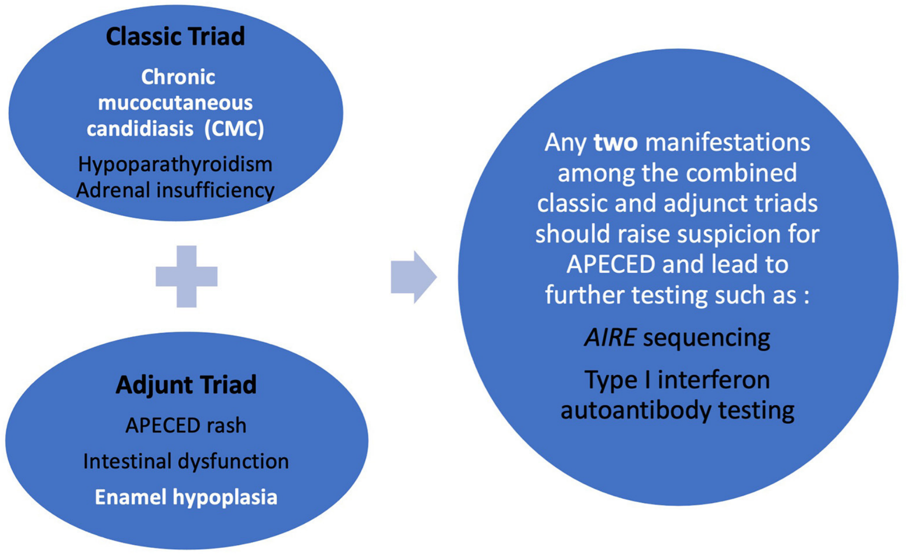

FIGURE 1 | Refined diagnostic criteria (combined classic and adjunct triad) designed to enhance earlier diagnosis of APECED.

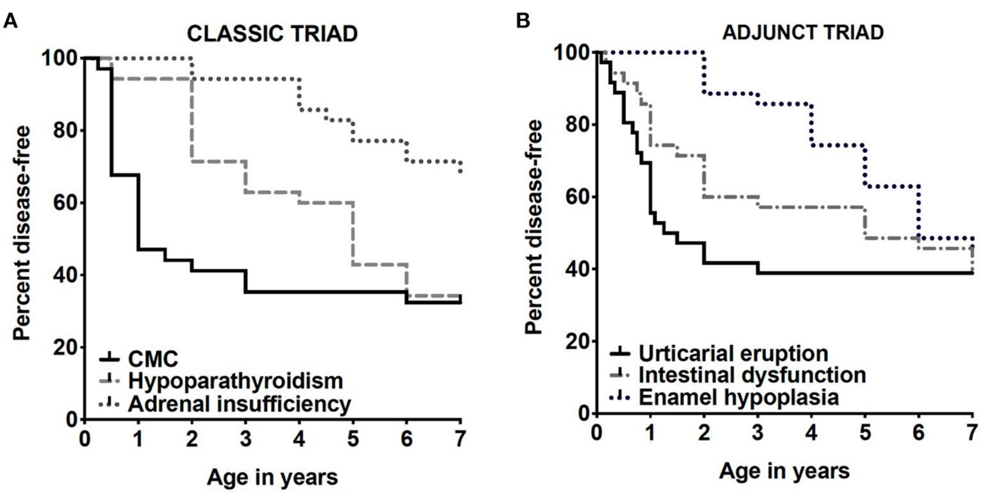

FIGURE 2 | Shown are Kaplan-Meier curves demonstrating prevalence by age of classic triad manifestations **(A)** and adjunct triad **(B)** appearing by age 7 years, the average age of diagnosis by classic diagnostic criteria among the first 35 patients with APECED. These images are derived from Ferre et al. (10).

CASE DESCRIPTION

Here we present a 15-year-old Caucasian male of European descent with confirmed biallelic *AIRE* gene mutations enrolled in protocol NCT01386437 who presented to the NIH dental clinic with concerns regarding the esthetics of his smile. His medical history included the appearance of an intermittent rash during his first year of life that resembled flat red macules that could not be explained by the pediatrician at that time; reflecting back to the presentation, this rash was one of the early primary clinical indicators of APECED. During his third year of life, he presented to his physician with the development of alopecia and finger/toenail dystrophy. In these very early years, the patient was otherwise clinically well. However, by his sixth year he began suffering from abdominal pain which led to an emergent visit to the emergency room. During this visit the patient presented with significant abdominal discomfort, fatigue, increased thirst and salt cravings and was found to have severely low sodium levels at 115 mmol/L leading to diagnosis of adrenal insufficiency.

In addition, his dental history and exam revealed that he had several tooth extractions due to breakdown of the clinical crown; a note of enamel hypoplasia was made. Over the next 3 years other clinical complications included gallstones, vitamin D deficiency and iron deficiency. He underwent a liver biopsy at age 10 for persistently elevated transaminases and was diagnosed with autoimmune hepatitis, a condition

TABLE 2 | Frequency of diseases appearing in combination with enamel hypoplasia as the first two consecutive clinical manifestations in 35 patients with APECED.

Clinical manifestation	Number (%) of patients
CMC	1 (3)
APECED rash	1 (3)
Hypoparathyroidism	1 (3)

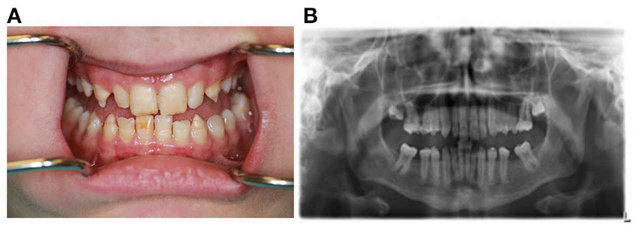

FIGURE 3 | Clinical intraoral photograph and panoramic radiograph of 15-year-old Caucasian male APECED patient demonstrating abnormal dental development with enamel hypoplasia (photo, **A**), taurodontism (radiograph, **B**).

affecting ~40% of APECED patients (18). At this point, APECED was suspected prompting *AIRE* sequencing, which identified homozygous c.967_979del13 deletions. Importantly, he did not have any history of CMC or hypoparathyroidism at that time, which reiterates the heterogeneity of clinical manifestation development and disease progression of APECED.

The dental findings in this case depict developmental anomalies associated with APECED that can be detected with routine dental examinations in early age (**Figure 3**). Upon examination extra-orally, there was no palpable lymphadenopathy. Intraorally, the patient presented with adult dentition that exhibit dental manifestations of APECED including irregular clinical crown size with pointy cusp tips and narrow shape. The buccal tooth enamel was chalky white and yellow with horizontal grooves and pitting of the enamel surfaces. The cusp tips were white, and the remaining enamel was thin and opalescent. There was a deep bite with an overbite of 100%. There was spacing between the teeth which may have been because of the narrower teeth, but also the patient was missing all maxillary and mandibular first permanent molars. In addition, radiographic findings reveal taurodontism of all maxillary and mandibular second molars. There was no clinical or radiographical evidence of caries or oral candidiasis.

DISCUSSION

When treating patients with APECED, co-operation of a multidisciplinary team is imperative. While APECED is commonly diagnosed by gene sequencing, not all patients with clinical APECED have biallelic *AIRE* mutations (5, 7, 10). Some patients may have large *AIRE* deletions, or non-coding gene variants, or non-*AIRE* gene variations (5, 10). Importantly, genetic confirmation will typically follow the disclosure of clinical findings which will suggest the diagnosis of APECED. Therefore, early detection of oral manifestations can be fundamental for a targeted differential diagnosis.

Enamel hypoplasia is an important early clinical sign that can aid in diagnosis. It is a common finding in the permanent dentition among those that have been diagnosed with APECED, however, it was a less reported observation in deciduous teeth until the recent reporting of enamel hypoplasia, occurring in 17.3% of the cohort of patients at NIH. In fact, based on this recent study it is the first or second clinically reportable manifestation and overall 5th most common occurring manifestation of APECED (10). In addition, at least one scanning electron microscopy study evaluating the prismatic structure of enamel in patients with confirmed *AIRE* gene mutations has demonstrated compromised enamel matrix structures in deciduous and permanent teeth (19).

Children with APECED may present with patchy white-yellow discoloration on their teeth, or enamel hypoplasia which may cause the dentition to appear ridged and pitted or mis-shaped. Although APECED and other primary immunodeficiencies aforementioned are the focus of this paper, it does not go without mention that enamel hypoplasia has also been associated with prenatal abnormalities such as maternal vitamin D deficiency (20), low birth weight (21), or environmental factors such as trauma to the teeth during development (22) or systemic infection (23). Enamel hypoplasia in combination with another manifestation of the classic and adjunct triad should alert clinicians of a possible APECED diagnosis.

Early detection of oral developmental anomalies and caries is one of the primary reasons to have a child's first oral examination by 12 months of age. Defects of the enamel matrix predispose teeth to an increased risk of dental caries and erosion from acids in foods and beverages. Management of enamel hypoplasia in the primary dentition should focus on early diagnosis and preventive care. Routine topical fluoride application is one of the most effective anti-caries strategies as it helps reduce dentinal sensitivity, enamel remineralization, inhibits acid production and bacterial metabolism. In addition, treatment with other re-mineralizing agents such as casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or silver diamine fluoride (SDF) can help re-mineralize the hypo-mineralized areas and early carious lesions on the tooth surface (24, 25). The patient we discuss in this case report did not present with active carious lesions at the time of their dental visit at our clinic. The patient was referred back to his primary care dentist for future treatment, with our suggestion to consider the mentioned anticaries strategies in the ongoing preventive care and treatment of this patient's dentition.

Patients with APECED will need preventive services with a 3–4 month interval so the oral status can be reviewed and evaluated. In cases of extensive enamel hypoplasia multidisciplinary team management involving general practitioners, specialist pediatric dentists and orthodontists may be necessary. A thorough dietary analysis in collaboration with the primary care physician and dietitian may assist with educating patients on how to improve their nutritional intake, especially of calcium and fluoride which are imperative to oral health.

Importantly, the diagnosis of enamel hypoplasia by oral health professionals may identify patients early in the course of the disease. In fact, two of the early clinical manifestations of APECED (enamel hypoplasia and oral candidiasis) can be identified by oral health professionals, suggesting a potential primary role for oral healthcare providers in disease diagnosis. CMC, commonly known as oral thrush, often occurs as an early primary symptom of APECED and can vary in appearance and severity. Thrush typically appears as a white coating on the tongue, oral mucosa, palate, gingiva, throat, or commissures of the mouth that can be wiped off with a gauze. Thrush can also present as redness and soreness that can prohibit eating spicy or acidic foods. Treatment for oral *Candida* infections includes topical antifungal agents such as miconazole, clotrimazole, amphotericin B or nystatin (5). APECED patients are also susceptible to *Candida* infections of the esophagus, vagina, and nails. Therefore, systemic treatments that may be considered also include fluconazole, voriconazole, posaconazole, the echninocandin antifungals or amphotericin B (5). Resistance can occur to oral antifungal agents which can make long-term management of CMC a challenge. Acute episodes should include a fungal swab culture with susceptibility testing to determine the pattern of *in vitro* susceptibility because different *Candida* strains can be differentially susceptible to antifungal therapeutics, and some strains may become resistant over time (5, 26). Treatment with antifungals lasting 4+ weeks typically allows sufficient time of therapeutic intervention and reduces the potential for relapse. If left untreated *Candida* infections can lead to esophageal strictures or esophageal carcinomas (26, 27). However, additional novel treatments may be considered based on our recent findings in the pathogenesis of APECED-related mucosal candidiasis (28).

Beyond early diagnosis and management of early APECED signs, an oral healthcare provider may be also involved in the prevention and treatment of oral manifestations that may present throughout the disease process. The patient discussed in this case report did not present with any of the common oral symptoms at the time of exam. However, patients with APECED are at increased risk for xerostomia, and incidence of caries, aphthous ulcers, aphthous stomatitis, atrophic glossitis and importantly an increased risk of oral cancer due to chronic inflammation in association with CMC including oral and esophageal carcinomas (29). Sjogrens's-like syndrome may present early in life with a rise in incidence over time. Dry mouth symptoms can lead to discomfort and interfere with speech, eating and may contribute to burning mouth syndrome and increased caries risk.

Oral cancer screenings should be a routine part of every dental examination as alcohol intake and smoking are additional risk factors that may promote oral carcinogenesis (30). Awareness of patient social behaviors and risk as well as through documentation of oral candidiasis patterns and pseudomembranous lesions presenting with erosion, or ulceration noted during routine exams, can be helpful in the diagnosis of cancers at an early stage. Oral health professionals should instruct patients how to perform oral self-examinations and implement excellent oral hygiene, while stressing the importance of reporting any new or unusual oral symptoms and frequent dental follow up appointments. Oral candidiasis should be treated aggressively with antifungal therapies as mentioned earlier. While there are few guidelines for medications in managing oral ulceration, a primary objective is pain management to reduce and control symptoms, therefore adjunctive therapies include topical steroids and analgesics that can provide short-term pain relief to sooth aphthous ulcers (1). In cases where patients describe generalized oral sensitivity, use of an extra soft toothbrush and other recommendations such as elimination of spicy foods, carbonated beverages and toothpastes that contain sodium laurel sulfate may be suggested.

With increased screening, the recognition of APECED is growing especially in the US. Patients may seek dental care without knowing of their condition. Oral health professionals are well-positioned to note this disease's oral signs and symptoms. A thorough medical, family and dental history will aid in proper diagnosis and treatment. Oral health professionals who suspect APECED should speak with the patient's physician and or dietitian to determine an effective treatment strategy. This multidisciplinary approach will support the successful management of APECED as well as mitigate its effects on health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NIH IRB. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LB and NM conceived and wrote the manuscript. LB and PG performed clinical work. LB, EF, MS, PG, ML, and NM were evolved in the study conception, data analysis, and interpretation. EF, MS, PG, ML, and NM critically edited the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Dental Medicine

CASE REPORT
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Case Report: Rare Presentation of Dentin Abnormalities in Loeys-Dietz Syndrome Type I

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Loeys-Dietz syndrome type 1 (LDS1) is caused by a mutation in the transforming growth factor-beta receptor 1 (*TGFBR1*) gene. We previously characterized the oral and dental anomalies in a cohort of individuals diagnosed with LDS and showed that LDS1 had a high frequency of oral manifestations, and most affected individuals had enamel defects. However, dentin anomalies were not apparent in most patients in the cohort. In this cohort, we had identified dentin anomalies in a patient with LDS1, harboring mutation *TGFBR1* c.1459C>T (p.Arg487Trp), and in this report, we present clinical and radiographic findings to confirm the dentin anomaly. The proband had gray-brown discoloration of most teeth typical for dentinogenesis imperfecta (DI). A radiographic exam revealed obliterated or very narrow pulp canals, with maxillary anterior teeth being affected more than the posterior teeth. The son of the proband, who also has the same mutation variant, had a history of DI affecting the primary teeth; however, his permanent teeth were normal in appearance at the time of exam. *TGFBR1* is expressed by odontoblasts throughout tooth development and deletion of *TGFBR1* in mouse models is known to affect dentin development. In this report, we present a rare case of abnormal dentin in two individuals with LDS1. These dental anomalies may be the first obvious manifestation of a life-threatening systemic disease and demonstrate the variable and multi-organ phenotypic effects in rare diseases.

Keywords: Loeys-Dietz syndrome, TGFBR1 mutation, TGF-beta signaling, dentin defect, dentinogenesis imperfecta, case report

INTRODUCTION

Transforming growth factor-beta (TGF-β) signaling plays a crucial role during mammalian development (1). It has been implicated to be critical to cell proliferation and maturation, including the craniofacial (2–5) and dental mineralized tissues (6, 7). More recently, mutations in the TGF-β family of genes were discovered in a cohort with Marfan-like features, and the disease was classified as Loeys-Dietz syndrome (LDS) (8). LDS is caused by mutations in genes encoding various components of the TGF-β signaling pathway (9) and is currently classified into six subtypes based on the gene involved. LDS1 (MIM# 609192) is associated with transforming growth factor-β receptor type I (*TGFBR1*), TGF-β receptor type II (*TGFBR2*) mutations are classified as LDS2

(MIM# 610168), mothers against decapentaplegic homolog 3 (*SMAD3*) mutations cause LDS3 (MIM# 613795) (10), LDS4 (MIM#61481) and LDS5 (MIM#615582) are caused by mutations in TGF-β2 (*TGFB2*) and the TGF-β3 (*TGFB3*) ligands, respectively (11–14). *SMAD2* mutations were recently found to cause LDS (LDS6, no MIM# assigned) (15).

We previously reported the oral manifestations in a cohort of 40 individuals with LDS from five subtypes (LDS1-5) and reported a high frequency of abnormal palate morphology, enamel defects, bifid uvula, or submucous cleft palate, malocclusion, dental crowding, and delayed eruption of permanent teeth (16). We concluded that individuals with LDS2 followed by LDS1 had the most severely affected oro-dental region, which is also true for the systemic manifestations reported in LDS literature. Additionally, we have also shown that these dental anomalies significantly worsen the oral health-related quality of life for individuals with LDS (17).

Dentinogenesis imperfecta (DI) is a rare hereditary condition affecting the teeth, which manifests as grayish or yellow-brown discoloration of teeth (18). The condition is characterized by abnormal dentin formation leading to weak teeth which are susceptible to fracture and breakage. DI is a common manifestation in individuals with osteogenesis imperfecta Type III or IV with mutations in Collagen type 1 (*COL1A1* or *COL1A2*) genes (19, 20). Mutations in dentin sialophosphoprotein (*DSPP*) may also lead to non-syndromic forms of DI (21). While several genes have been implicated in the manifestation of dentin abnormalities in human case reports (19, 22, 23), to date, there has been no report describing dentin abnormalities associated with the TGF-β pathway in humans. However, *TGFBR1* has been shown to play a role in dentin development in mouse models (24–26). In this report, we present a rare manifestation of dentin abnormality in two individuals with a diagnosis of LDS1. Additionally, we also present a comparison between the severity of oral manifestation and systemic manifestations in LDS1, reported in previous literature and individuals in this report.

METHODS

Study Participant

A 53-year-old male (II-1) with a diagnosis of LDS1 who was enrolled in the Natural History and Genetics of Food Allergy and Related Conditions study (NCT02504853) was seen in the NIDCR Dental Clinic along with his wife and 14-year-old affected son (III-1). All three participants agreed to enroll and consented to the Natural History of Craniofacial Anomalies and Developmental Growth Variants study (NCT02639312).

Genetic Test

Targeted mutation analysis for the LDS genes panel was performed for the proband and his family by the primary care physician through GeneDX (GeneDx Inc., Gaithersburg, Maryland). Subsequently, whole exome sequencing (WES) was performed through National Institute of Allery and Infectious Diseases (NIAID) Centralized Sequencing Initiative during their visit to the National Institutes of Health.

Genomic DNA was extracted from the submitted blood specimen of both individuals and subjected to massively parallel sequencing on an Illumina sequencing system. The exonic regions, flanking splice junctions, and both 5′ and 3′ untranslated regions (UTR) were sequenced with 100 bp or greater paired-end reads. Subsequently, the reads were aligned to the human genome build GRCh37/UCSC hg19, and analysis was performed using a custom-enhanced analysis tool (SEQR). The interpretation of the variants was performed according to the ACMG guidelines (27) and the nomenclature of the identified variants is consistent with the Human Genome Variation Society (HGVS) guidelines. Confirmation of potentially relevant findings was performed using capillary sequencing or other appropriate methods. Minimum coverage is 95% > x20 for targeted genomic regions.

Oral and Dental Evaluation

The oral and dental evaluation included a detailed clinical exam, performed by the NIH Craniofacial Anomalies Team (PJ, RM, and JSL). The intra-oral exam consisted of the inspection of the oral structures and soft tissue, including the palate, uvula, and gingiva for basic periodontal assessment without periodontal probing. The dental and hard tissue evaluation included the occlusion, eruption pattern, tooth morphology, jaw relationship, and TMJ function. A standardized oro-dental evaluation form was used in all cases.

Radiographic Evaluation

Cone beam computed tomography (CBCT) (Planmeca Promax 3D Max, 400 μm resolution; Planmeca USA Inc., IL) was performed to further assess dental phenotype including findings such as tooth impaction, dental decay, enamel or dentin defects, and alveolar bone loss. CBCT images were used to generate panoramic x-rays and individual tooth slices using Planmeca Romexis software.

Photography

Extraoral and intraoral photographs (Canon EOS 5D Mark II camera, Canon USA Inc., VA) were obtained for each participant. For each patient, seven intraoral photos were taken: the frontal view of dentition in occlusion, the frontal view of dentition at rest (2–3 mm leeway space), the maxillary arch, the mandibular arch, the left lateral view (maxillary and mandibular teeth in occlusion), the right lateral view, and the oropharyngeal region. Facial photos included frontal and profile views.

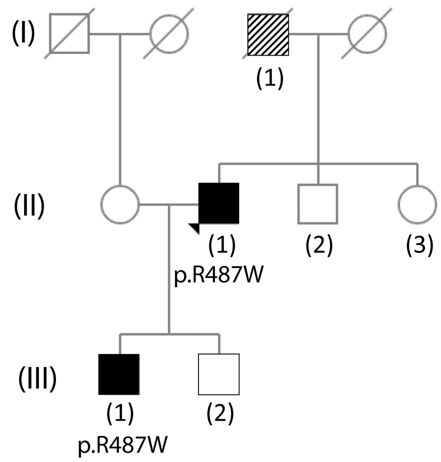
CASE REPORT

History of Present Illness

The proband (II-1), a 53-year-old male, was seen at the dental clinic for evaluation of his oral health and LDS-related manifestations. He presented with his wife (unaffected, 40 years old) and son (III-1, affected, 14 years old). The timeline for proband and son are shown in **Figure 1B**. At age 40, the proband suffered abrupt chest and tooth pain with subsequent diagnosis

Abbreviations: LDS, Loeys-Dietz syndrome; LDS1, Loeys-Dietz syndrome type 1; TGF-β, Transforming growth factor beta; TGFBR1, TGF-β receptor type I; DI, Dentinogenesis imperfecta; CBCT, Cone beam computed tomography.

A



B

Event	Age (Years) II-1	Age (Years) III-1
Clinical Diagnosis of LDS	40	2
Genetic confirmation of LDS1	46	7
Dental assessment for LDS	53	14
Follow up dental assessment	55	16

FIGURE 1 | Pedigree tree showing affected family members and timeline of events. **(A)** The (II-1) father of the proband is suspected of having Loeys-Dietz syndrome (LDS) as he died from an aneurysm at age 49. The mother of the proband has early-onset dementia. The brother of the proband is healthy, and the sister has skin carcinoma. Proband has two sons, one of whom (III-1) carries the LDS mutation. **(B)** Timeline of events for the proband (II-1) and the son of the proband (III-1) since diagnosis of LDS.

TABLE 1 | Comparison of oral manifestation with previously reported literature.

Systemic manifestation	TGFBR1 %	II-1	III-1	Oral manifestation	TGFBR1 %	II-1	III-1
Arterial tortuosity	75–100	+	+	Abnormal palate	100.0	+	+
Aortic root aneurysm	75–100	+	+	Retrognathic mandible	92.3	+	+
Pectus deformity	50–75	–	–	Gingivitis	61.5	–	+
Scoliosis	50–75	–	+	Class II malocclusion	61.5	+	–
Arachnodactyly	50–75	+	–	Enamel defects	46.1	+	–
Hernia	50–75	+	+	Submucosal cleft or bifid uvula	46.1	–	–
Osteoarthritis	25–50	–	–	TMJ abnormality	38.4	+	–
Striae	25–50	–	–	Deep bite	38.4	–	–
Dural ectasia	25–50	–	–	Dental crowding	7.6	–	+
Cervical spine malformation/instability	0–25	–	–	Delayed eruption	0	–	–
				Dentinogenesis imperfecta	0	+	+

–, Absent; +, Present. Systemic data for LDS1 adapted from (28); Oral data adapted from (16). Manifestation in bold are not previously reported in LDS.

of a type A aortic dissection. He underwent emergent aortic valve-sparing aortic root replacement. At age 46, his diagnosis of LDS1 was confirmed with a mutation in the *TGBR1* by candidate mutation analysis, specifically c.1459C>T, which resulted in the amino acid substitution p.R487W. At age 53, WES analysis was performed which confirmed the *TGFBR1* mutation but did not show the presence of any mutations in *DSPP*, the candidate gene for DI.

Family History

The father of the proband (I-1) died at 49 years of age from complications related to ruptured abdominal aorta; he had a history of myocardial infarction and pulmonary embolism. Although, the father did not have a known diagnosis of LDS, it is suspected retrospectively (**Figure 1A**). The proband (II-1) has two sons, one of whom shares the *TGFBR1* mutation (III-1). The wife of the proband and brother are healthy, whereas, his sister has a history of skin cancer.

Surgical History

The proband (II-1) had a history of Nissen fundoplication at age 36. He had undergone aneurysm repair at age 40 and mitral valve repair at age 51. He also had a history of inguinal hernia repair around age 45. The son of the proband (III-1) had a history of tympanostomy tube placement at age 1, inguinal hernia repair at age 9, and valve-sparing aortic root replacement at age 16. No adverse postsurgical outcomes were reported.

Systemic Findings

The proband (II-1) had multiple systemic findings including aneurysm in aorta, aneurysm in visceral/ileac arteries, atrial fibrillation, arterial tortuosity, mitral regurgitation, joint hyperflexibility, disc degeneration, translucent and stretchy skin, inguinal hernia, hiatal hernia, eosinophilic esophagitis, GERD, pes planus, asthma, and allergic rhinitis. Several of these findings were consistent with LDS (**Table 1**). More recently, at age 55, the proband was also diagnosed with Waldenstrom macroglobulinemia; however, its implications to oral health were uncertain as the proband was not aware of this diagnosis at the time of exam.

The son of the proband (III-1) presented with fewer systemic manifestations which included joint hyperflexibility, scoliosis, bone fracture, food allergies, atopic dermatitis, asthma, pes planus, translucent skin, arterial tortuosity, aortic root dilation, and inguinal hernia. These findings were also consistent with LDS.

Craniofacial/Extraoral Findings

The proband (II-1) had an oblong face with symmetrical soft and skeletal tissue. His vision was normal with the help of corrective lenses. He had significant bilateral ptosis and mild nystagmus. His midface and infraorbital projection were flat, and he was noted to have a retrognathic mandible. He had occasional temporomandibular joint (TMJ) pain and bilateral joint sounds (crepitus). He reported TMJ dislocation in the past.

The son of the proband (III-1) had an oblong face with a long lower third. He had bilateral nystagmus and mild ptosis. Both his ears were slightly lowest. He had a retrognathic mandible with normal TMJ function. He also had generalized acne on the cheeks, chin, and lips.

Overall, these patients were noted to be on the mild craniofacial spectrum compared to previous reports of craniofacial findings in LDS[1].

Intraoral Findings

The proband (II-1) had complete adult dentition with 28 teeth (wisdom teeth were extracted). He had a history of multiple cavities and had been told that his teeth are more susceptible to decay; root canal with tooth #7. His palate was high vaulted as seen in most other individuals affected by LDS. He had a Class II molar relationship with an increased overjet (7 mm) associated with mandibular retrognathia, a common feature in LDS. His teeth had grayish-brown discoloration which was unusual and prompted further investigation (**Figure 2A**). There were no signs of fracture or chipping of teeth, clinically, or radiographically. The discoloration affected the anterior teeth more than the posterior teeth which correlated with more restorations specifically in the anterior teeth (**Figure 2B**). He had mild enamel defects, grade 1 as per the enamel index (16). He did not report any bleeding of the gums and had no signs of gingivitis at the time of the exam. Mild plaque accumulation at the cervical margins of posterior teeth was noted.

The 14-year-old son of the proband (III-1) had an adult dentition with 28 teeth (**Figure 2C**); wisdom teeth were yet to erupt. He had a history of gray discoloration and early loss of his primary teeth. However, his permanent teeth did not have clinically discernable discoloration. He had a very mild anterior open bite with a parafunctional habit of resting his tongue in this space. He had mild crowding of teeth in the lower anterior region. He had a Class II molar relationship. He had mild generalized gingivitis and there was moderate plaque accumulation on most teeth; however, he did not report bleeding gums during routine activities like brushing his teeth. Thin occlusal enamel was noted on tooth #3, 14, 19, and 30 (first molars) with wear facets from opposing cusps which was unusual for his age. The anterior teeth did not have any apparent enamel defects, grade 0 as per the enamel index (**Figure 2D**). While both proband and his son had several features consistent with findings in LDS, they did not present with severe enamel defects or bifid uvula, common findings in LDS. Both individuals were seen after 2 years for a follow-up, but no changes in their oral health were noted.

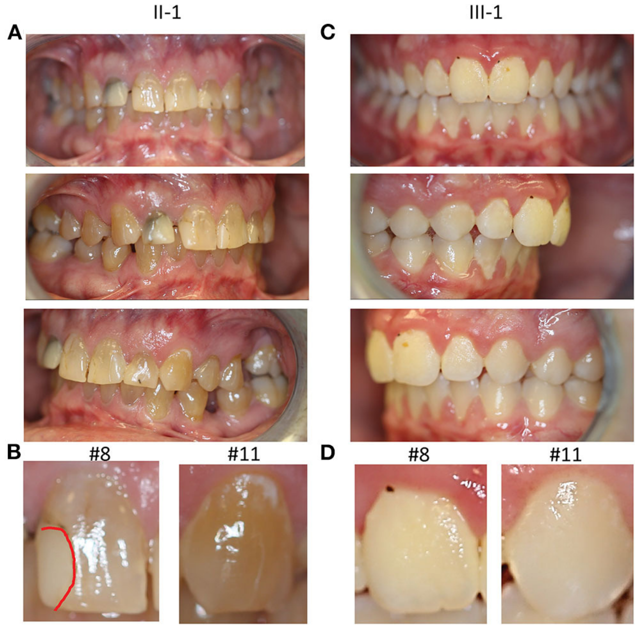


FIGURE 2 | Clinical oral manifestations. **(A)** Frontal, right lateral, and left lateral view of teeth showing tooth discoloration in proband II-1. **(B)** Magnified photos of tooth #8 and 11 with a red dotted line showing demarcation of the restoration on #8. **(C)** Frontal, right lateral, and left lateral view of teeth in the son of the proband III-1 **(D)** Magnified views of tooth #8 and 11 in III-1, showing normal appearance of teeth.

Radiographic CBCT Exam

The missing teeth of proband (extractions) were confirmed in the panoramic image generated from CBCT images (**Figure 3A**). Bilateral tori on the medial surfaces of the mandible and small exostoses on the lateral surfaces were noted in the CBCT images (**Figure 3C**). Posterior teeth as well as mandibular anterior teeth showed thin pulp chambers (**Figure 3B**). All maxillary anterior teeth had narrow or obliterated pulp chambers indicating a phenotype mimicking DI Type II (**Figure 3D**). Small osteophytes involving the mandibular condyles and articular fossae were also visible explaining the TMJ abnormality experienced by the

[1]Almpani et al., 2021, Loeys-Dietz and Shprintzen-Goldberg Syndromes: analysis of TGF-β-opathies with craniofacial manifestations using innovative characterization methods, manuscript under revision.

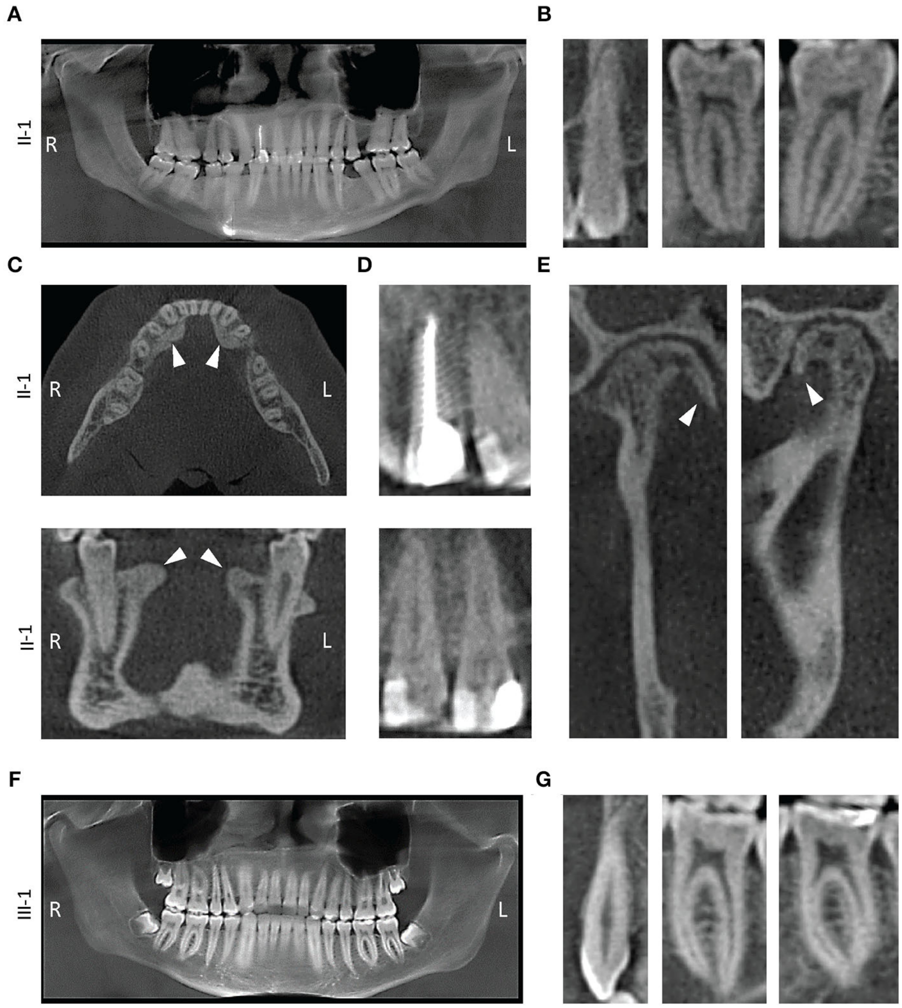


FIGURE 3 | Radiographic findings. **(A)** Panoramic x-ray from proband II-1 showing thickened dentin and obstructed pulp chambers. **(B)** 2D slices from II-1 cone beam computed tomography (CBCT) exam showing tooth # 11, 21, and 30 with constricted pulp canals. **(C)** Transverse (top) and a coronal (bottom) slice of the mandible showing lingual tori (white arrowheads). **(D)** Restorations in the teeth of proband with a root canal on tooth #7 (top) and class V restorations with teeth # 8 and 9 (bottom). **(E)** Coronal (left) and a sagittal (right) slice of the right mandibular condyle showing osteophytes (white arrowhead). **(F)** Panoramic x-ray from III-1. **(G)** 2D slices showing tooth # 11, 21, and 30.

proband (**Figure 3E**). Mild horizontal bone loss was noted in the CBCT images in both the upper and lower arch.

The son of the proband (III-I) had developing wisdom teeth visible in the radiographic exam (**Figure 3F**). His teeth did have long and slender roots with somewhat constricted pulp, although, not severe enough to be considered abnormal at the time of exam (**Figure 3G**). His alveolar bone was within normal limits and no bone loss was seen in the CBCT scans during the exam.

Correlation With Systemic Health

We analyzed the relationship between the systemic and oral manifestations in these two patients by linking the systemic findings (28) and oral findings (16) reported previously in LDS1 with the findings in these two patients (**Table 1**). While the proband (II-1) had multiple systemic conditions, several systemic findings were absent when compared to the LDS1 systemic findings reported in the literature (28). Similarly, the proband (II-1) had fewer oral manifestations compared to LDS1 affected individuals from the previous report (16), though, the DI in this individual is the first report of this dental finding in LDS. In the same fashion, the son of the proband (III-1) was on the milder spectrum of systemic and oral abnormalities, which may indicate that milder oral manifestations correlate with milder and fewer systemic conditions in individuals with LDS.

DISCUSSION

In this case report, we show the manifestation of dentin anomalies associated with LDS1. While enamel defects have been associated with LDS, and we also showed the correlation of enamel defect severity with mutations in LDS (16), it was not identified that dentin could also be adversely affected in individuals with LDS. To our knowledge, these are the only patients with LDS1 who exhibited a phenotype recapitulating DI type II with the pathognomonic tooth discoloration in this cohort. If a larger cohort of individuals with LDS were to be thoroughly examined for oral manifestations, more reports of dentin abnormalities are possible. Thus, individuals with LDS should be screened more thoroughly, both clinically and radiographically to rule out dentin abnormalities.

One limitation of this report is that the role of *TGBR1* in causing DI phenotype could not be confirmed with just two cases. As LDS is a rare disease with arterial aneurysms as a common finding, the oral findings and symptoms are often overlooked. We have studied the oral manifestations in LDS in detail in a cohort of 40 patients, including 15 patients with LDS1, and so far, these were the only two individuals with the manifestation of dentin abnormality. The dental manifestation reported in this case study may be unique to these two individuals or as more affected individuals are studied, more details about the dental abnormalities may be revealed. Nonetheless, screening more individuals with mutations in the TGF-β signaling pathway for oral manifestations is warranted. In addition to detailed dental history and a thorough clinical exam to confirm changes in dentin, a radiographic assessment should be performed to follow the progression of the disease. Moreover, advanced genetic analysis of the two patients affected with DI in this cohort will be necessary to investigate the presence of additional mutations that may be involved in this dental manifestation which is not common in LDS but is beyond the scope of this report.

The involvement of TGF-β signaling in dentin development is supported by numerous studies in mice (7, 29, 30). Odontoblasts are the cells that form dentin and line the inner wall of the pulp cavity. TGF-β ligands and receptors are known to be expressed by odontoblasts (26, 31, 32), and stimulate the secretion of predentin and dentin. The expression of TGF-β receptor 1 in human teeth has also been reported (32). These studies suggest that TGF-β signaling does play a vital role in dentin development. While we can confirm the dentin abnormality in these patients clinically and radiographically, further, ultrastructural and histological analysis of the teeth is necessary to investigate the effects of LDS-causing mutations on dentin formation. However, extraction of teeth is not an option unless clinically indicated. The son of proband did not clinically show the discoloration of his permanent teeth despite having a history of grayish discoloration of primary teeth. However, we suspect that the DI could be progressive and as the patient ages, his teeth may eventually discolor after pulp constriction.

The two individuals in this case report do not have the many systemic manifestations as other reported cohorts with LDS1 and their craniofacial findings are also on the milder spectrum for LDS (see footnote **1**). Similarly, the patients presented fewer and milder oral manifestations compared to the LDS1 cohort in the previous study (16). This suggests that the severity of oral manifestations may be related to the severity of systemic manifestations and a more thorough analysis of the correlations between oral health and systemic health is warranted. This report further emphasizes the vital role of diagnosing oral and dental abnormalities by dentists and physicians alike, as they may reflect the overall systemic health of an individual. Dental care providers could be the first to diagnose rare conditions based on the oral manifestations, following the accurate recording of history, thorough clinical exam, educating the patients about their oral conditions, and alerting the primary physicians of their findings. It is important to note that the unusual discoloration of the proband consistent with DI was likely visible well-before his aortic dissection was diagnosed and treated at age 40. As DI is relatively rare, this unusual presentation should alert clinicians and care providers that other systemic manifestations may need evaluation.

As science and medicine continue to move toward a multidisciplinary approach, dentists and oral health providers could play a critical role to advance the diagnosis, health management, and quality of life of the patient by considering the integration of oral health with systemic health and collaborating across disciplines and professions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, National Institutes of Health. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PJ, RM, and JL performed the clinical evaluation of patients. PJ and OD performed the analysis and interpretation of data. JL and PF-G obtained IRB approval, secured research funding, and identified and recruited LDS patients. PJ, OD, and JL wrote the manuscript. All the authors reviewed the manuscript critically for important intellectual content and approved the version to be published.

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frontiers in Dental Medicine

CASE REPORT
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Hyperphosphatemic Familial Tumoral Calcinosis Hidden in Plain Sight for 73 Years: A Case Report

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While dental pulp calcifications and root anomalies may be inconsequential incidental findings in dental radiographs, they can, especially in combination, represent a clue, hidden in plain sight, for the diagnosis of hyperphosphatemic familial tumoral calcinosis (HFTC). HFTC is an autosomal recessive disease of mineral metabolism characterized by sometimes massive, painful calcification around large joints, systemic inflammation, dental pulp calcification, and thistle-shaped roots. This paper describes a woman with HFTC who endured not only the symptoms of HFTC for decades, but also the frustration of not knowing the cause. The diagnosis was finally made at the age of 73 years, when the connection between a large right shoulder calcification and hyperphosphatemia was made. The dental findings were likely present on her initial radiographs taken in childhood. Increased awareness of the association between characteristic dental findings and HFTC may allow for earlier diagnosis and interventions to improve the care of patients with this rare condition.

Keywords: fibroblast growth factor 23, dental pulp calcification, root anomaly, phosphate metabolism, hyperphosphataemia

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INTRODUCTION

In 2000, the U.S. Surgeon General's Report on Oral Health in America reported numerous ways in which oral and general health are interconnected (1). A thorough oral examination can reveal signs and symptoms of endocrinopathies, systemic infections, immunologic disorders, and nutritional deficiencies (2). Identifying these oral manifestations of systemic disorders may enable early diagnosis and treatment.

Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare autosomal recessive disease characterized by high blood phosphate, calcific masses, and dental anomalies (OMIM 211900) (3). The dental anomalies are the most penetrant phenotypic finding in the condition (4). The extra-dental clinical symptoms cover a broad spectrum, ranging from no significant involvement to lesions that are large, painful, and debilitating (5). HFTC is caused by deficiency of, or resistance to the phosphorus regulating hormone fibroblast growth factor 23 (FGF23) (6). Absence of FGF23 promotes renal tubule phosphate reabsorption that leads to hyperphosphatemia, which promotes ectopic calcifications in tissues exposed to trauma (7). Pathogenic variants in *FGF23*, *GALNT3*, or *KLOTHO*, have been found to cause HFTC (6); an acquired form due to FGF23 autoantibodies has also been described (8). Current treatment interventions focus on managing blood phosphate, reducing pain and inflammation, and addressing calcifications and their complications (6).

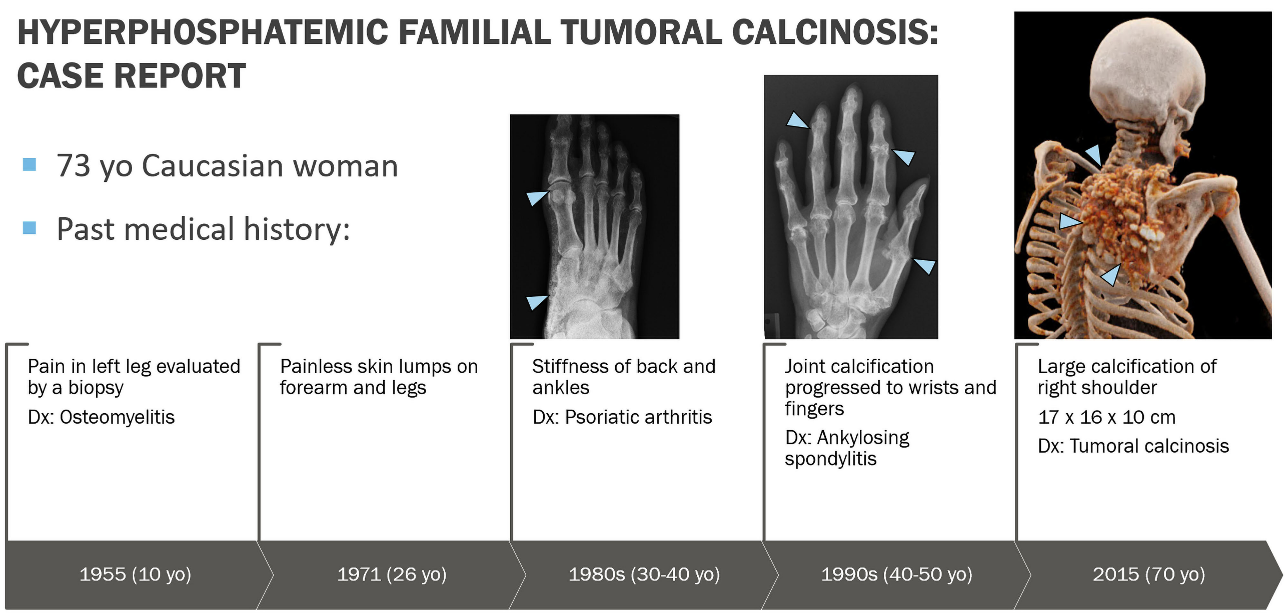

FIGURE 1 | Graphic representation of clinical course. At age 10 years, patient experienced unusual pain in her left leg that represented hyperostosis-hyperphosphatemia syndrome, which was evaluated with a biopsy and misdiagnosed as osteomyelitis. At age 26 years, she started noticing painless skin lumps on her forearm and legs. In her 30s, she started experiencing back pain and joint stiffness in her ankles and fingers. She was then evaluated by a rheumatologist and was diagnosed with an ill-defined rheumatologic disorder, possibly psoriatic arthritis. Over the next 30 years, the arthritis slowly progressed to involve almost all joints of her body. Eventually this was determined to be an aggressive form of osteoarthritis, currently felt not to be related to underlying HFTC. In 2015, a large bump appeared around her right shoulder, which was initially thought to be a sarcoma. Upon biopsy, bone calcifications were found with the possibility of tumoral calcinosis.

The unique dental phenotype of HFTC has been recently described in detail by our group (4). Internal pulp calcification and thistle-shaped, short roots with midroot bulging were most commonly observed in almost all of our cohort of 17 patients. The pulp can be partially to completely obliterated. Maxillary and mandibular premolars are most severely affected. In addition, primary dentition from pediatric patients with HFTC had findings similar to the permanent teeth.

Here we present a patient with hyperphosphatemic familial tumoral calcinosis who, despite numerous symptoms throughout her life, was not diagnosed with HFTC until the age of 73. Her diagnostic evaluation and treatment are presented and discussed.

CASE REPORT

A 73-year-old Caucasian woman was referred in December 2019 to the National Institute of Dental and Craniofacial Research at the National Institutes of Health by her endocrinologist at Oregon Health and Science University for evaluation of recently diagnosed HFTC. Review of the patient's medical history revealed several symptoms associated with HFTC that arose throughout her life since childhood (**Figure 1**). She had been in her usual state of health until age 10, when she experienced unusual pain in her left leg, which was evaluated with a biopsy and diagnosed as osteomyelitis. She received IV antibiotics for 10 days. As a teenager, she had no major health issues and participated in sports such as basketball and volleyball. During her regular dental checkups, she was told that she has abnormal pulp stones, but was not further evaluated (**Figure 2**).

At age 26, she started noticing painless skin lumps on her forearm and legs. In her 30s, she experienced back pain and joint stiffness in her ankles and fingers. She was then evaluated by a rheumatologist and was diagnosed with an ill-defined rheumatologic disorder. Over the next 30 years, the arthritis slowly progressed to involve almost all joints of her body. Her finger joints have fused, and she is unable to make a fist or pick up small items. She has been treated with prednisone, methotrexate, and infliximab. Multiple steroid injections in her back have provided temporary relief. On re-evaluation, the prevailing diagnosis of her rheumatologic findings is aggressive osteoarthritis, which is not believed to be related to the diagnosis of HFTC. In 2015, a large bump was noted around her right shoulder (**Figure 3**). Initial concern was that it might represent a sarcoma. On biopsy, paucicellular calcific material was seen, characteristic of tumoral calcinosis. In 2019, she was diagnosed with peripheral vascular disease requiring angioplasty.

Biochemical evaluation for causes of tumoral calcinosis revealed hyperphosphatemia and led to a referral to an endocrinologist in April 2019. HFTC was suspected and genetic testing identified two heterozygous variants in *GALNT3* (c.746_749del and c.926T>G), consistent with HFTC. The first change (c.746_749del) is in exon 4 of the *GALNT3* gene.

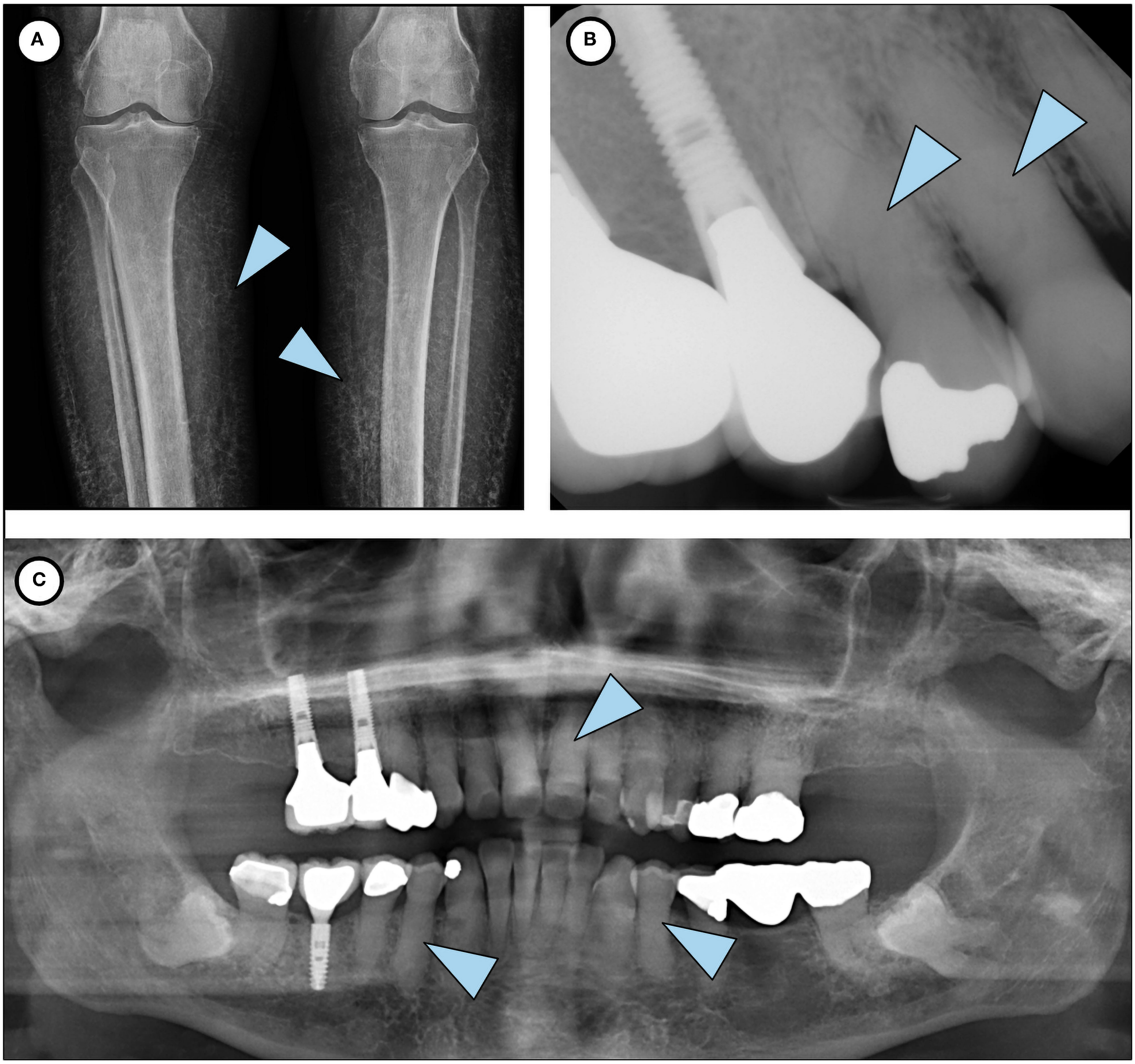

FIGURE 2 | Phenotypic features of HFTC. **(A)** Lower limb radiograph shows subcutaneous calcification of her legs, an unusual and rare finding seen in older patients with HFTC. **(B)** Periapical radiograph of teeth # 5 and 6 shows complete pulp obliteration and thistle-shaped roots. **(C)** Panoramic radiograph shows short bulbous root with complete pulp obliteration in all teeth.

This four-nucleotide deletion causes a frameshift and results in aberrant mRNA processing. This change has been previously reported as a variant associated with HFTC (9). The second change (c.926T>G) is in exon 5 of the *GALNT3* gene. This variant converts an isoleucine to arginine. To our knowledge, this change has not been previously reported as a disease-causing variant. Pathogenic variants in *GALNT3* often result in excessive cleavage of the active, intact FGF23 molecule, causing deficiency of functional FGF23 (10).

Following the diagnosis, the patient was referred to the NIH for further evaluation including blood and urine assessments and skeletal imaging. Laboratory studies showed elevated phosphorus 5.4 mg/dL (normal 2.5–4.5) and markers of systemic inflammation such as erythrocyte sedimentation rate 71 mm/h (0–42) and C-reactive protein 44 mg/L (0.00–4.99). Intact FGF23 was inappropriately low-normal 31 pg/mL (22–63) for the degree of hyperphosphatemia, while C-terminal FGF23 was markedly elevated 2,450 RU/mL (≤180), consistent with HFTC.

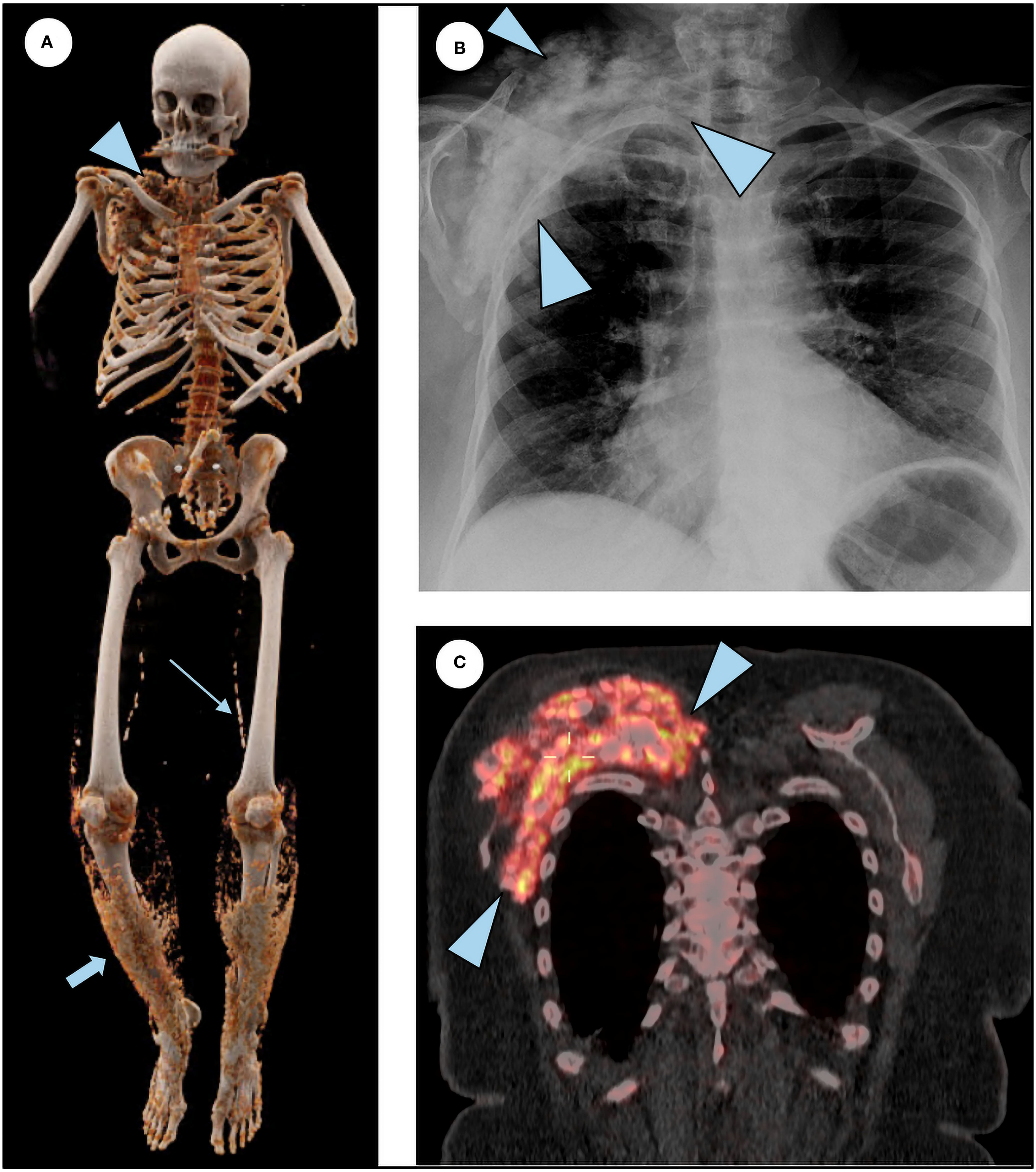

FIGURE 3 | Additional features of HFTC. **(A)** 3D reconstruction of a total body CT scan illustrates subcutaneous calcifications surrounding the right shoulder (arrowhead), superficial lacey calcification in the lower extremities bilaterally (short arrow), and calcifications of femoral arteries (long arrow). **(B)** Chest radiograph shows right shoulder calcification (arrowheads). **(C)** Coronal slice of the merged ^{18}F NaF PET/CT scan demonstrating intense tracer uptake in the actively forming calcific lesion seen in the chest radiograph (arrowheads).

Extraoral and intraoral examination revealed healthy mucosal tissues and well-restored permanent dentition. Panoramic radiograph showed moderate alveolar bone loss around mandibular anterior teeth, fully impacted # 17 and 32 with dilacerated roots, and changes in the roots consistent with HFTC (**Figure 2**). Complete pulp obliteration with short, thistle shaped

TABLE 1 | The diagnostic criteria of hyperphosphatemic familial tumoral calcinosis (HFTC).

Hyperphosphatemic familial tumoral calcinosis (HFTC)
Biochemical findings (common, required for diagnosis):
High serum phosphate
High C-terminal FGF23
Low/normal intact FGF23
Dental pathology (most common phenotypic feature):
Pulp calcification and thistle-shaped roots
Ectopic calcification (common):
Lateral hips, elbows, shoulders, hands, pressure/trauma points
Systemic inflammation (common, especially with new lesion formation):
Recurrent fevers, fatigue, anemia, polyarthritis, increased C-reactive protein and/or erythrocyte sedimentation rate
Vascular calcification:
Femoral/iliac arteries, aorta, carotids, cerebral vasculature
Hyperostosis (childhood only, often presenting symptom):
Tibiae (common), rarely ulnae, radii, and/or metacarpals
Stocking foot calcification (age-related/late finding):
Feet and legs
Ocular involvement (rare):
Calcification of eyelids/conjunctiva/cornea, retinal angioid streaks, vision loss

roots are observed in most of the teeth. Radiographs provided by her general dentist (taken 2008) also showed the altered tooth structure.

DISCUSSION

The earliest clinical features of HFTC can include characteristic dental findings, painful cortical hyperostosis of certain long bones (especially the tibiae), subcutaneous masses, and calcification around joints (especially the hips and/or shoulders) (**Table 1**) (6). Most diagnosed patients develop symptoms by 13 years of age (11). The patient in this case developed clinical symptoms at age 10, but it was not until the patient presented with a much larger calcification of her shoulder in combination with hyperphosphatemia that prompted genetic testing confirming the diagnosis of HFTC at age 73. The painful tibial lesions this patient experienced in childhood and misdiagnosed as osteomyelitis represented hyperostosis-hyperphosphatemia syndrome, one of the early manifestations and part of the spectrum of phenotypic findings of HFTC (OMIM 211900) (10). Despite the numerous symptoms throughout her life, the patient was not correctly diagnosed for many years partly due to the fact the mutation in *GALNT3* was not discovered until 2005 (12) and due to the rarity of the disorder.

Patients present with a moderate to severe dental phenotype with root bulging, pulp calcification and shortened thistle-shaped roots. It is believed that the severity of the dental phenotype in HFTC does not appear to progress over time, but there is insufficient longitudinal data to know definitively (4). Based on her current dental radiographs and review of past dental history, it is likely that the patient had similar dental findings in her primary dentition. Early identification and recognition of the dental phenotype of the disorder by an astute dentist may have contributed to a timelier diagnosis in this case.

In this case, we did not observe mineralization in the PDL space. The alveolar bone appears to be within normal limits as well. The patient has had multiple implants placed without complications. In addition, patients with HFTC have been able to get extractions without any complications and have had successful orthodontic treatment. In histological analysis of a previous study, widening of the cellular cementum layer was observed (4).

Upon review of the biochemical studies and confirmation of the diagnosis, the patient was encouraged to have routine evaluation of phosphorous and calcium metabolism. She was recommended to follow a low-phosphate diet, limiting meat, nuts, beans, and dairy, as well as avoiding excessive calcium and vitamin D supplements. The patient was encouraged to maintain physical activity as tolerated.

The patient was instructed to continue treatment with sevelamer, which reduces hyperphosphatemia by binding to dietary phosphate in the gut. The patient was started on anakinra, an interleukin-1 receptor antagonist, to address the marked degree of systemic inflammation. Infliximab was discontinued, but she remained on low dose prednisone and methotrexate. She had a significant degree of overall improvement in well-being on this regimen, probably related to the decrease in inflammation brought about by the anakinra.

In conclusion, this report describes the oldest known living patient with HFTC and highlights the importance of recognizing dental phenotypes that may be a sign of systemic disorders. In patients with HFTC, dental changes are often the first sign of disease. Dentists can contribute to early diagnosis and interdisciplinary care of systemic conditions that manifest in the oral cavity.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB of the NIDCR. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors contributed to manuscript preparation, revision, read, and approved the submitted version.

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Periodontitis Is Associated With Risk of Conventional Stent Restenosis: Pilot Case-Control Study

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Objectives: Percutaneous coronary angioplasty with stent implantation has been established as the main form of treatment of atherosclerosis. However, 16 to 44% of patients may evolve with stent restenosis. Periodontitis is an inflammatory condition associated with bacterial infection, that may lead to periodontal tissue destruction and tooth loss. This study aimed to evaluate the association between stent restenosis and periodontitis.

Materials and Methods: Coronary angiography exams presenting stent imaging with and without restenosis were analyzed. Patients meeting the inclusion and exclusion criteria were selected and allocated in 2 groups: case (restenosis) and control (without restenosis). We evaluated if systemic and periodontal variables were predictors of restenosis (primary outcome) using a multivariable stepwise logistic regression. Additionally, we compared clinical and periodontal conditions between the control and case groups (secondary outcomes) using Chi-square test and ANOVA test.

Results: Data from 49 patients (case $n = 15$; control $n = 34$) were analyzed. The results showed that stages III and IV periodontitis and lack of physical activity were significant predictors of stent restenosis (OR 5.82 and 5.98, respectively). Comparisons regarding the diagnosis of periodontal conditions between control and case groups did not present significant differences in the incidence of periodontitis and alveolar bone loss.

Conclusion: Stages III and IV periodontitis increased the incidence of stent restenosis. These findings suggest that advanced stages of periodontal disease might lead to the occurrence of negative outcomes after coronary angioplasty with stent placement.

Keywords: atherosclerosis, cardiovascular disease, stent restenosis, periodontitis, inflammation

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INTRODUCTION

Atherosclerosis is a progressive fibroproliferative chronic systemic inflammatory process that affects the intima layer of the middle and large vessels, culminating in the formation of atherosclerotic plaque. Its etiology is multifactorial with dyslipidemia, systemic arterial hypertension, diabetes, smoking, and the genetic hereditary component as the main risk factors for the development of atherosclerosis and coronary artery disease (CAD) (1). These factors increase the permeability of the intima to plasma lipoproteins in the subendothelial space, which when oxidized by macrophages become foam cells that are the main component of fatty striae. These immunogenic components stimulate the migration and proliferation of smooth muscle cells from the middle to the intimal layer to produce extracellular matrix that will form part of the fibrous cap of the atherosclerotic plaque (2, 3).

In the last three decades, interventional cardiology has established itself as the main form of myocardial revascularization in the treatment of coronary artery disease. Despite advances in procedural techniques and materials, about 16 to 44% of patients eventually evolve into an event called stent restenosis (4, 5). Restenosis is the onset of new obstruction >50% in the segment previously treated with stent (6) and occurs between the second and sixth month (7, 8) up to the 8 months after implantation of a conventional stent (9). Clinically it may manifest with the return of signs and/or symptoms of myocardial ischemia, associated with angiographic confirmation of new obstruction of the stent. This is the most commonly used concept and is based on vascular physiology studies where from this degree of obstruction we can observe impairment of the coronary flow reserve (10, 11).

Periodontal diseases are inflammatory diseases associated with bacterial infection (12). The initial clinical presentation is gingivitis, which perpetuates the infectious-inflammatory process over the years. In susceptible individuals, gingivitis may be modified by multiple host response genes and, in combination with lifestyle and environmental factors, can culminate in the destructive form of periodontal disease, namely periodontitis (13). Periodontitis is considered a worldwide health problem (14) that over the years has demanded global health policies and programs that can assist in its prevention and treatment (15). It is a highly prevalent disease, with its moderate form affecting 50% and a severe form affecting 5 to 15% of the global adult population (16). Since it was suggested that periodontitis could decrease life expectancy (17), much has been researched on the influence of this disease on quality of life and systemic health of individuals, including cardiovascular disease (18, 19), pregnancy complications (20), neurological diseases (21, 22) and diabetes (23, 24).

Host-microbe interaction in the periodontium can initiate or even aggravate atherosclerotic processes through the activation of innate immunity, bacteremia, and direct involvement of cytokines and inflammatory proteins of oral microbiota (25–27). The association between atherosclerosis and periodontal diseases has already been corroborated in both acute coronary disease and acute myocardial infarction (28, 29), indicating the presence of periodontal diseases as a factor of clinical decompensation of coronary atherosclerosis (30). Despite this, we do not know whether the chronic inflammatory process triggered by periodontal diseases can interfere with the long-term outcome of patients undergoing coronary angioplasty with a consequent episode of restenosis. Whether periodontal diseases, due to their chronic systemic inflammatory state, would be contributing to an increase in restenosis rates of conventional stents is not defined in the literature. Besides that, it is not routine in the clinical practice of interventional cardiologists to consider the oral health status before performing surgical coronary angioplasty. To date, there are no studies evaluating the possible relationship between conventional stent restenosis and periodontal diseases. Therefore, the aim of the present study is to evaluate the association between stent restenosis and periodontitis.

MATERIALS AND METHODS

Experimental Design

This was an observational, retrospective, case-control, population-based study designed to evaluate the association between conventional stent restenosis and periodontal diseases. This study was approved by the human subjects ethics board of UNESP (CAAE: 60607916.9.0000.0077) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Study Population and Inclusion and Exclusion Criteria

Data from coronary angiography examinations performed at Pio XII Hospital (São José dos Campos, SP, Brazil) from January 4th, 2016 to February 28th, 2018 were analyzed. The study population consisted of patients who underwent coronary angiography at the referred hospital during the established period. Detailed medical records were obtained. Volunteers who fulfilled the inclusion criteria were invited to participate in the study. Inclusion criteria were prior coronary angioplasty with conventional stent implantation; aged ≥40. Exclusion criteria were: edentulism; diabetes mellitus with glycated hemoglobin (HbA1c) levels >7.0%; pharmacological stent implantation; restenosis in stents implanted over the previous 2 years. Informed consent was provided by each volunteer after a thorough explanation of the nature, risks, and benefits of the clinical investigations.

Allocation

Patients were allocated into two groups according to the criteria below:

- Case Group: Patients who underwent coronary angiography examination of stent with restenosis, whose stent implantation occurred within 2 years.
- Control Group: Patients who presented coronary angiography with stent image without restenosis regardless of the implantation period.

Cardiovascular Evaluation

For the screening and selection of candidates for both study groups, the reports previously made by interventional cardiologists at the Pio XII Hospital were used. For the definition of angiographic restenosis in coronary angiography reports, the Interventional Cardiology societies criteria were used. These criteria are based on studies of vascular physiology, in which the impairment of coronary flow reserve can be observed considering the degree of obstruction, and consists of the presence of >70% from the lesion in the stent-treated segment (within the stent and within 5 mm beyond the stent) (4). Restenosis was classified using the Guideline Reference for Percutaneous Coronary Intervention by the American Heart Association (31, 32). This classification is based on the geographic distribution of intimal hyperplasia in reference to the implanted stent. Peripheral blood was collected to evaluate HbA1c levels and lipid profile. Anthropometric measures including weight and height were recorded. Body mass index (BMI) was calculated as the weight divided by the square of height (kg/m^2).

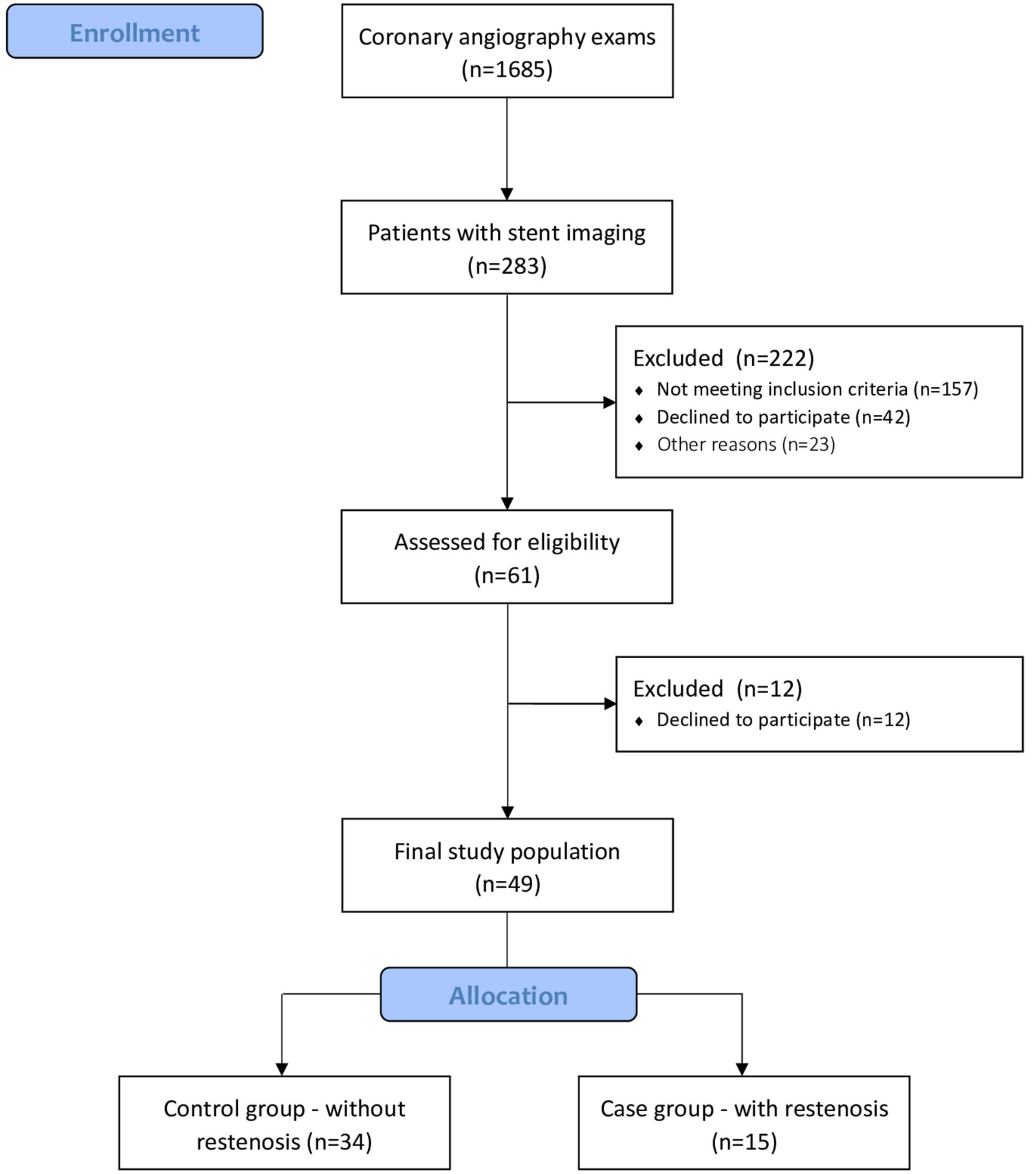

FIGURE 1 | Study flowchart.

Periodontal Evaluation

All patients were scheduled for a periodontal evaluation at the Department of Periodontology at the Institute of Science and Technology, São Paulo State University–Unesp (São José dos Campos, SP, Brazil). In this session, a throughout periodontal examination was performed by two trained and calibrated periodontists (CFA and NCCS). The examiners participated in a calibration exercise in which PD and CAL of 10 patients were measured twice within a 24-h interval. These measurements were subjected to an intraclass correction test. The agreement for the variables was >90%.

The evaluated parameters were: (1) Probing depth (PD); (2) Clinical attachment level (CAL); (3) Gingival recession (GR); (4) Bleeding on probing (BoP); (5) Supragingival biofilm accumulation (Pl) (33). All clinical measures were assessed using a manual probe (University of North Carolina Probe PCPUNC-BR 15, Hu-Friedy).

The presence or absence of periodontal diseases, the diagnosis, and classification of the diseases, the quantification of the extent and severity of the diseases, and the estimated duration of the diseases were determined (34, 35).

Alveolar Bone Loss Analysis

Panoramic radiographs were obtained by a radiologist and evaluated by a trained examiner. The examiner was blind to the status of each group of participants. The severity of alveolar bone loss was measured as a percentage of bone loss in the interproximal sites of each tooth (36). Each site was assigned a score from 1 through 4 according to alveolar bone (1: 0 to 24%; 2: 25 to 49%; 3: 50 to 74%; 4: 75 to 100%). We defined a mean bone loss score ≤2 as mild to moderate periodontal bone loss and score >2 as severe alveolar bone loss.

Statistical Analysis

Data were recorded as mean and standard deviation, median with quartiles or percentage according to the different variables analyzed. Normal distribution was tested by Shapiro-Wilk. For the comparison of quantitative variables, the mean and standard deviation were used. For percentages, Chi-square test (χ^2) was used for qualitative variables. ANOVA test was used to compare groups for mean age and BMI. A multivariable stepwise logistic regression was performed to verify if there is a relationship between restenosis (dependent variable) and independent variables. All data analyses were performed using IBM SPSS, Minitab, and Excel Office. A significance level of 0.05 (5%) was defined for this study, and all confidence intervals throughout the study were constructed with 95% statistical confidence.

RESULTS

A total of 1,685 coronary angiography examinations performed during the period from January 4th, 2016 to February 28th, 2018 were analyzed. At the end of volunteer selection, 61 patients were eligible. Of these, 49 patients accepted to participate in the study and underwent periodontal evaluation (**Figure 1**). **Table 1** presents sociodemographic characteristics of the control group ($n = 34$) and the case group ($n = 15$). There was no statistical difference between most of the variables analyzed, except for previous smoking history (**Table 1**).

TABLE 1 | Socioeconomic and clinical characteristics for control and case groups.

Variables	Control group ($n = 34$)	Case group ($n = 15$)	*P*-value
Gender (male)	24 (70%)^A	13 (86%) ^{A}	0.228
Age (years)	60.60±8.00 ^{A}	59.10±8.50 ^{A}	0.542
BMI (kg/m^2)	27.91±3.50 ^{A}	27.12±3.46 ^{A}	0.495
Arterial hypertension	31 (96%) ^{A}	12 (85%) ^{A}	0.158
Diabetes mellitus	8 (23%) ^{A}	5 (33%) ^{A}	0.474
Dyslipidemia	27 (84%) ^{A}	12 (86%) ^{A}	0.907
CAD	16 (50%) ^{A}	9 (64%) ^{A}	0.371
Smoker	7 (22%) ^{A}	2 (14 %) ^{A}	0.550
Former smoker	9 (28%) ^{A}	9 (64%) ^{B}	0.021
Obesity	9 (28%) ^{A}	3 (21%) ^{A}	0.634
Brushing	30 (96%) ^{A}	14 (100%) ^{A}	0.497

BMI, body mass index; CAD, coronary artery disease.
Different uppercase indicates statistically significant differences between groups. Age and BMI were compared using one-way ANOVA. Intergroup percentages were compared using Chi-square test (χ^2).

TABLE 2 | Stepwise logistic regression considering restenosis as an outcome variable for all volunteers ($n = 49$).

	Restenosis		
	OR	**95% C.I.**	***P*-value**
Periodontitis			
No	1.0		
Stages III and IV	5.82	1.35–25.07	0.018
Physical activity			
Yes	1.0		
No	5.98	1.07–33.62	0.042

Covariables included are periodontitis, diabetes, obesity, smoking, physical activity, age, gender, number of teeth, and alveolar bone loss.
Nagelkerke $R^2 = 0.248$.

A binary logistic regression was performed to determine if demographic, systemic, and periodontal variables were predictors of restenosis. "Stages III and IV periodontitis" and "No regular physical activity" were significant predictors when restenosis was a dependent outcome variable (OR 5.82 and 5.98, respectively). Other stages of periodontitis, controlled diabetes, obesity, current smoking, age, gender, number of teeth, and severe alveolar bone loss were not statistically significant (**Table 2**).

We evaluated the groups according to the frequency of different diagnoses and classifications of periodontal diseases. There was a higher percentage of gingivitis and Stages I and II periodontitis when the control group was compared to the case group. On the other hand, Stages III and IV periodontitis presented higher percentages in the case group than

TABLE 3 | Incidence of periodontal diseases for the control and case groups.

Variables	Control group		Case group		*P*-value
	n	%	*n*	%	
Gingivitis	8	23.5	2	13.3	0.414
Stage I periodontitis	5	14.7	1	6.7	0.466
Stage II periodontitis	10	29.5	3	20.0	0.492
Stage III periodontitis	5	14.7	5	33.3	0.111
Stage IV periodontitis	6	17.6	4	26.7	0.470

Chi-square test (χ^2) was used to compare the frequency of periodontal diseases between groups ($p < 0.05$).

in the control group. Despite these differences, no statistical significance was observed ($p > 0.05$) (**Table 3**).

For the comparison of alveolar bone loss scores between groups, the case group presented 4 (36%) patients with alveolar bone loss score ≤2, while 7 (63%) patients presented score >2. In the control group, we observed that 11 (38%) patients presented score ≤2, and 18 (62%) patients presented score >2. No statistical significance was observed in the intergroup comparison.

DISCUSSION

Stages III and IV periodontitis increased the risk of chances for stent restenosis. These results suggest that periodontitis is an important factor to be considered in the clinical cardiological evaluation routine before and after coronary angioplasty interventions.

Growing evidence suggests a link between periodontitis and cardiovascular disease, especially regarding the risk factors shared between these conditions. In this study population, all patients presented atherosclerosis and had already received conventional stent implantation treatment. Thus, the high prevalence of periodontal disease found in our study population is justified, confirming the same results found in a previous study (37). Besides having common risk factors, a mechanism linking the two diseases has been elucidated in a recent longitudinal study. Van Dyke et al. (38) evaluated the F-fluorodeoxyglucose positron emission tomography/computed tomography of 304 individuals, quantifying periodontal and arterial inflammation. The authors showed that periodontitis is associated with arterial inflammation and that periodontitis predicted subsequent major adverse cardiovascular events (38). These findings corroborate the main results of our study, which underscore the hypothesis that periodontitis could influence the occurrence and treatment of CAD.

In addition to periodontitis, we observed that physical activity was associated with a lower restenosis rate. It is well-documented that physical activity helps to control many cardiovascular risk factors (39). In patients with stable CAD, the measurement of C-reactive protein (CRP) may be useful as an independent marker to assess the likelihood of recurrent events, including death, myocardial infarction, or stent restenosis (40), and physical activity in this type of patient is a factor that in itself reduces inflammatory markers such as CRP (41). Thus, the regular practice of physical activity could contribute as a protective factor for restenosis by reducing inflammation.

Risk factors associated with the development of periodontitis comprise local, systemic, and genetic factors, including smoking, diabetes, and possibly obesity (42). Contributions for cardiovascular disease are also multifactorial, which encompass ethnicity, age, family history of CAD, dyslipidemia, hypertension, smoking, obesity, and diabetes. Hence, there are many potentially important confounders for the association between periodontitis and atherosclerotic disease (19). The presence of confounding factors is a relevant limitation aspect of several observational studies (43). In the present study, we assessed if there was an association between risk factors shared by the two diseases and restenosis, but no significant results were observed.

Although diabetes mellitus is considered a risk factor that increases the likelihood of restenosis, patients with controlled diabetes (HbA1c <7.0%) do not present high restenosis rates after conventional stent implantation (44, 45). For this reason, patients with controlled diabetes were included in this study. As expected, controlled diabetes was not associated with an increased risk for restenosis in this study. One of the exclusion criteria was the presence of pharmacological stents, for the use of pharmacological stents alters the physiology of the stent endothelialization phenomenon by inhibiting the cell cycle in different stages, thus delaying the stent phenomenon of cell migration and proliferation (46). Despite the benefits of pharmacological stents observed in large randomized controlled clinical trials, the use of drug-eluting stenting implies longer dual anti-aggregation therapy, thereby increasing the risk of bleeding (47) and decreasing the cost-effectiveness of the procedure (48).

The findings of this study demonstrate that periodontitis is an important predictor of stent restenosis. Nevertheless, this result should be interpreted with caution. The main limitation of this study is the small sample size. Of the 1,685 coronary angiography examinations, 1,402 patients did not present stent imaging, which resulted in 283 possible volunteers for the study. Then, volunteer selection was particularly difficult for the exclusion criterion "edentulism," which was highly prevalent in the analyzed population. Possibly, most individuals presenting edentulism had lost their teeth due to periodontitis previously to this study. Thus, the number of observed events (restenosis) was modest (15 patients). The main strength of the present study is that periodontal diseases were evaluated as possible predictors for stent restenosis for the first time. This hypothesis was mechanistically plausible and demonstrated to be clinically relevant in this population. Additionally, evaluating the association between periodontal diseases and negative outcomes after cardiological interventions help to increase the awareness of the relevance of periodontal evaluation and treatment in patients with atherosclerosis.

Stages III and IV periodontitis is associated with the incidence of stent restenosis. These findings suggest that advanced stages of periodontal disease might lead to the occurrence of negative outcomes after coronary angioplasty with stent placement.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human subjects ethics board–UNESP. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RO: conception and design, selection of volunteers, and interpretation of data. NC: data acquisition, analysis, interpretation of data, and drafting article. CA: data acquisition and interpretation of data. FA: interpretation of data. MF: interpretation of data and drafting article. MS: conception and design, direction and implementation, interpretation, and drafting article. All authors contributed to the article and approved the submitted version.

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Corrigendum: Periodontitis Is Associated With Risk of Conventional Stent Restenosis: Pilot Case-Control Study

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In the original article, Magda Feres was incorrectly listed as the corresponding author. The correct corresponding author is Dr. Mauro Santamaria.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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The Advent of COVID-19; Periodontal Research Has Identified Therapeutic Targets for Severe Respiratory Disease; an Example of Parallel Biomedical Research Agendas

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The pathophysiology of SARS-CoV-2 infection is characterized by rapid virus replication and aggressive inflammatory responses that can lead to acute respiratory distress syndrome (ARDS) only a few days after the onset of symptoms. It is suspected that a dysfunctional immune response is the main cause of SARS-CoV-2 infection-induced lung destruction and mortality due to massive infiltration of hyperfunctional neutrophils in these organs. Similarly, neutrophils are recruited constantly to the oral cavity to combat microorganisms in the dental biofilm and hyperfunctional neutrophil phenotypes cause destruction of periodontal tissues when periodontitis develops. Both disease models arise because of elevated host defenses against invading organisms, while concurrently causing host damage/disease when the immune cells become hyperfunctional. This represents a clear nexus between periodontal and medical research. As researchers begin to understand the link between oral and systemic diseases and their potential synergistic impact on general health, we argue that translational research from studies in periodontology must be recognized as an important source of information that might lead to different therapeutic options which can be effective for the management of both oral and non-oral diseases. In this article we connect concepts from periodontal research on oral inflammation while exploring host modulation therapy used for periodontitis as a potential strategy for the prevention of ARDS a deadly outcome of COVID-19. We suggest that host modulation therapy, although developed initially for management of periodontitis, and which inhibits proteases, cytokines, and the oxidative stress that underlie ARDS, will provide an effective and safe treatment for COVID-19.

Keywords: COVID-19, SARS-CoV-2, periodontal research, ARDS, PMN hyperactivation

INTRODUCTION

The outbreak of viral pneumonia cases from SARS-CoV-2 was first reported by the Chinese government in December 2019 (1). As with other viral diseases SARS-CoV-2 can cause various respiratory infections, including multifocal interstitial pneumonia which was leading to admission to intensive care and death in infected patients (2). This infection, named Coronavirus disease 2019 (COVID-19) (3), can cause complications including the development of acute respiratory distress syndrome (ARDS); an often fatal disorder (2, 4).

ARDS is caused by many pathogens including influenza and coronavirus. Although its precise pathophysiologic mechanisms are not completely clear, it could be the result of direct damage caused by the viral pathogen and then, more importantly, the triggering of a complex dysregulation of the inflammatory environment (5, 6). Indeed, it has been argued that the host-mediated lung and other tissue damage has more to do with the massive infiltration of polymorphonuclear neutrophils (PMNs) in the lungs rather than purely direct viral effects in relation to morbidity and mortality (4, 6, 7).

Immuno-Inflammatory Pathogenesis of COVID-19

Data from cohorts of critically ill patients with COVID-19-related pneumonia provide evidence of cytokine profiles like those of hyperinflammatory states seen in bacterial and viral pneumonias (4, 8). SARS-CoV-2 invades the host cell by binding of its viral spike glycoprotein to the host's cellular receptor for ACE2. Once in the cell, the virus may "deceive" the immune system through strategies that prevent pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) from recognizing pathogen-associated molecular patterns (PAMPs) and will start replicating freely within the infected cells using their own organelles and other cellular components (9). In addition, SARS- CoV-2 has also evolved strategies that interfere in the production of type I/III IFN which are essential for the development of effective immunity (9). As a result of this state of unchecked replication, SARS-CoV-2 can reach high titres shortly after initial infection that leads to an exponential production of PAMPS, cell damage and release of damage-associated molecular patterns (DAMPS), all of which triggering a hyperactive inflammatory responses (10).

The attachment of SARS-CoV-2 to ACE2 for host cell entry leads to down-regulation of ACE2 and a subsequent increase of angiotensin II (ANGII) (11–16) which dysregulate the renin-angiotensin system (RAS) (17). In elevated levels, ANGII acts as a pro-inflammatory mediator that ultimately activates NFκB, disintegrin, and metalloprotease 17 (ADAM17) (18). This activated pro-inflammatory environment triggers the production of reactive oxygen species (ROS), fibrosis, matrix metalloproteinases (MMPs), production of cytokines such as IL-6 and IL-8 by macrophages and recruitment of PMNs. The virus also activates NFκB (11, 15) that amplifies downstream signaling for cytokine production (14, 15). The release of cytokines activates pathogenic T helper type 1 (Th1) cells rapidly which then secrete additional pro-inflammatory cytokines (11, 12, 19). This is followed by additional infiltration of macrophages and PMNs into alveolar cavities where they begin to contribute to the hyper-inflammatory response (11, 14, 15). ANGII is also known to trigger the coagulation cascade by activating platelets through surface AngII receptors binding and inducing platelet shape change (20) both of which associated with thrombosis (21). In summary, SARS-CoV-2 binding to ACE2 for cell invasion is likely the first step for activation of the cytokine storm which releases uncontrolled levels of cytokines, including IL-1β, 1L-6, IL-8, and IL-10 (22), that prime the host for development of hyperactive inflammatory responses. Manifestation of the cytokine storm is extremely complex but in general in addition to virus-induced infiltration of inflammatory cells to the lungs causing oxidative stress and initial inflammation it relies on even more PMN infiltration into the lung whereby cytokines, MMPs, PMN elastase, ROS, and nitric oxide (NO) are released into the inflamed tissue (22, 23) causing diffuse alveolar damage, pulmonary edema, pulmonary fibrosis, acute lung tissue destruction, multiple organ failure and death. These developments essentially describe ARDS as seen in patients suffering from COVID-19 (11–16).

PMNs are the first and most numerous innate immune cells to reach the infection site and therefore play a central role in the resolution of inflammation through specific mechanisms of virus inactivation including the release of MMPs, cytokines, ROS, peroxidases and PMN extracellular traps (NETs) (24). This is of course protective. But PMNs can also become "hyperactive," and when this happens, PMNs contribution to antiviral defense can cause harmful effects to the host including the development of pneumonia and ARDS (25–27). Paradoxically then, despite the critical roles played by PMN cells insofar as clearance of viral pathogens and other infectious disease is concerned it's recognized that excessively sensitized/activated PMN responses promote a vicious cycle of inflammatory damage to the very tissues to which they were dispatched as a consequence of a PMN-induced cytokine storm (24). Notably, MMP-2 and—9 destroy the extracellular matrix in the lungs by degrading collagen found in the basement membrane comprising their parenchymal architecture (22). The virucidal effects of ROS and the recruitment and activation of even more PMNs through the production of cytokines can perpetuate the hyperinflammatory response thereby leading to lung and other tissue injuries including the development of vasculitides and thrombotic conditions characteristic of ARDS (24, 27). In addition, ROS production further increases vascular and epithelial permeability, allowing for continuous infiltration of PMNs and serosanguinous exudates into the alveolar space (27). Finally, the formation of NETs aided by activated platelets in response to endothelial damage, ROS and IL-1β production and virus replication may increase the risk of thromboembolic events in COVID-19 patients by triggering complement activation and further fuelling the coagulation cascade (9) (**Figure 1**).

A summary of the role of PMNs on the severity of COVID-19 in recent studies is shown in **Table 1**.

To prevent this, we hypothesize that any treatment which could prevent excess PMN infiltration and hyperactivation while also blocking excessive levels of MMP activity, elastase activities

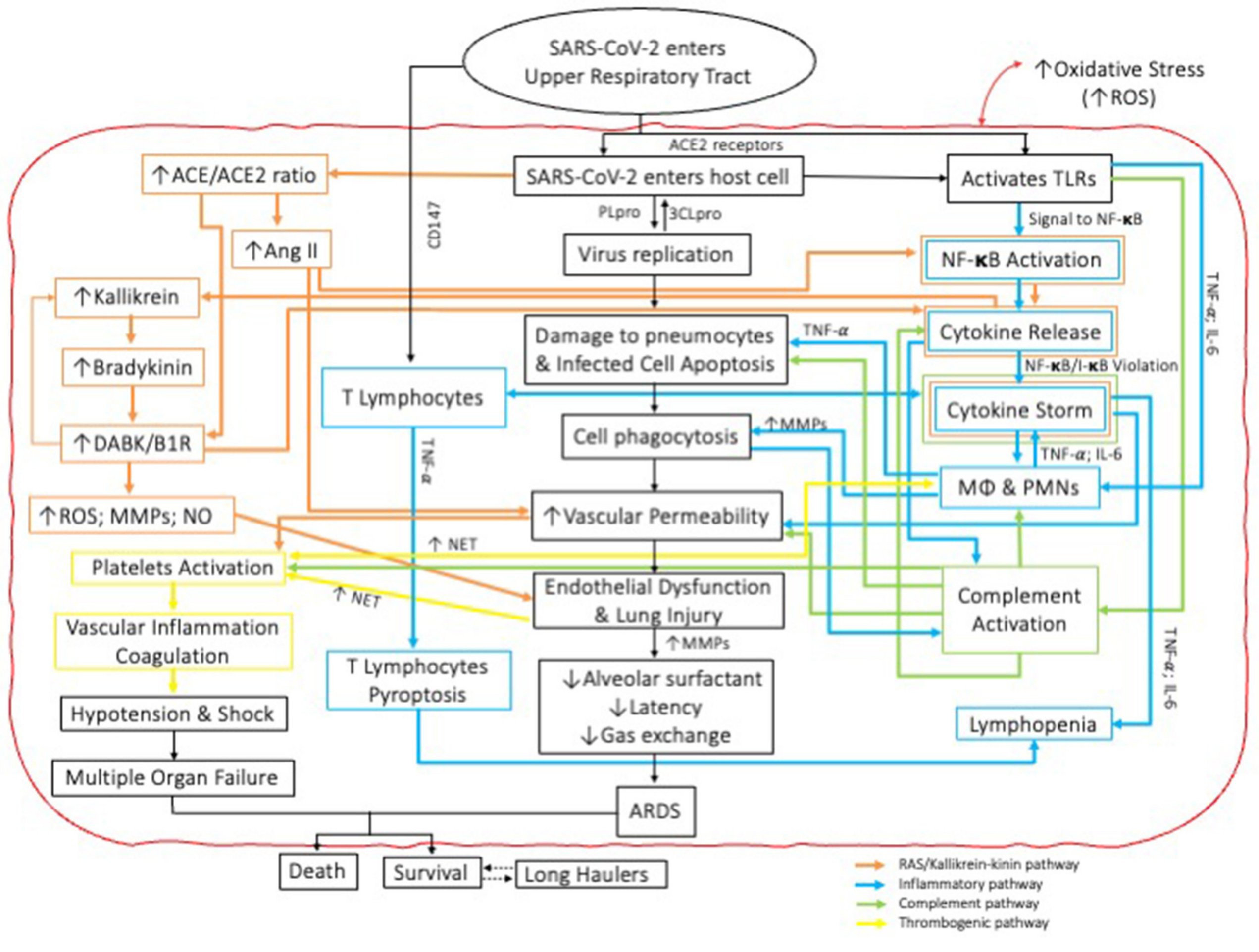

FIGURE 1 | Schematic representation of the interactions amongst and between four independent pathophysiologic pathways involved in the cytokine storm cascade during COVID-19. Note mechanisms for COVID parallel those also described for periodontal diseases.

and simultaneously reducing excessive ROS levels or activity might represent a useful approach to the prevention and/or amelioration of the morbidity and mortality associated with the cytokine storm/ARDS in patients with COVID-19.

Links Between Oral Inflammation and Systemic Disease

As researchers begin to understand the link between oral and systemic diseases more clearly and their potential synergistic impact on general health, we argue that translational research from studies in periodontology must be recognized as an important source of information that might lead to new and different therapeutic options which can be effective for the management of both oral and non-oral diseases.

While evidence of associations between periodontal diseases and systemic conditions have long been noted (36), there has been increased interest in determining the underlying mechanisms that might explain the oral-systemic pathophysiology. We suggest that a causal and indeed bidirectional link may exist between periodontitis and systemic non-communicable diseases. However, we also have to recognize that they could also be manifestations of common underlying pathophysiological mechanisms. This said, these two concepts are not mutually exclusive, and therefore we must emphasize that both putative mechanisms could be involved in those associations, as demonstrated by studies that show bidirectionality of association. For instance, early epidemiological studies have demonstrated the bidirectional adverse interrelationship between an altered host inflammatory response in PD and the metabolic imbalance in diabetes (37) while more recently, a causal association was demonstrated between periodontitis and chronic kidney diseases mediated *via* oxidative stress (38), which seems highly relevant to this argument. We also point out that oxidative stress is a key element of PMN hyperfunctionality related to overproduction of ROS and downregulation of endogenous antioxidants such as NrF2 mediated expression of superoxide dismutase (39). Inflammation is therefore the common factor amongst periodontitis and the chronic diseases of aging, or simply "the disease" (40). Insofar the individual's susceptibility to systemic diseases, our research support the hypothesis that PD sensitizes or primes the peripheral innate immune system, and predominantly the

TABLE 1 | Summary of the role of PMNs on the severity of COVID-19 in recent studies.

As predictors of poor outcomes	Higher PMN counts in non- survivors than in survivors (4)
	Increased NET formation associated with COVID-19–related ARDS (28)
	Increased NET formation as a potential biomarker for disease severity (28)
	PMN-to-lymphocyte ratio as the most promising predictive factor for critical illness incidence of COVID-19 pneumonia (29)
	Markers of PMN activation amongst the most potent discriminators of critical illness (30)
	PMN activation preceding the onset of critical illness and predicting mortality (30)
	Higher levels of specific markers of NETs in patients receiving mechanical ventilation than in those breathing room air (31)
	Neutrophilia observed In the last 24 h preceding death (32)
	NETs infiltrate in lungs of patients with a fatal outcome (32)
	Dramatic increase of PMNs with COVID-19 severity and ARDS (33)
	Increased number of circulating PMNs as an indicator of worse outcomes (2)
Linked to dysregulated immune response	Blood PMNs produce high levels of NETs; NETs are highly detected in the tracheal aspirate and lung tissue (34)
	SARS-CoV-2–activated PMNs induce lung epithelial cell death through the release of NETs (34)
	PMN activation-associated signatures prominently enriched in severe patient groups (35)
	Dysregulated NET formation in lungs (6)

PMNs in such a manner as to allow those cells to trigger and/or exacerbate inflammatory diseases in distant organ systems (41).

Periodontal Disease-Induced Immunopathology and COVID-19

The oral cavity is unique in that the teeth are the only structures in the body that *de facto* protrude through the lining epithelium, in this case the gingival tissues. As such a unique seal exists between the gingiva and tooth surfaces and therefore between the oral cavity and its contents thereby preventing ingress of microbial or other pathogens into the body (42). This biologic seal, specifically a connective tissue and epithelial attachment to cementum, is not perfect and is permeable even in health but moreso in states of inflammation. To enhance protection from pathogens, cells of the innate immune system such as PMNs, are recruited constantly to the oral cavity as part of a healthy and self-limiting inflammatory response against the challenges imposed by the oral microorganisms found in the dental biofilm (43). Interestingly, while bacteria or their by-products may lead to periodontal tissue damage, the host immunoinflammatory response to microorganisms in dental biofilms, when uncontrolled, is considered the main cause of periodontal pathogenesis (40, 44), something akin to destruction of lung tissues observed in ARDS. In parallel to what is seen in ARDS, the initial host immune response starts when PRRs expressed in the membrane of epithelial cells and gingival fibroblasts interact with PAMPs, including lipopolysaccharide (LPS) found in the cell wall of specific periodontal bacteria (45). LPS is considered a potent ligand for TLR4 (46) and activation of both the TLR2 and TLR4 pathways has been described in studies with *Porphyromonas gingivalis* (47). PAMP-TLRs binding and MyD88 signaling results in the activation of the downstream signaling pathways associated with inflammation and upregulation of pro-inflammatory transcription factors, such as NFκB (48), leading to the release of inflammatory cytokines and chemokines (49, 50). The most common cytokines involved in this process are TNF-α, IL- 1β, IL-6, and IL-8 (51, 52), while chemokines include CXCL8/IL-8, CCL2, CCL3, and CCL5 (49, 50) and their release causes vasodilation and chemical gradients that facilitate the migration of leukocytes, mostly PMNs from the vasculature to the site of injury (53). Infiltration of such inflammatory cells leads to release of ROS, MMPs and NETs, as well as to chemotaxis and phagocytosis as defense mechanisms against infection and inflammation (54–58). However, as periodontal diseases are not considered as a classic bacterial infection but rather a dysbiotic disease such mechanisms are necessary but possibly not sufficient to cause disease (59). Periodontal dysbiosis leads to a disturbance of the local homeostasis and immune subversion that increases microbial colonization, virulence, and persistence to disease, and result in persistent recruitment of PMNs (60) with hyperfunctional or hyperactive phenotypes (43, 54–56, 61–63). Similar to what happens in patients with COVID-19, these now hyperactivated PMNs pour out high levels of ROS and degradative enzymes along with ever increasing levels of proinflammatory cytokines (55, 56, 62). These actions lead to severe destruction of the connective tissues about the affected teeth leading to pain, bleeding and ultimately tooth loss (58, 64).

This phenotype of hyperinflammatory PMNs has also been observed to play an important role in the pathogenesis of systemic diseases such as diabetes and cardiovascular disease, suggesting an epidemiological association between periodontal diseases and systemic conditions (65, 66). More importantly, these hyperactivated phenotypes have been observed in severe cases of COVID-19 (67, 68), as well as in aging-related conditions (69). Therefore, the presence of periodontitis in patients who are infected with SARS-CoV-2 could represent an as yet unrecognized comorbidity that could contribute to more severe symptoms of COVID-19. While there are now emerging scientific publications that align with this suggestion (70, 71), it still stands in the grounds of scientific inference. Two plausible mechanisms may explain this association: one being related to the periodontitis-induced inflammatory response; a pre-existing pro-inflammatory state. This could act synergistically and therefore amplify the systemic inflammatory response induced by infection with SARS-CoV-2. Another possibility includes the notion there could be a genetic predisposition of the host to develop hyperinflammatory conditions that are favorable to both the development of PD or COVID-19. Regarding the former, our team's previous research has shown that an increase in the level of hyperactivated PMNs in bone marrow and blood can be caused by periodontal inflammation and that this predisposes to an exacerbated PMN response to distant inflammatory conditions. In other words, PD primes the immune system and thus intensifies the overall innate immune response, thus exacerbating general inflammatory disease (41) including COVID-19.

Similarly, in an experimental study of the respiratory mucosa before, during, and after respiratory syncytial virus (RSV) infection in humans, participants who succumbed to infection had more activated PMNs in their airways before exposure to the virus than those who staved off infection. After viral exposure, a reduction in antiviral response in the neutrophilic mucosal environment was observed, more specifically suppression of interleukin-17 (IL-17), followed by disease onset. The authors hypothesized that primed PMNs, typically associated with immune response to previous bacterial infections might increase the individual's susceptibility to symptomatic viral infections and potentially even COVID-19 (72). A strong hyperactivation phenotype in peripheral PMNs has already been directly associated with severe cases of COVID-19, including increased phagocytosis, degranulation and chemotaxis, and increased expression of genes involved in pro-inflammatory cytokine release. Within these severe cases, the emergence of an immature PMN population, characteristic of emergency myelopoiesis, was the main difference observed between the immune responses in fatal and non-fatal cases of COVID-19 (73). NET formation in tissue injury and thrombotic complications are additional pathogenic mechanisms whereby circulating PMNs can lead to more severe COVID-19 (6, 28, 31, 32, 34). This highlights another potential mechanisms linking PD as a potential comorbidity in COVID-19 cases: the pro-thrombotic state as a result of PD-associated haemodynamic, endothelial, and inflammatory triggers that may lead to an abnormality in the coagulation or fibrinolysis system (74).

From Bench to Chairside With a Bridge to the Bedside—Host Modulation Therapy (HMT)

We suggest that the SARS-CoV-2 pandemic has highlighted the need for a greater understanding of the role of PMNs in combating viral infections, as COVID-19-related PMN-mediated inflammation in the lungs can be life-threatening (6). While supporting the potential role of PD-related innate immune response in systemic inflammatory conditions, our team proposes the use of host modulation therapy (HMT), as designed initially for treatment of PD for treatment of systemic inflammatory diseases that interact with PD (41), as well as in the prevention and treatment of ARDS, given the similarity of the underlying inflammatory mechanisms. Hereunder we describe the tenets of HMT.

HMT has been established in periodontology as a successful therapeutic approach for management of chronic periodontal and refractory periodontal diseases, all of which are PMN-mediated disorders. This therapy, pioneered by our group (notably Dr. Golub's group), was a paradigm shift in periodontal therapy for using tetracycline-based molecules and *not* reliant on their antimicrobial properties, to downregulate the activities of PMN-derived MMPs, suppression of inflammatory cytokines, and for quenching of ROS (75–78). In relation to periodontitis, work has focused on the use of subantimicrobial dose doxycycline (Periostat®), but higher dose use over a short term is certainly feasible when treating extreme cases of inflammation as in the acute stage of COVID-19. This has also led to the development of effective treatment for rosacea using sub-antimicrobial-dose doxycycline slow release form (Oracea®/Aprillon®) (79) More recently, this concept was boosted by Serhan's studies on pro-resolving lipid mediators in which he argues that a failure in resolution of inflammation rather than its hyperactivation leads to chronic inflammation (80, 81). Pre-clinical studies have shown that treatment with lipid mediators after experimentally induced periodontitis in animals was associated with bone loss prevention, regeneration of periodontal tissues and bacterial shifts in the subgingival microbiota (82–84). In humans, differences in pro-resolving lipid mediator profiles were observed between periodontally healthy and periodontitis participants and thus associated with the state of periodontal inflammation (85). These targets are important factors contributing to the breakdown of periodontal tissues, but also to other tissues being attacked by dysregulated inflammation-mediated destruction observed in periodontitis and ARDS (including stimulation of the vasculitides). Along similar lines, our group has shown that the flavonoids, resveratrol, and curcumin, downregulate ROS-mediated oxidative stress, inhibit ROS production/activity, and inhibit pro-inflammatory cytokine formation in animal model studies of periodontitis, which should protect tissues under inflammatory attack (86, 87). In animals subjected to cigarette smoke inhalation, we showed that resveratrol effectively blocks the harmful effects of aryl hydrocarbons found in cigarette smoke and the environment, which could be very important inasmuch as smoking represents a significant comorbidity for COVID-19 and is also a major risk factor for periodontitis and favor healing (88, 89). There is also evidence animal model data showing that by using HMT, the development of ARDS can be blocked (90, 91).

We suggest that the effectiveness of HMT could be independent of the type of infectious virus because it targets the host's cellular mechanisms that propagate ARDS (and of course PD) and not only the virus itself. Therefore, we suggest that mutations of the virus should be equally less material insofar as the putative effectiveness of HMT in prevention and treatment of ARDS. Recent evidence showed that tetracyclines have *in vitro* activity in post-entry stages of the infection with SARS-CoV-2 (92) and resveratrol blocks replication of coronavirus and other respiratory viruses (93, 94). We propose that the use of drug/nutraceutical HMT described initially for periodontitis could reduce morbidity, mortality, and possibly longer-term sequelae of COVID-19.

The concept of HMT emerged for the treatment of periodontitis almost 40 years ago, after the identification of host-response mechanisms as the mediators of the destruction

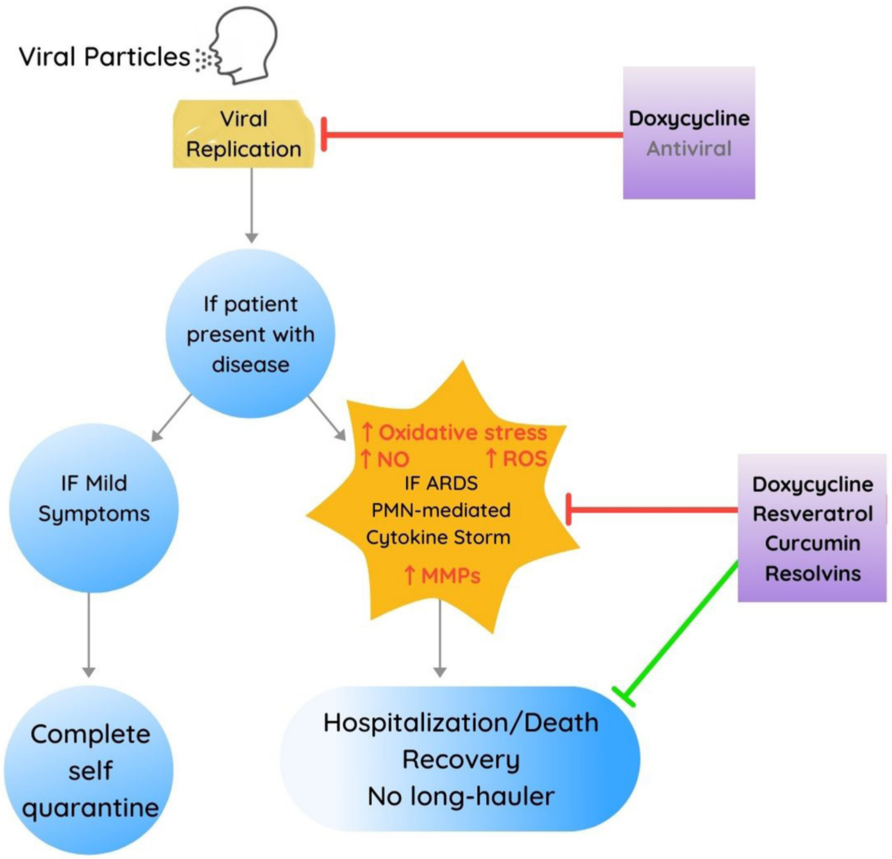

FIGURE 2 | Proposed multidrug treatment approach, developed in part from therapeutic targets identified for management of periodontal diseases for each phase of Covid-19 presenting both inhibitory (in red) and stimulating or improvement-associated effects (in green). Note also that the use of antivirals (other than doxycycline) is depicted in a slightly faded font to delineate that these other therapeutics were not developed from or based on periodontal research investigations.

of the collagen-rich periodontal tissues and subsequent experiments with systemic drugs that inhibited collagen- and bone-destructive enzymes. Around the same time HMT was shown to be effective for downregulation of pathologically elevated levels of inflammation in systemic conditions such as arthritis, cancer, lung and cardiovascular diseases and rosacea (95). Based on this concept, we have presented evidence, described initially in the periodontal research literature, about the protective properties of a new approach to therapy, HMT, that fits precisely the treatment needs of patients with COVID-19/SARS-CoV-2 infection. And, unlike other medications being investigated for the treatment of COVID-19-mediated lung disease there are virtually no concerns about potential toxicity.

The rationale for this proposed treatment approach is based on the use of some or all the compounds identified above to inhibit the cytokine storm/ARDS, including PMN-mediated hyperinflammatory responses and tissue destruction and including the development of thromboembolic disorders. This approach should reduce hospitalization, ICU admissions, and death associated with COVID-19 markedly as suggested in **Figure 2**.

CONCLUSION

We suggest that we've demonstrated how research focused initially on oral inflammatory diseases has illuminated therapeutic targets that can be attacked by relatively simple and safe compounds, thereby reducing hospitalization, morbidity and mortality associated with COVID-19.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HT, LG, MGo, and MGl contributed to conception and design of the study. NF, LG, HT, and MGl, contributed to the experimental analyses and performance. EC and HT wrote the first draft of the manuscript while all others wrote or edited sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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frontiers in Dental Medicine

PERSPECTIVE
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A Perspective: Integrating Dental and Medical Research Improves Overall Health

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The past decade has seen marked increases in research findings identifying oral-systemic links. Yet, much of dental research remains poorly integrated with mainstream biomedical research. The historic separation of dentistry from medicine has led to siloed approaches in education, research and practice, ultimately depriving patients, providers, and policy makers of findings that could benefit overall health and well-being. These omissions amount to lost opportunities for risk assessment, diagnosis, early intervention and prevention of disease, increasing cost and contributing to a fragmented and inefficient healthcare delivery system. This perspective provides examples where fostering interprofessional research collaborations has advanced scientific understanding and yielded clinical benefits. In contrast are examples where failure to include dental research findings has limited progress and led to adverse health outcomes. The impetus to overcome the dental-medical research divide gains further urgency today in light of the coronavirus pandemic where contributions that dental research can make to understanding the pathophysiology of the SARS-CoV-2 virus and in diagnosing and preventing infection are described. Eliminating the research divide will require collaborative and trans-disciplinary research to ensure incorporation of dental research findings in broad areas of biomedical research. Enhanced communication, including interoperable dental/medical electronic health records and educational efforts will be needed so that the public, health care providers, researchers, professional schools, organizations, and policymakers can fully utilize oral health scientific information to meet the overall health needs of the public.

Keywords: medical-dental integration, oral-systemic research, clinical trials, interoperable electronic health records, microbiome

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INTRODUCTION

Biomedical research grew dramatically after World War II with the generation of new antibiotics, the unraveling of the genetic code, the birth of molecular biology, and the first successful organ transplants, among major milestones. The National Institutes of Health (NIH) expanded accordingly, but in ways reflecting traditional clinical specialties that divide the body into disparate organs and systems, a division that perpetuates the sharp divide between dentistry and medicine.

But the very discoveries and technologies that are rapidly transforming our understanding of life and life processes demand we put the body back together again (**Table 1**). For example, we know that a gene associated with a particular organ can manifest in other organs, or turn other genes on or off, and we know that a drug targeted to a particular pathogen can wreak havoc elsewhere in the body. But what is also now clear is that the body is even more extensively and deeply connected than had been thought. The coronavirus pandemic is a case in point. A member of a family of viruses typically associated with respiratory symptoms, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19), can result in fatigue, loss of smell and taste, gastrointestinal problems, cognitive deficits, depression, life-threatening pneumonia, neurological disorders and symptoms that can persist in some individuals long after initial infection (15–18). Yet the mouth and oral health considerations continue to be treated as a class by themselves, separate from the rest of the body, ignored and omitted from research studies large and small. This gap results in missed opportunities to reveal important oral-systemic interactions or explain how other parts of the body regulate functions in the mouth. This perspective provides examples of the consequences resulting from the lack of integration and the benefits gained when oral-systemic integration is in place. This is a perspective, not a review, but we provide additional references to a few scientific papers and reviews within the last 6 years, which expand on the examples provided here (19–27).

THE FAILURE TO CONNECT

Not Really All Parts of Us, but Getting Close

The goal of this innovative Precision Medicine initiative, launched by the NIH in 2015, named *All of Us*, is to build one of the most diverse health databases in history by inviting one million Americans, 18 and older, of all backgrounds, to voluntarily submit biologic samples and personal information to enable investigators to learn how biology, lifestyle and environment affect health (28). Participants are asked to answer surveys; they can submit data from wearable measuring devices and allow researchers access to their electronic health records (29). Early on, to get the program going, they were not able to include dental questions in the survey. More recently, two dental questions were added i.e., have you seen a dentist in the last 12 months and do you have access to dental care, with plans to include a more comprehensive oral-dental history, plus collecting salivary samples within the coming year, behind schedule due to the pandemic. We are optimistic that oral-dental health data will be included within the context of total health. On another positive note, UK Biobank now includes collecting salivary samples along with an oral health survey (30).

Incompatible EHRs

The goal of integrated oral and overall health data from *All of Us* is exacerbated by the general lack of interoperability between medical and dental electronic health records making it difficult to obtain an individual's inclusive dental and medical history. Exclusion of oral health data can delay diagnoses and treatment by missing characteristic oral signs of particular conditions, syndromes and diseases, with repercussions on overall health over the lifetime. Establishing a fully integrated dental-medical electronic health record must be a priority to ensure research advances provide optimal clinical care and guidance (28, 29). We recognize the current siloed approaches are on both the medical and dental side. Many dental communities have not fully embraced interprofessional models of teaching and clinical practice, favoring the technical aspects of dentistry. We need buy-in from all healthcare teams to be successful in delivering the concepts discussed in this perspective.

Childhood Caries Risk

Failure to include oral health in other large genomic-phenomic studies also limits understanding of oral conditions directly. For example, childhood dental caries remains the number one chronic disease in children, more prevalent than asthma (30). This state of affairs is amplified by health disparities that disproportionately affect poorer groups, minorities and other underserved and vulnerable populations who lack access to care (31). While some progress has been made toward identifying genetic contributions to periodontal disease and caries (2), failure to include oral health research in large-scale genomic-phenomic initiatives of gene-environment interactions impedes mechanistic understanding of caries risk in children.

Oral Health in Aging

Biological aging is considered a normal physiological process known to be influenced by an individual's risk to include, but not limited to, hormonal changes, chronic inflammatory diseases, diet (nutrition/sugar intake/alcohol), and smoking. There is increasing evidence that periodontal disease, as a chronic infection with persistent inflammation locally and systemically, may contribute to unhealthy aging (32–35). The increasing evidence that severity of periodontal disease has a negative effect on telomere length, where decrease in telomere length is a measure of biological aging, highlights the importance of including oral health status as part of determination of one's total health across a life span (36). Another area needing attention relates to salivary flow with aging. Studies have demonstrated that even though there is some decrease in salivation and a change in salivary composition with aging, it is adequate in healthy aging individuals (37, 38). However, the onset of systemic diseases and the addition of many commonly used drugs as well as radiation therapies can irritate oral tissues and directly cause xerostomia, raising the risk of caries. Yet, how many providers recognize these risks or ask their patients if their various therapies or drug regimens have had any effects on their oral/dental tissues? The inclusion of oral health in aging research is critical to better serve older individuals and develop therapies to preserve oral health.

THE NEED FOR DENTAL SCIENTISTS IN CLINICAL TRIALS

The knowledge dental scientists bring to characteristics of oral tissues can provide valuable clues in diagnosing systemic diseases as well as predicting and elucidating the impact of new therapies

TABLE 1 | Tools and technologies informing clinical practice and oral health outcomes.

Artificial Intelligence and Machine Learning: New technologies are being applied to craniofacial disease detection, including advanced imaging and the use of artificial intelligence/machine learning. The exciting area of facial recognition has exploded with the common use of personal smart phones, security cameras, and social media. These technologies are being applied for identifying rare and undiagnosed diseases that have a craniofacial phenotype. The ability to link a 3D graphic phenotype to a mutation variant is only possible with ongoing research in quantitative imaging modalities and large-scale application to genetic data, such as the efforts of Face2Gene[1]. Importantly, and with growing attention, is the need to establish careful guidelines for appropriate use of A.I. and machine learning, where improvements made in patient care do not compromise an individual's privacy (1, 2). Further, dental educators need to incorporate information in their curricula to ensure graduates are prepared to execute these and other emerging tools and technologies.

Imaging Advancements: The increasing use of cone-beam computed tomography, particularly by oral and maxillofacial surgeons and orthodontists, for evaluation of craniofacial growth, skeletal malocclusions and placement of dental implants has added an important tool to the expanding technology for research. The development of 3D craniofacial landmarks (3), deep learning segmentation and malocclusion classification methods (4–6) and application of geometric morphometric analysis to 3D skeletal imaging in disease cohorts such as cleft lip/palate (7) has opened the possibility of understanding developmental biological processes in patients and overcoming limitations of animal models that often do not reflect the human disease. The addition of 3D oral scans can improve the quantification of oral anomalies typically associated with many systemic diseases (8, 9). Very often, oral manifestations may be the earliest signs of disease or genetic anomaly and the easiest to quantify, biopsy or collect as biospecimens for detailed analysis.

Regenerative Medicine: New scaffold designs, improved imaging and technologies to track genes, cells and proteins during development and regeneration, and use of organoids as 3D miniatured models derived from stem cells are among major innovations that are advancing regenerative medicine in the quest to replace tissues/organs lost to trauma or disease. Some ongoing activities in this space include the National Academy of Medicine Regenerative Medicine Forum started in 2016[2] and Armed Forces Institute of Regenerative Medicine (AFIRM), a multi-institutional, interdisciplinary network[3], with opportunities for funding projects focused on wounded servicemen and women, e.g., repair of muscles, nerves and body parts (10–13).

Electronic Health Records: As the value of Precision Medicine/Individualized Healthcare has become more apparent the need for interoperable electronic health records has emerged as a key element needed for establishing accurate databases linking genomics data with other data about an individual, e.g., health history, race/ethnicity, demographics. This has resulted in significant improvements in EHR, however there have been limited attempts in the dental arena to have electronic dental records interoperable and even less related to developing platforms so that medical-dental records are interoperable. Importantly, initiatives to date indicate that interoperable electronic records result in increased preventive care visits and decreased costs associated with medical-dental diseases.

Genetics/Genomics/Proteomics: The development of sophisticated tools and technologies has resulted in an exponential growth in studies focused on identifying genes, proteins, cells, factors (host-immune responses) and microbes and in new knowledge toward understanding health and disease over a person's life span. The ability to use systematic genetic mapping in families and communities has assisted researchers in identifying genetic variants and thus, improve diagnosis and treatment, including new drugs and some gene therapy (14). Fortunately, as presented in this perspective, oral-dental researchers, in collaborations across disciplines, have taken advantage of these tools and technologies to include: improved/earlier diagnosis of certain genetic disorders, better understanding of microbial-host interactions, locally and systemically and development of salivary diagnostics for COVID-19.

[1] *https://www.face2gene.com/clinic-deep-phenotypingof-genetic-disorder-dysmorphic-features/*
[2] *http://www.nationalacademies.org/hmd/Activities/Research/RegenerativeMedicine.aspx*
[3] *https://www.afirm.mil/*

on the oral cavity. Recent examples of clinical trials conducted without input from dental scientists illustrate the delays in diagnosis and potential harms in patient outcomes.

Dental Phenotypes

Individuals with genetic mutations often exhibit specific dental phenotypes (observable traits), which may be seen on oral examination. For example, individuals with hypophosphatasia (HPP), caused by mutations in the alkaline phosphatase gene, often have defects in the formation of tooth root cementum, dentin and enamel. Yet clinical trials using alkaline phosphatase enzyme replacement therapy for HPP failed to include an examination of participants' teeth (39). The effects of such therapies on the teeth are just now being analyzed. Several other disorders where oral tissues are now included in the research study have resulted in recognition of substantial oral tissue phenotypes that can lead to more rapid and earlier diagnosis and treatment (8, 40–42).

New Immuno-Cancer Treatments

Other examples of dental contributions to clinical studies and trials are related to broader effects of new therapies on oral tissues. For example, many drugs may affect salivary gland function, alter tooth color, affect mucosal function or cause oral lesions—at times so severe that patients must discontinue therapy. As a result, new drug treatments for a variety of serious disorders require the involvement of oral health scientists as key members of the research team at the outset. The development of immune checkpoint inhibitors (ICI) to treat cancers has identified the concerning side effect of profound xerostomia after a few weeks or months of treatment (43). While this has encouraged research on how ICI disrupts salivary gland function, it underscores why inclusion of dentist scientists is critical.

Osteonecrosis of the Jaw

Without dental-medical integration the oral side effects of new therapies can take years to fathom. This was the case for medication-related osteonecrosis of the jaw (44). It has now been established that anti-resorptive drugs used not only to treat osteoporosis but also some cancers, can result in severe jaw problems as well as other anomalies of bone metabolism. The research confirming cause and effect was the result of intense cross collaboration between dental and non-dental researchers including animal studies, case reports and patient records. It is currently part of clinical endocrinology guidelines to consult a dentist when initiating these therapies, especially cancer therapies (45). Similar best clinical practices include obtaining early dental consultation prior to the initiation of head and neck radiation therapy (for oral cancers). This integration of dental with medical care has lowered the risk of the devastating side effect of osteoradionecrosis of the jaw and improved the quality of life for patients undergoing radiation therapy.

Hospital Acquired Pneumonia

Hospital acquired pneumonia (HAP) accounts for 25 percent of all hospital-acquired infections (46) and presents a serious risk for patients hospitalized with COVID-19 (47). Studies conducted in a veterans' hospital setting have supplied evidence that non-ventilator-associated HAP was reduced significantly by providing standard oral health care (48), improving patient outcomes while lowering costs of care. This study has been expanded to include eight VA hospitals with plans for national VA deployment. While substantial evidence exists that oral health care is a modifiable risk factor for HAP and other infectious diseases, it has not been adopted universally (49, 50).

Human Papillomavirus Virus (HPV) Vaccine

This is an example where dental patient evaluation was omitted in clinical trials to evaluate the effectiveness of HPV vaccines. HPV vaccines are now recognized for their potential to prevent HPV-related oropharyngeal cancers, which have risen dramatically in recent years, especially in younger-aged groups (51). It took collaborative research efforts to reveal that this sexually transmitted disease can cause devastating manifestation in the oral cavity, and to increase research support to better understand the biologic implications of HPV +/− oral cancers. Since research has shown that some individuals are more likely to seek dental care (including for cosmetic reasons) compared with medical care, dental professionals need appropriate training so they can counsel their patients appropriately and even administer HPV and other vaccines, including COVID-19 (52). In fact, several states have approved providing vaccines in the dental setting, a view supported by the American Dental Association (53, 54).

GAINS WHEN DENTAL SCIENTISTS ARE PART OF THE TEAM

Several areas of research are benefiting from new broad-based initiatives, cross-collaborations and multidisciplinary teamwork, specifically: microbiology, salivary studies, and craniofacial anomalies.

The Human Microbiome

From the initial discoveries that dental caries and periodontal disease were associated with specific bacterial species, oral health scientists have analyzed the complex microbial communities lining oral and dental surfaces in what were called biofilms. These complex microbial communities continue to be explored for relationships with many other diseases, including malignancies (55–57). With availability of newer tools and technologies researchers have expanded their horizons beyond mapping the human genome with its 20,000 genes to explore the much larger domain of the human microbiome, including previously uncultivable microbes. The Human Microbiome Project (HMP) was launched by NIH in 2007 (58) to map the human microbiome, choosing five sites: mouth, nasal, skin, gastrointestinal and urogenital tract. It is a stunning example of the information that can be gleaned when the dental domain is included in transdisciplinary research projects (59). One of the HMP outcomes has been a deeper awareness that microbes have a major influence on the host in health and disease, a story which is just beginning to unfold (60–68). As far as the mouth is concerned, it is a domain where oral scientists have been pioneers (69).

The *immune-microbiome complex* has become an area of intense investigation comparing the effects of a healthy vs. a diseased microbiome on the host-immune response. Intriguingly, Klebsiella can induce an inflammatory response in the gut, but not in the oral mucosa (60), while Fusobacterium nucleatum, an oral bacterium associated with severe periodontal disease, is linked to colon cancer (70). Porphyromonas gingivalis, a keystone pathogen in chronic periodontal disease, has been identified in amyloid plaques of individuals with Alzheimer's disease (71, 72).

The Periodontitis-Diabetes Story

The observation that patients with uncontrolled diabetes often have severe periodontitis inspired yet another major success story of the payoff when dental and non-dental researchers work together. Initial observations among the Pima tribe (73, 74) led to a focus on host-immune-microbial interactions and the key observation that in cases of uncontrolled diabetes, oral tissues, along with other tissues in the body, exhibit a hyperinflammatory response to local insults, such as infection or trauma. Addressing the hyperinflammatory issues early proved to be effective in managing, and in some cases preventing, the periodontal disease consequences of diabetes. Provision of non-surgical treatment has been associated with reductions in metabolic markers of dysglycemia, primarily glycated hemoglobin (75–77). Further, analyses of insurance databases have suggested that the provision of non-surgical periodontal treatment to persons with diabetes is associated with improved health outcomes, including reduced utilization and costs (78–80). So persuasive have been the findings from these studies that a number of U.S. insurance companies now offer additional dental care for their diabetic clients as a way to forestall more serious complications and hospitalizations. The establishment of the diabetes-periodontitis connection has important implications for addressing health disparities. Diabetes and obesity (a risk factor for diabetes) disproportionately occur in poor and minority groups. If they lack access to dental care, the impact of the two diseases will be more severe.

Salivary Diagnostics

The attractiveness of using saliva, known to contain, among other things, viral pathogens, shed cellular material (including genetic), and circulating antibodies, coupled with ease of sampling, has resulted in research targeted at detecting specific diseases or disorders and some success in the commercial development of diagnostic kits for this purpose. However, as saliva is a diluted exudate compared with blood, the amount of a given biomarker in saliva may be inadequate to detect with current tools and

TABLE 2 | Approaches toward achieving integration of oral health within the context of total health.

Collaborative and trans-disciplinary efforts are needed to integrate dental science research into broad areas of biomedical research in both the public and private sectors, where its omission has limited progress and in some cases led to adverse health outcomes (97).
Implementation science programs and learning health care systems should be deployed to ensure that the biomedical knowledge generated by an integrated research enterprise is translated into clinical practice, public policies, and consumer-directed applications, including programs to improve health literacy (19, 98). Educational efforts, along with policies that ensure equitable access to oral health care for all communities, locally, nationally and globally, can help eliminate the health disparities that persist in our nation.
The development of interoperable electronic health records (EHRs) that collectively track medical and dental health histories for patients and providers is essential to further understanding of an individual's health profile over the life span, noting risk factors, acute and chronic illnesses, and other critical information (28).
Advance Communications/Networking across disciplines: Several communities over the last few years have developed initiatives highlighting the importance of attending to all aspects of the body, including the oral region, in research, clinical care, education and policy development, in order to improve total health for all. Yet interactions and the exchange of ideas among the various constituencies are often lacking and consequently possibilities for advancing transdisciplinary approaches to health improvement are missed. Perhaps an "Oral-Systemic Health Hub" is needed where events and publications of importance to the larger community are posted regularly. For example, the Santa Fe Group has organized a *Continuum on the Benefits of Integrating Oral Health into Overall Health* [a series of webinars, a Salon and other resources on this topic (www.santafegroup.org/events)], and other groups are working on initiatives with a similar focus. And at the time of submission of this *Perspective* a Resource Library for the Integration of Primary Care and Oral Health was announced: https://resourcelibrary.hsdm.harvard.edu/. This site has already been populated with many publications and events. These and similar efforts reflect the mounting interest in integration and transdisciplinary approaches to health improvement which it is hoped *Frontiers in Dental Medicine* and *Frontiers in Oral Health* will continue to seed.

technologies Advanced technologies may improve that situation and indeed the advent of the coronavirus pandemic has already led to the development of safe and effective salivary test kits to detect SARS-CoV-2 in an individual (81). Symptomatic and asymptomatic spread of this virus is likely from saliva droplets and respiratory fluids (82, 83). Additionally, saliva may serve as a better source for detection of oral conditions such as oral pharyngeal HPV cancer than currently used blood tests and may be an ideal source for a "liquid biopsy" for point of care application (84–87).

Craniofacial Conditions

One of the best examples of comprehensive, collaborative care that includes dental specialists in a multidisciplinary setting is the craniofacial anomalies team. The American Cleft Palate-Craniofacial Association (ACPA) recognizes craniofacial teams who meet standards based on parameters of care that have been shown through research to provide optimal care for children with cleft lip and palate or other craniofacial anomalies. Dental specialists are integral to these teams with a direct impact on improved quality and outcomes of treatment. Several areas of research have advanced the care of children with congenital craniofacial anomalies and the understanding of disease processes leading to potential novel therapeutics for ectodermal dysplasia (88–90), promising intrauterine therapies to rescue cleft palate in mouse models (91–95), and better understanding of post-natal craniofacial development in patients with cleft lip and palate (7).

THE PANDEMIC AND DENTAL RESEARCH

While the dental community has long implemented safe practices of infection control and personalized protective equipment (PPE) resulting in very low infection rates among dentists during the pandemic (96), the potential for engaging the dental community in enhanced testing and sampling technologies is huge. Through the simple act of touching a dental mirror to the inside cheek of a patient, a dentist can be the "point of contact" for sampling saliva as a diagnostic fluid. Additionally, biosensors incorporated in a dental mirror or toothbrush can record vital signs, including temperature fluctuations and oxygen saturation, which could detect the early presence of disease in a community. Realtime data collection from such smart tools can protect the US population by predicting early hotspots of disease, as noted by Kinsa smart thermometers during the early phase of the SARS-CoV-2 pandemic[1].

CONCLUSIONS: A CALL TO ACTION FOR RESEARCHERS, EDUCATORS AND CLINICIANS

The goal of this perspective is to increase awareness of these issues and to activate researchers, healthcare providers, economists, policy drivers, advocacy groups and the communities we serve, locally and globally, to advance collaborations across all disciplines/communities. We cannot afford to ignore data from the dental, oral and craniofacial part of the body. A few suggested action items are presented in **Table 2**.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

[1]https://www.nytimes.com/2020/03/18/health/coronavirus-fever-thermometers.html

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Diabetes and Oral Health: Summary of Current Scientific Evidence for Why Transdisciplinary Collaboration Is Needed

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This Perspective provides a brief summary of the scientific evidence for the often two-way links between hyperglycemia, including manifest diabetes mellitus (DM), and oral health. It delivers in a nutshell examples of current scientific evidence for the following oral manifestations of hyperglycemia, along with any available evidence for effect in the opposite direction: periodontal diseases, caries/periapical periodontitis, tooth loss, peri-implantitis, dry mouth (xerostomia/hyposalivation), dysbiosis in the oral microbiome, candidiasis, taste disturbances, burning mouth syndrome, cancer, traumatic ulcers, infections of oral wounds, delayed wound healing, melanin pigmentation, fissured tongue, benign migratory glossitis (geographic tongue), temporomandibular disorders, and osteonecrosis of the jaw. Evidence for effects on quality of life will also be reported. This condensed overview delivers the rationale and sets the stage for the urgent need for delivery of oral and general health care in patient-centered transdisciplinary collaboration for early detection and management of both hyperglycemia and oral diseases to improve quality of life.

Keywords: diabetes mellitus, early diagnosis, health care costs, interdisciplinary communication, interprofessional relations, periodontal diseases, prevention and control, referral and consultation

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INTRODUCTION

Regrettably, dentistry was separated from general health care and became an independent profession (1), leaving little education and awareness regarding oral health and its links to general health among the other health professions (2–10).

The most prevalent chronic diseases share the same "common risk factors" (11–13) (**Figure 1**) and hence often occur in the same patients, regardless of whether causal links and not merely associations exist. Nonetheless, rapidly emerging scientific evidence demonstrates that oral diseases and hyperglycemia (elevated blood glucose concentration), including manifest diabetes mellitus (DM), independently and mutually affect each other.

The term "transdisciplinary" is used to include practitioners of all health care disciplines, such as physicians, assistants of the physician, nurses, nurse practitioners, midwives, dietitians, DM educators, speech therapists, social workers, etc., in contrast to "interprofessional" that implicitly accepts the siloed approach regarding dentistry and general health care as separate professions.

This research summarizes, in a nutshell, the current evidence for links between oral diseases and DM to support the need for transdisciplinary collaboration.

HYPERGLYCEMIA/DM AND ORAL HEALTH MUTUALLY AFFECT EACH OTHER

While type 1 DM (T1DM) is due to no or insufficient insulin production affecting about 5% of patients with DM, type 2 DM (T2DM) is a syndrome characterized by elevated blood glucose levels due to insufficient insulin production, insufficient insulin uptake, or both (15–17). About 463 million (9.3%) adults suffer from DM, with 700 million (10.9%) expected by the year 2045 (18, 19). An additional 374 million people have prediabetes (preDM) and are at risk of developing T2DM (18).

Systemic hyperglycemia causes complications such as retinopathy; nephropathy; neuropathy; heart, peripheral arterial, and cerebrovascular disease; obesity, cataracts; erectile dysfunction; and non-alcoholic fatty liver disease (20). Regardless of DM type, it is the hyperglycemia, not the diagnosis of DM *per se*, that leads to several oral complications (21) and oral health-related decreased quality of life (QoL) (22).

These oral manifestations are described, followed by any effects in the opposite direction.

For succinct brevity, DM is used for any type of diabetes or hyperglycemia; and the comparison group is non-traditionally omitted. For example, in the sentence "*People with DM have greater xxxx*," the comparison "*than people without DM*" is implicit, but not shown.

Periodontal Diseases

Periodontal diseases affect up to 90% of adults globally, with the reversible form, gingivitis, affecting almost everybody (23). In contrast, periodontitis is chronic, irreversible destruction of soft and hard tissues around the teeth that results from an interplay between polymicrobial dysbiosis in the plaque microbiome in the gingival sulcus and the especially susceptible host (24, 25). Periodontitis affects 42.2% of US dentate adults (26), likely varies globally, and is the 12th of 291 most prevalent diseases worldwide (27), with "severe" periodontitis being the sixth most prevalent disease (28), affecting 11.2% of adults (28).

Periodontitis and hyperglycemia share the same risk factors (29, 30) and hence often occur in the same individuals with compromised immune systems or exhibiting hyperinflammatory responses; and they additionally adversely affect each other.

A much greater proportion of people with DM suffer from periodontitis (31–33), and the severity of periodontitis is much greater, especially in poorly or uncontrolled DM (31, 34, 35). Citing clinical studies from Denmark (36), Australia (37), Finland (38), Argentina (39), and the US (40, 41), including among the Pima Indians in Arizona (42–46), periodontitis was declared the sixth complication of DM in 1993 (47), but with negligible effect on the medical and dental communities.

In the opposite direction, people with periodontitis are much more likely to have T2DM (33, 48). Periodontitis, *via* bacteremia (49, 50) and inflammatory responses of which hyperglycemia is a normal part (**Figure 1**), is a risk factor for DM, that is, incident T2DM, gestational DM, poorer glycemic control in existing DM, and more severe DM complications (51, 52). Furthermore, periodontitis is increasingly regarded as an independent risk factor for the macro-vascular DM complications cardiovascular disease (CVD) (53–58) and ischemic stroke (54, 56), and is associated with the microvascular DM complications: neuropathy (54, 59), nephropathy (54, 60–62), and retinopathy (54, 60).

Cognitive Impairment in DM

Alzheimer's disease has been named "type 3 DM" (63) as a DM complication (64) partly due to glucose hypometabolism causing cognitive decline (65). Novel research supports the role of especially *Porphyromonas gingivalis (Pg)*, a key periodontitis-associated bacterium, in Alzheimer's disease (66–72), with promising experimental treatment with gingipain inhibitors to reduce *Pg* brain colonization and neurodegeneration reported (73).

COVID-19

With DM being a risk factor for COVID-19, oral manifestations of the SARS-CoV-2 virus (74, 75) are reported in DM, such as painful ulcers (76, 77) and necrotizing periodontitis (78).

In COVID-19, a radiographic study found periodontitis to be associated with more intensive unit admissions, increased ventilation needs, and mortality in COVID-19 (79), and gingivitis is also reported (80). This is probably the case also in DM with its weakened immune system. Likely, periodontal pockets (81, 82), gingival crevicular fluid (83), and saliva acting as reservoirs for SARS-CoV-2 virus (81, 84–86) may even facilitate COVID-19 development (87), persistence (88), and mortality especially in people with DM (89).

Caries/Periapical Periodontitis

Untreated caries in permanent teeth is the most prevalent condition of the world affecting 2.4+ billion people (90). The evidence for links to DM is mixed, although adolescents with DM have 2- and 3-fold greater numbers of filled teeth and teeth with untreated caries, respectively (91). Patients with DM receiving hemodialysis have more caries (92); and periapical infections and their abscesses seem to be more prevalent in DM (93, 94).

Tooth Loss

Worldwide, people with DM have lost many more teeth (36, 37, 95–101), [about twice the magnitude (102)], especially if uncontrolled (103), and at an earlier age (96).

Tooth loss is a risk factor for hyperglycemia that is not usually mentioned as such, even though this has possibly the greatest immediate importance for DM management. Having loose teeth (due to periodontitis), sensitive teeth (due to deep caries lesions), few teeth left (104), or removable dentures will automatically cause problems with mastication, resulting in people not being able to eat crisp foods that need biting off or proper mastication. That is, such people are simply unable to follow the recommendations for a proper diet intended for controlling their DM by consuming appropriate

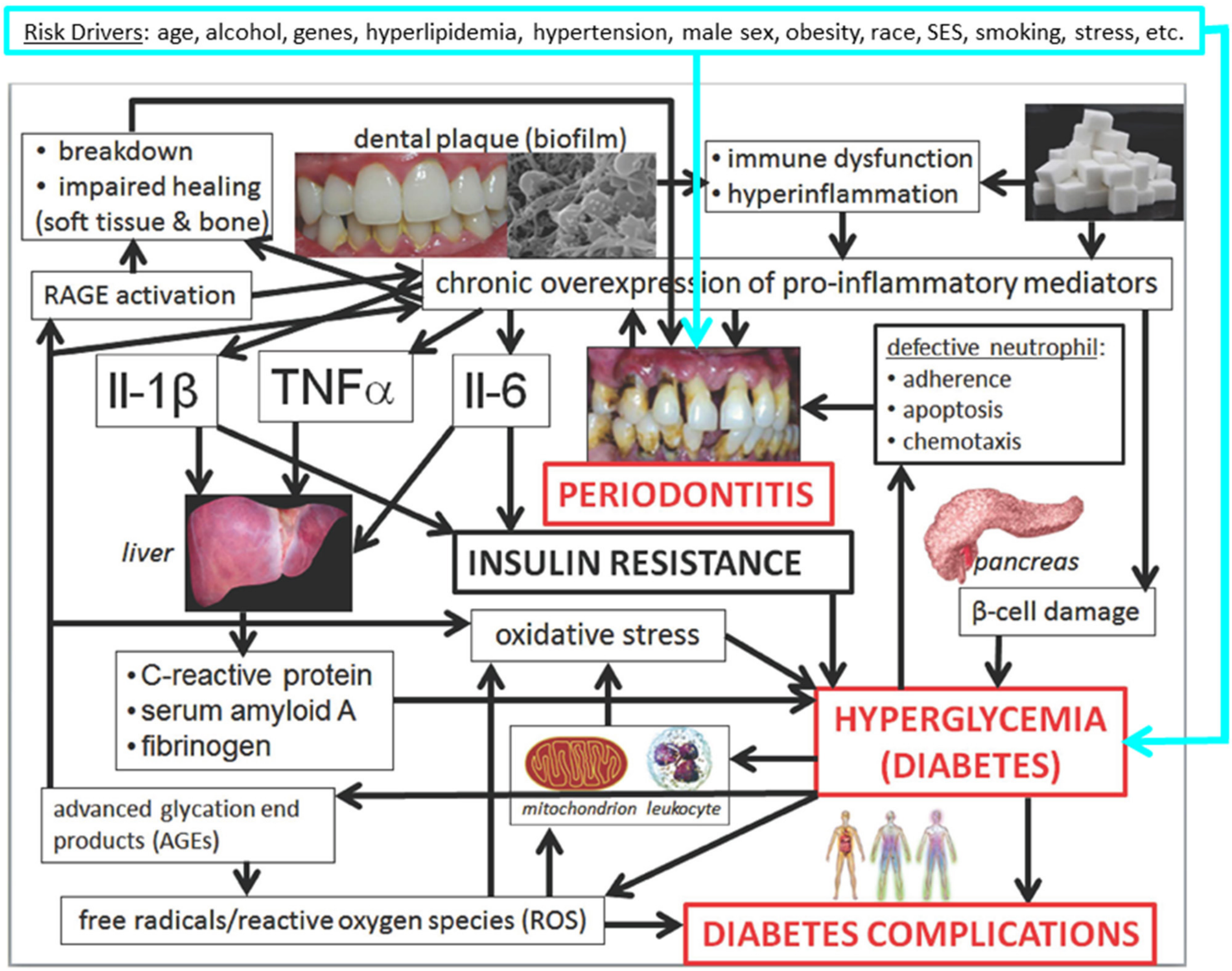

FIGURE 1 | Mechanisms underlying the associations between periodontitis and hyperglycemia/diabetes and its complications: conceptual model (14). Slightly modified Figure 31.10 in Borgnakke et al. (14). Please see the full description and accreditations at https://www.ncbi.nlm.nih.gov/books/NBK567985/.

amounts and kinds of healthy nutrients (105–107). In contrast, they resort to soft, processed food items with high Glycemic Index scores (108) and high Dietary Inflammatory Index scores (105, 106), typically laden with fat, sugar, and salt but deficient in fibers and vitamins (109), as opposed to fresh vegetables and fruit and whole-grain products. Alone for this reason, sincere efforts to prevent tooth loss should be invested in transdisciplinary DM management including dietitians (109).

Missing teeth are also associated with DM complications, such as myocardial infarction (110, 111) and retinopathy (36, 112); and lack of proper mastication negatively impacts cognitive function (113, 114).

Peri-Implantitis

Even though dental implants can osseointegrate, albeit delayed (115), and survive in patients with poorly controlled DM (116), hyperglycemia is a risk factor for peri-implantitis (breakdown of peri-implant soft and hard tissues) that is independent of smoking (117–119).

Dry Mouth

Individuals with DM often suffer from dry mouth, meaning xerostomia (subjective feeling of mouth dryness) or hyposalivation (decreased salivary production), decreasing QoL. Patients with DM often suffer from bad breath (halitosis), foul taste, and multimorbidity with polypharmacy (22, 32, 120). All major groups of pharmaceuticals can cause mouth dryness and various periodontal complications (121). Hyposalivation also majorly impacts the oral microbiome composition (122).

Hyposalivation can lead to trouble keeping removable dentures in place, mastication, swallowing (dysphagia), and speech (104); and greater incidence of coronal and root caries and periodontitis, ultimately leading to tooth loss.

In transdisciplinary collaboration, physicians can prescribe fewer or less xerogenic medications or change the dosage and frequency. Since both hyposalivation and cancer are more prevalent in DM, they should also ensure proper protection of the (unaffected) salivary glands during radiation therapy in the head and neck region.

Microbiome Dysbiosis

Hyperglycemia causes changes (123) such as in composition (122, 124, 125) and decreased diversity (126, 127) and abundance (126, 128) of certain bacteria in the subgingival microbiome in periodontitis. Moreover, severities of DM and periodontitis are associated (129, 130). DM treatment leads to changes in the salivary microbiome (131).

Oral and gut microbiomes are closely linked (132); even a small number of periodontal bacteria predict change in glucose level in young healthy adults (133). *Pg* alters the gut microbiome and causes metabolic syndrome (134) and preDM (135).

Candidiasis

DM is an independent predictor of oral candidiasis (136), especially in hyposalivation (137), as DM favors the acidogenic bacteria that in turn promote the development of caries and candidiasis. *Candida albicans,* a commensal yeast in the oral microbiome causing candidiasis, can bind to the oral mucosa and, hence, contribute to the cumulative burden of inflammation, directly or *via* denture stomatitis caused by unclean dentures (138). Over 900 different species of microbes reside in biofilm adhering to dentures (139) and are an important source of sepsis that is largely unnoticed (138).

Taste Disturbances (Dysgeusia, Ageusia, and Hypogeusia)

Due to hyposalivation, neuropathy of nerves sensing taste, microangiopathy in taste buds or medications, (120), and taste impairment and disorders occur frequently in DM (59). Altered taste (gustatory changes) could be the first sign of T2DM, a useful fact for all health professionals. Ageusia is also a COVID-19 symptom (140).

Burning Mouth Syndrome

DM can contribute to the complex burning mouth syndrome that likely is caused by neuropathy and other local and systemic factors and, therefore, needs transdisciplinary treatment (32, 120, 141–143).

Cancer

Cancer is associated with inflammation and occurs more frequently in DM (144), including oral cancer that has a 4.3-fold greater risk of developing and a 2.1 times greater risk of mortality in DM than in non-DM (145). Potentially malignant oral mucosal lesions are also associated with DM, such as leukoplakia, erythroplakia, lichen planus and other lichenoid lesions, and actinic cheilitis (145).

Other Oral Mucosal Lesions and Conditions

People with DM have a greater risk of traumatic ulcer, infections of oral wounds, delayed wound healing, melanin pigmentation, fissured tongue, and benign migratory glossitis (geographic tongue), and temporomandibular disorders (21, 32).

Osteonecrosis of the Jaw (ONJ)

DM is an established risk factor for ONJ in general (146–148) and medication-related ONJ (MRONJ) (149–154). Microvascular complications (angiopathy, ischemia, endothelial cell dysfunction) impair blood circulation and hence bone nutrition and quality with reduced remodeling (155). DM also causes increased apoptosis of osteoblasts and osteocytes and changes in immune cell function, promoting inflammation (155).

Quality of Life

DM decreases QoL with a further decrease in oral health-related QoL (OHRQoL) (59, 156–160). Importantly, QoL correlates strongly with OHRQoL (161), so treating oral diseases increases QoL in DM (160, 162, 163).

DENTAL TREATMENT IN DM

Non-surgical periodontal treatment (NSPT) consisting of scaling and root planing (SRP), or "deep cleaning," home oral hygiene instruction, and maintenance follow-up visits can be performed in any dental office by dental hygienists or dentists and improves the periodontal health status also in DM (164, 165). However, advanced cases need treatment by periodontists or other especially skilled clinicians. Adults with DM and periodontitis manage to incorporate new, effective oral hygiene measures into daily life (166); and frequent tooth brushing is negatively associated with incident DM (167).

Glycated Hemoglobin Level

Non-surgical periodontal treatment can lead to a decrease in glycated hemoglobin (HbA1c) level in T2DM after 3 months, which is of clinical significance as it is of the same order of magnitude as adding a second oral antidiabetic medication to metformin (156, 168, 169). Results of meta-analyses upon systematic reviews are displayed in **Table 1**. Greater effect is seen with greater baseline HbA1c levels (186).

Few studies last longer than 3 months. Noteworthy is a definitive 12-months study ($N = 133$) demonstrating that intensive periodontal treatment (including surgery) reduced the crude mean HbA1c level from 8.1 (±1.7)% to 7.8 (±0.2)% (187). Upon adjustment, intensive treatment reduced the mean HbA1c value by 0.6 (95% CI; 0.3–0.9)% more than routine NSPT (187).

Inflammatory Markers

Non-surgical periodontal treatment can lead to decreased levels of inflammatory markers, such as C-reactive protein and leukocyte counts that are risk indicators for CVD (188, 189), and the subgingival periodontal biofilm is disturbed, mitigating periodontitis progression (123).

Full-mouth extraction, the ultimate treatment of terminally periodontally diseased teeth, significantly lowers systemic inflammatory markers (190).

TABLE 1 | Effect of non-surgical periodontal treatment (scaling, root planing, and oral hygiene instruction) (NSPT) on glycated hemoglobin (HbA1c) level in type 2 diabetes (T2DM) 3 and 6 months post-intervention: meta-analyses.

References	# Studies	# RCTs	Pooled # Subjects	Mean HbA1c% Change	95% CI	*P*-value
Janket et al. 2005 (170)	4	1	268	−0.66$	−2.2; +0.9	n.s.
Darré et al. 2008 (171)	9	5	485	−0.46†	−0.82; −0.11	0.01
Simpson et al. 2010 (172) (Cochrane Review)	3	3	244	−0.40	−0.78; −0.01	0.04
Teeuw et al. 2010 (173)	5	3	180	−0.40$	−0.77; −0.04	0.03
Corbella et al. 2013 (174) (3 mos)	15*	15*	678	−0.38	−0.53; −0.23	<0.001
(6 mos)	3	3	235	−0.31	−0.74; 0.11	n.s.
Engebretson and Kocher 2013 (175)	9	9	775	−0.36	−0.54; −0.19	<0.0001
Liew et al. 2013 (+/–antibiotics) (176)	6##	6##	473##	−0.41##	−0.73; −0.09	0.013
(–antibiotics)	2#	2#	270#	−0.64#	−1.06; −0.23	0.002
(+antibiotics)	4#	4#	203#	−0.09#	−0.52; +0.30	n.s.
Sgolastra et al. 2013 (177)	5	5	315	−0.65$	−0.88; −0.43	<0.05
Wang et al. 2014 (178) (+ doxycycline)	3	3	143	−0.24†	−0.62; +0.14	0.217
Li et al. 2015 (179)	9	9	1,082	−0.27	−0.46; −0.07	0.007
Simpson et al. 2015 (3–4 mos)	14	14	1,499	−0.29	−0.48; −0.10	<0.05
(Cochrane Review) (180) (6 mos)	5	5	826	0.02	−0.20; 0.16	n.s.
Teshome et al. 2016 (181) (3 mos)	7	7	940	−0.48	−0.18; −0.78	<0.00001
(study end)	7	7	940	−0.53	−0.24; −0.81	<0.00001
Cao et al. 2019 (182) (3–12 mos)	14	14	649	−0.399	−0.088; −0.79	sig.
Jain et al. 2019 (183)	6	6	812	−0.26%	−0.63; 0.11	0.17
Yap and Pulikkotil (184) (+ doxycycline)	6	6	208	−0.13	−0.41; 0.15	n.s.
Baeza et al. 2020 (185) (3 mos × 6 studies; 6 mos × 3 studies)	9	9	623	−0.56	−0.75; −0.36	<0.00001
Chen et al. 2021 (186) (3 mos) (+/–	19	19	1,660	−0.514$	−0.730; −0.298	=0.000
antibiotics; +/– surgery) (6 mos)	10	10	1,441	−0.548$	−0.859; −0.238	=0.000

*+/−antibiotics, with or without antibiotics; CI, confidence interval; HbA1c, glycated haemoglobin; mos, months posttreatment; n/a, not available; n.s., nonsignificant; RCT, randomized controlled trial; sig., significant. *Including one study with 30 T1DM and one study with 12 T1DM. $Weighted mean difference (WMD). †Standardized mean difference (SMD). #Including one study with 6 mos. follow-up only. ##Including two studies with 6 mos. follow-up only.*

Tooth Loss

Scaling and root planing in patients with T2DM is modeled to significantly decrease tooth loss by 34.1% overall (191) and in microvascular diseases by 20.5% in nephropathy, 17.7% in neuropathy, and 19.2% in retinopathy, respectively (191). Nonetheless, insurance data identify DM as a risk factor for tooth loss during periodontal maintenance (95).

DENTAL TREATMENT REDUCES HEALTHCARE-RELATED COSTS IN DIABETES

Dental care has been shown to reduce overall medical care costs in people with DM. Acknowledging inherent methodologic issues (192), population studies and analyses of claims data, from people with DM simultaneously insured for dental, medical outpatient care, hospitalization, and pharmacy expenses, report savings in medical care costs, hospitalization, and introduction of insulin among insureds with DM from studies in Germany (193), Japan (194, 195), the Netherlands (196), United Kingdom (197), and the US (191). A correlation between periodontitis severity and future increases in medical care costs was found among older Japanese (198).

Adults with DM consistently have fewer regular dental check-ups than their non-DM peers (22, 199–208) with between 25 and 60% having had a dental visit the last year. Nonetheless, patients with DM who do receive dental care experience incremental higher costs for more complex treatment and restoration of missing teeth rather than preventive visits (203).

TRANSDISCIPLINARY CARE

Transdisciplinary Care Initiated in the Medical Setting

Screening for Periodontitis in the Medical Office

Attainment of good oral health deserves the attention of medical care providers as a novel tool in DM management (209, 210). Medical care providers recognize grossly cavitated (carious) teeth and thrush (Candidiasis) and could suspect undiagnosed periodontitis based on evident signs such as having few or loose teeth, bad breath, or swollen and spontaneously bleeding gums.

Several questionnaires for assessing the risk of periodontitis by self-report exist. For example, the U.S. Centers for Disease

Control and Prevention (CDC) jointly with the American Academy of Periodontology (AAP), developed a set of eight easy-to-pose-and-respond-to items that were validated and found to associate with clinically diagnosed periodontitis (211–213). These or similar questions could be included in the medical visit (22, 214). Such screening in medical practice is well-accepted by both patients (206) and medical professionals (206, 215).

Guidelines for Medical Care Providers and Their Patients

Acknowledging the importance of good oral health in DM management, several professional organizations have published guidelines for (a) medical care professionals in DM practice: AAP (156); American Diabetes Association (ADA) (20); International Diabetes Federation (IDF) (**Appendix 1**, available online only) (169); and the European Federation of Periodontology (EFP) (156, 169) (**Appendix 1**); and (b) people with DM or at risk for T2DM in medical practice: AAP (156); ADA (216); IDF (169, 217) (**Appendix 1**), and EFP (156, 169) (**Appendix 1**).

Transdisciplinary Care Initiated in the Dental Setting

Screening for T2DM in the Dental Office

Because about half the people with manifest DM and 90% of those with preDM are unaware thereof (18), the dental setting can be important for T2DM screening and referral (218–220), especially for dental patients who do not see a physician regularly (221). It is crucial to identify T2DM in its early stages during which the chances for reversal or mitigation are greatest (222–225). Periodontitis can serve as an early sign of T2DM (226), just like few teeth and recurrent periapical abscesses (93, 94). Random blood glucose or HbA1c levels can be measured chairside by quick finger-prick blood sample analysis (221, 227–241).

Interestingly, 30–54% of dental patients who denied having DM had T2DM with 1.3–5.8% having manifest T2DM as reported from studies in Denmark (227), Saudi Arabia (228), Spain (229), United Kingdom (230, 231), and the US (232–238), aided by electronic health records (239). Whereas, 7.8% of US minority elders (240), 17.2% of patients with Dutch periodontal, and, respectively, 14.6% (241) and 19.1% (221) of Indians had T2DM.

PreDM was found in 9.9% of unaware dental patients in Sweden (242), 28.7% in the US (235), and 46.6% among patients with Dutch periodontal (243).

Guidelines for Dental Care Providers and Their Patients

Acknowledging the importance of identifying undiagnosed T2DM early in dental patients, several professional organizations have published guidelines for a) dental care professionals in dental practice: AAP (156); EFP (156, 169) (**Appendix 1**); IDF (169) (**Appendix 1**); Indian Society of Periodontology (244); and Research Society for the Study of Diabetes in India (244); and b) people with DM or at risk for DM in dental practice: AAP (156); EFP (156, 169) (**Appendix 1**); and IDF (169) (**Appendix 1**).

Such screening in dental offices is well-accepted by patients (245–247), dentists (246–250) and physicians (251), and their professional organizations (252), and can lead to positive lifestyle changes and decreased HbA1c level (253, 254).

DISCUSSION

Research to promote the understanding of mechanisms underlying reciprocal links between various aspects of oral health and DM is rapidly emerging. However, the current evidence is sufficient to act. The major causes of tooth loss are the two most common oral diseases, namely caries and periodontitis that occur in great proportions of populations globally. These diseases are associated as their respective prevalence in large population studies are not independent of each other (255). Nonetheless, both are largely preventable or treatable/manageable when developed, resulting in the survival of the teeth. Edentulism (having no natural teeth) is decreasing globally, so people keep their teeth at higher ages (28, 256). Furthermore, life expectancy also increases (28, 256); and the prevalence of DM is increasing rapidly all over the world (18). Consequently, increasing numbers of people with DM worldwide are at risk for the oral manifestations described here.

In conclusion, all health care professionals must join forces. However, such transdisciplinary patient-centered collaboration requires paradigm shifts in awareness, attitude, education, and medical and dental practice delivery systems for all health care professionals.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdmed.2021.709831/full#supplementary-material

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Evaluating the Effectiveness of Medical–Dental Integration to Close Preventive and Disease Management Care Gaps

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Background: The integration of medical care into the dental setting has been shown to facilitate the closure of care gaps among patients with unmet needs. However, little is known about whether program effectiveness varies depending on whether the care gap is related to preventive care or disease management.

Materials and Methods: We used a matched cohort study design to compare closure of care gaps between patients aged 65+ who received care at a Kaiser Permanente Northwest (KPNW) Medical–Dental Integration (MDI) clinic or a non-MDI dental clinic between June 1, 2018, and December 31, 2019. The KPNW MDI program focuses on closing 12 preventive (e.g., flu vaccines) and 11 disease management care gaps (e.g., HbA1c testing) within the dental setting. Using the multivariable logistic regression, we separately analyzed care gap closure rates (yes vs. no) for patients who were overdue for: (1) preventive services only ($n = 1{,}611$), (2) disease management services only ($n = 538$), or (3) both types of services ($n = 429$), analyzing closure of each care gap type separately. All data were obtained through the electronic health record of KPNW.

Results: The MDI patients had significantly higher odds of closing preventive care gaps (OR = 1.51, 95% CI = 1.30–1.75) and disease management care gaps (OR = 1.65, 95% CI = 1.27–2.15) than the non-MDI patients when they only had care gaps of one type or the other. However, no significant association was found between MDI and care gap closure when patients were overdue for both care gap types.

Conclusions: Patients with care gaps related to either preventive care or disease management who received dental care in an MDI clinic had higher odds of closing these care gaps, but we found no evidence that MDI was helpful for those with both types of care gaps.

Practical Implications: MDI may be an effective model for facilitating the delivery of preventive and disease management services, mainly when patients are overdue for one type of these services. Future research should examine the impact of MDI on long-term health outcomes.

Keywords: integration, Medicare, chronic conditions, preventive, elderly health

INTRODUCTION

Poor oral health, particularly periodontal disease is associated with many common systemic health conditions, including diabetes (1–7), cardiovascular disease (CVD) (7, 8), coronary artery disease (CAD) (9–11), cerebral vascular disease (9, 11–13), hypertension (HTN) (14, 15), cancer (16) and rheumatoid arthritis (RA) (17, 18). Adults aged 65 years and older represent a population at high risk for both and oral and systemic disease, with over 65% having periodontal disease (19, 20) and over 80% having two or more chronic systemic diseases (21, 22).

Previous research has demonstrated that the dental setting can be an ideal setting to promote preventive health for those at risk of developing chronic systemic conditions. For example, Jontell and Glick (23) found that dental healthcare providers can effectively screen and identify patients for serious complications from CVD that they may not be aware of. A systematic review (24) found that screening for dysglycemia in dental clinics was effective in identifying individuals who required triage for further glycemic management.

In a recently published study, we found that a comprehensive medical–dental integration (MDI) program at the Kaiser Permanente Northwest (KPNW) was successful at facilitating the closure of medical care gaps among a population of patients aged 65 years and older who were overdue for either preventive (e.g., flu vaccines) or disease management medical services (e.g., HbA1c testing for persons with diabetes) (25). This research was the first to show that the dental setting can facilitate the provision of recommended evidence-based preventive and disease management medical services for elderly populations (26–28).

Although we found that MDI at KPNW was effective at closing care gaps for preventive and disease management care gaps, there is limited research on whether the effectiveness of MDI on care gaps closure differs by service type: preventive medicine or disease management. For example, MDI is more effective at closing preventive medicine services, such as flu vaccines as opposed to disease management services, such as HbA1c testing for adults with diabetes. Accordingly, the primary objective of this study was to separately examine the association of MDI with the closure of medical care gaps among populations overdue for (1) preventive and/or (2) disease management care gaps. The rationale for conducting this stratified analysis was for program evaluation purposes, namely to understand whether care gaps were closed differently based on the type of medical care gap. Such information can be used for quality improvement purposes to revise and refine the MDI programs.

MATERIALS AND METHODS

The methods for this analysis were presented previously (25). The study population included a retrospective matched cohort analysis of KPNW medical and dental members ($n = 2{,}578$) who received care at any of four MDI clinics of KPNW and those who received care at a non-MDI clinic during the same time period ($n = 2{,}578$; total $n = 5{,}156$). Briefly, we identified all patients who met four inclusion criteria: (1) aged 65 or older; (2) had a dental visit at a KPNW MDI dental clinic between June 1, 2018 and December 31, 2019; (3) had at least one medical care gap at the time of their first (index) dental visit during that time period; and (4) had 12 months of continuous health plan enrollment prior to index dental visit. Using a matching algorithm, we then identified a 1:1 matched sample of patients who met the inclusion criteria except that their index dental visit occurred at one of 13 non-MDI dental clinics during the same time period. Patients from each MDI dental clinic were matched with patients from one of three to four non-MDI dental clinics with a similar total volume of dental staff full-time equivalents (FTEs) and an annual volume of dental visits. Patients were also matched based on sex, care gap type (preventive only, disease management only, or both), age (within 5 years), and index visit date (±60 days). MDI and non-MDI were further propensity-matched based on seven characteristics: Charlson comorbidity index (CCI; 0, 1, 2+); smoking status (yes vs. no); emergency department (ED) utilization in the previous 12 months (any vs. none); hospitalization in previous 12 months (any vs. none); the presence of any of five systemic conditions [diabetes mellitus (DM), RA, CVD, CAD, and HTN; yes vs. no]; periodontal disease status (healthy/early, moderate, and advanced); and a total number of open care gaps at the index visit (continuous).

To assess whether care gap closure varied by service type, we stratified the population into three cohorts based on care gap type(s) at baseline: (1) preventive care gaps only, (2) disease management care gaps only, and (3) both preventive and disease management care gaps. A list of all care gaps and their categories has been described previously (25). Data from the electronic health record (EHR) of KPNW were used for matching and analysis.

The IRB Approval

The protocol for this study was approved by the institutional review board (IRB) within KPNW, who approved a waiver of individual consent for data use (IRB# 00000405 and FWA# 00002344). As this was a "data-only" no-patient contact study, all data storage and analytic practices adhered to the research compliance standards of KPNW.

Setting

The KPNW is a comprehensive healthcare system that currently serves ∼605,000 medical members and 250,000 dental members in Oregon and Washington. The KPNW MDI program includes three distinct model types employed in four dental clinics that are in their level of integration (25). The MDI model with the least integration was implemented on June 1st, 2018; the other two models were implemented on August 1st, 2018. Each model is described below.

Least Integration

This model consists of a dental office located in the same building as medical offices (e.g., lab, vision, and nurse treatment center for immunizations) with no medical staff embedded in the dental office. In this model, a dental member assistant (DMA) identifies care gaps at the time of dental visits using the EHR and coordinates closely with other medical departments located within the building to complete the overdue care gaps.

Moderate Integration

In this model, a licensed practice nurse (LPN) is embedded within a stand-alone dental clinic to address care gaps. The LPN can provide immunizations, collect samples for lab-based tests, and provide other basic services [e.g., HbA1c testing, BP screening, and DM foot exams] directly in the dental setting. The LPN also coordinates all other medical services that require offsite referrals (e.g., mammography) or offsite follow-up with primary care (e.g., follow-up regarding abnormal HbA1c results).

Most Integration

This model, implemented in two KPNW locations, consists of co-located medical and dental offices with an embedded LPN within the dental clinic itself. The LPN provides direct services and coordinates with other co-located medical staff to complete additional services. At both clinics following this model, a DMA works closely with the LPN to identify care gaps prior to dental visits. The LPN then provides service to close care gaps that can be directly addressed in the dental setting (e.g., immunizations) and coordinates with other co-located medical departments to address other care gaps after the dental visit (e.g., DM retinopathy screening). The LPN also arranges follow-up care as needed with primary care for care coordination regarding chronic conditions.

Non-MDI dental offices have no embedded medical staff to complete on-site care gap closure or care coordination to complete needed follow-up services. Within the non-MDI clinics, the dental staff uses an EHR-based decision support tool (described below) to remind patients of any care gaps they may have.

Identification of Medical Care Gaps and Outcome Measures

The KPNW dental and medical clinics use an EHR-based program called the panel support tool (PST) to identify patient care gaps. The PST, which has been in use since 2006 (29), uses informatics to track care gaps, patient reminders, and follow-up care (29). The PST lists care gaps based on the current clinical guidelines and evidence for ongoing screening tests and disease management services (26–28).

The primary outcome measure of this study was closure of *all* relevant (1) preventive and (2) disease management medical care gaps present at the index dental visit in each of the three care gap cohorts. For 18 of the 23 measures, care gap closure was assessed at 30 days following the index visit; fecal immunochemical testing, mammography, annual DM exam, retinopathy exam, and smoking cessation were assessed at 60 days following the index visit.

Statistical Analysis

As part of the stratified analysis, we first conducted descriptive analyses of analytic variables to confirm assumptions and as a quality assurance process. In order to assess the performance of our matching algorithm, we calculated standardized differences of demographic and clinical characteristics between MDI and non-MDI patients within each of the three care gap cohorts (**Tables 1.1–1.3**). We used a threshold of $\geq$0.2 to identify variables that are meaningfully different between groups (30); this threshold has been used previously in observational studies (31, 32). Because no differences of 0.2 or higher were found after matching, we did not conduct further adjustment in the stratified regression analysis. Finally, we used three separate logistic regression models to compare rates of closure of care gaps between MDI and non-MDI patients within each of the three care gap cohorts (**Table 2**).

RESULTS

Population Characteristics: Care Gap Cohorts

The preventive care gap cohort included 62.5% ($N = 3{,}222$) of the study population, whereas the disease management cohort included 20.9% ($N = 1{,}076$) and the combined preventive and disease management gap cohort included 16.6% ($N = 858$) of the population. Within the three cohorts, patients in the MDI and non-MDI groups were well balanced for care gap type, age, and sex, area deprivation index (ADI) (33) (as a proxy for socioeconomic status), and most clinical and demographic variables after matching (**Tables 1.1–1.3**). Although there was variation between the three cohorts with respect to demographics, comorbidities, systemic conditions, periodontal disease status and open care gaps at baseline, none of these differences exceeded the standard difference $\geq$0.2.

Association Between MDI and Care Gap Closure by Cohort

Table 2 shows the results of the logistic regression analyses testing associations between MDI and care gap closure for each cohort. In the preventive care gap and disease management cohorts, patients seen at MDI clinics had 1.51 the odds of closing all preventive gaps and 1.65 the odds of closing all disease management gaps than patients seen at non-MDI clinics. In the cohort of patients with both types of care gaps, there was no significant association being seen at an MDI clinic and closure of all care gaps.

TABLE 1.1 | Population Characteristics: Preventive Care Gaps Only.

Population characteristics	MDI Clinics $N = 1,611$	Non-MDI Clinics $N = 1,611$	*p*-value	Standardized Difference
Baseline gap type				
Preventive alone	1,611 (100.0%)	1,611 (100.0%)	NA	NA
Exact-matched variables				
Age (mean ± S.D.; matched within 5 yrs.)	70.6 ± 5.0	70.8 ± 5.1	0.18	0.05
Sex (exact match)				
Male (vs. female)	580 (36.0%)	580 (36.0%)	1.00	0.00
Propensity-matched variables			0.04	
CCI 0	1,010 (62.7%)	946 (58.7%)		0.04
CCI 1	237 (14.7%)	282 (17.5%)		0.05
CCI 2+	364 (22.6%)	383 (23.8%)		0.02
Current smoker				
Yes (vs. no)	2 (0.1%)	6 (0.4%)	0.16	0.04
ED use in previous 12 months				
Yes (vs. no)	247 (15.3%)	276 (17.1%)	0.17	0.03
Hospitalization in previous 12 months				
Yes (vs. no)	99 (6.1%)	130 (8.1%)	0.03	0.05
Systemic conditions (% yes)				
Diabetes-Mellitus (DM)	166 (10.3%)	179 (11.1%)	0.46	0.02
Rheumatoid Arthritis (RA)	27 (1.7%)	26 (1.6%)	0.89	0.00
Cardiovascular Disease (CVD)	147 (9.1%)	181 (11.2%)	0.05	0.05
Cardiovascular Disease (CAD)	143 (8.9%)	179 (11.1%)	0.03	0.05
Hypertension (HTN)	624 (38.7%)	644 (40.0%)	0.47	0.02
Periodontal disease status			0.87	
Healthy/early	1,273 (79.0%)	1,276 (79.2%)		0.00
Moderate	236 (14.7%)	227 (14.1%)		0.01
Advanced	37 (2.3%)	35 (2.2%)		0.01
Missing	65 (4.0%)	73 (4.5%)		0.02
Total open gaps at index visit (mean ± S.D.)	1.6 ± 0.9	1.6 ± 0.9	0.94	0.00
Non-Propensity matched variables				
SES[b]: Area Deprivation Index (ADI) (Mean ± SD)	4.4 ± 2.4	4.5 ± 2.6	0.33	0.04

N = 3,222 (62.5% of total population)[a].
[a]*Population includes population of Medicare patients age ≥ 65 with 1+ care gaps at baseline. P-value from t-test for age, count of open gaps at baseline, and ADI state rank; P-value from chi-square for all other variables.*
[b]*SES, socioeconomic status.*

DISCUSSION

This study found that among patients with only preventive or disease management care gaps, receiving care in MDI clinics was associated with significantly greater odds of care gap closure than receiving care at non-MDI clinics. However, there was no significant difference in rates of closure of all care gaps between MDI and non-MDI patients among those with both preventive and disease management care gaps at their index visit. Taken with previously published results by our research team that found the KPNW MDI program was effective at closing care gaps overall (when combining all three care gap cohorts) (25), these findings suggest that the success of the KPNW MDI program may be driven by those who do not have both preventive and disease management care gaps—these cohorts made up over 80% of the eligible population.

This is the first study of which we are aware to examine the association of MDI with the closure of specific types of care gaps. Our findings suggest that MDI is effective at facilitating the use of needed medical services for either preventive or disease management care, suggesting the broad benefits of this approach. This research is consistent with research demonstrating the success of other integration efforts in the dental setting. A study by Jontell and Glick (23) found that oral healthcare professionals can successfully screen and identify patients who are not aware of their risk of developing serious complications from CVD and advise these individuals to seek medical care. Similarly, a recent study (34) found that screening for dysglycemia in dental clinics were effective at identifying high-risk patients who required triage for glycemic management.

The findings from our research have clear program significance. Currently, Medicare does not pay for dental services, except if the care is related to hospitalization. Because

TABLE 1.2 | Population Characteristics: Disease Management Gaps Only.

Population characteristics	MDI Clinics $N = 538$	Non-MDI Clinics $N = 538$	p-value	Standardized Difference
Baseline gap type				
Disease management alone	538 (100.0%)	538 (100.0%)	NA	NA
Exact-matched variables				
Age (mean ± S.D.; matched within 5 yrs.)	72.5 ± 5.4	72.6 ± 5.4	0.77	0.02
Sex (exact match)				
Male (vs. female)	285 (53.0%)	285 (53.0%)	1.00	0.00
Propensity-matched variables			0.73	
CCI 0	154 (28.6%)	149 (27.7%)		0.01
CCI 1	122 (22.7%)	133 (24.7%)		0.03
CCI 2+	262 (48.7%)	256 (47.6%)		0.01
Current smoker				
Yes (vs. no)	82 (15.2%)	73 (13.6%)	0.44	0.03
ED use in previous 12 months				
Yes (vs. no)	93 (17.3%)	96 (17.8%)	0.81	0.01
Hospitalization in previous 12 months				
Yes (vs. no)	44 (8.2%)	46 (8.6%)	0.83	0.01
Systemic conditions (% yes)				
Diabetes-Mellitus (DM)	325 (60.4%)	320 (59.5%)	0.76	0.01
Rheumatoid Arthritis (RA)	5 (0.9%)	7 (1.3%)	0.56	0.03
Cardiovascular Disease (CVD)	79 (14.7%)	75 (13.9%)	0.73	0.01
Cardiovascular Disease (CAD)	106 (19.7%)	95 (17.7%)	0.39	0.04
Hypertension (HTN)	429 (79.7%)	419 (77.9%)	0.46	0.02
Periodontal disease status			0.32	
Healthy/early	355 (66.0%)	372 (69.1%)		0.03
Moderate	124 (23.1%)	123 (22.9%)		0.00
Advanced	27 (5.0%)	23 (4.3%)		0.02
Missing	32 (6.0%)	20 (3.7%)		0.07
Total open gaps at index visit (mean ± S.D.)	1.5 ± 0.9	1.4 ± 0.9	0.47	0.04
Non-Propensity matched variables				
SES[b]: Area Deprivation Index (ADI) (Mean ± SD)	4.9 ± 2.2	4.5 ± 2.4	0.01	0.16

$N = 1,076$ (20.9% of total population)[a].

[a]Population includes population of Medicare patients age ≥ 65 with 1+ care gaps at baseline. P-value from t-test for age, count of open gaps at baseline, and ADI state rank; P-value from chi-square for all other variables.

[b]SES, socioeconomic status.

of the clear benefit in promoting the use of preventive and disease management services among the Medicare population, our results suggest that there may be benefits in the Medicare program offering dental insurance coverage to recipients aged 65 years and over.

We recognize several limitations associated with this analysis. First, all data were collected in one healthcare system, potentially limiting generalizability to other populations. While the KPNW membership reflects the underlying population of the area (29, 35), it has a higher proportion older than age 65 compared to the US population overall, suggesting that more research may be needed to determine if these strategies are equally effective in other populations specifically those who are younger (36). Another limitation is that the retrospective cohort design we used does not allow us to assess causality: other differences between MDI and non-MDI clinics, and patients could account for some of the differences between groups. However, this limitation is reduced due to a robust propensity matching of the samples, which reduced the potential impact of confounders on results.

CONCLUSION AND FUTURE RESEARCH

For about 80% of patients in our study, visiting an MDI clinic was associated with higher odds of closing all care gaps than visiting a non-MDI clinic. For patients overdue for both preventive and disease management of care gaps, we found no significant association between MDI and care gap closure.

Further research is needed to understand why there was no difference in care gap closure between MDI and non-MDI for those with both types of care gaps upon dental visit. Possible factors include more gaps to close at baseline and potentially less adherence among patients with both types of care gaps. In addition, future research should directly study the costs and benefits of the MDI model. For health systems and policymakers to evaluate the broader

TABLE 1.3 | Population Characteristics: Both Gaps.

Population characteristics	MDI Clinics *N* = 429	Non-MDI Clinics *N* = 429	*p*-value	Standardized Difference
Baseline gap type				
Both (Preventive and Management)	429 (100.0%)	429 (100.0%)	NA	NA
Exact-matched variables				
Age (mean ± S.D.; matched within 5 yrs.)	69.8 ± 3.9	70.1 ± 4.1	0.34	0.06
Sex (exact match)				
Male (vs. female)	175 (40.8%)	175 (40.8%)	1.00	0.00
Propensity-matched variables			0.55	
CCI 0	187 (43.6%)	173 (40.3%)		0.04
CCI 1	91 (21.2%)	102 (23.8%)		0.04
CCI 2+	151 (35.2%)	154 (35.9%)		0.01
Current smoker				
Yes (vs. no)	74 (17.2%)	72 (16.8%)	0.86	0.01
ED use in previous 12 months				
Yes (vs. no)	58 (13.5%)	62 (14.5%)	0.69	0.02
Hospitalization in previous 12 months				
Yes (vs. no)	23 (5.4%)	26 (6.1%)	0.66	0.02
Systemic conditions (% yes)				
Diabetes-Mellitus (DM)	216 (50.3%)	220 (51.3%)	0.79	0.01
Rheumatoid Arthritis (RA)	5 (1.2%)	4 (0.9%)	0.74	0.02
Cardiovascular Disease (CVD)	37 (8.6)	48 (11.2%)	0.21	0.06
Cardiovascular Disease (CAD)	60 (14.0%)	53 (12.4%)	0.48	0.03
Hypertension (HTN)	312 (72.7%)	322 (75.1%)	0.44	0.02
Periodontal disease status			0.53	
Healthy/early	289 (67.4%)	288 (67.1%)		0.00
Moderate	91 (21.2%)	80 (18.7%)		0.04
Advanced	18 (4.2%)	20 (4.7%)		0.02
Missing	31 (7.2%)	41 (9.6%)		0.06
Total open gaps at index visit (mean ± S.D.)	3.3 ± 1.4	3.4 ± 1.6	0.42	0.06
Non-propensity matched variables				
SES[b]: Area Deprivation Index (ADI) (Mean ± SD)	5.1 ± 2.5	4.8 ± 2.7	0.20	0.09

N = 858 (16.6% of total population)[a].
[a]Population includes Medicare patients age ≥ 65 with 1+ care gaps at baseline. P-value from t-test for age, count of open gaps at baseline, and ADI state rank; P-value from chi-square for all other variables.
[b]SES, socioeconomic status.
MDI clinics = dental offices with integrated medical and dental services.

TABLE 2 | Logistic Regression Analysis of Medical Care Gap Closure[a], by Care Gap Cohort.

	OR	95 % CI	p-value
Population with Preventive Care Gaps Only (*N* = 3,222)			
MDI Population	1.51	1.30-1.75	<0.0001
Non-MDI Population	1.00	–	–
Population with Disease Management Care Gaps Only (*N* = 1,076)			
MDI Population	1.65	1.27-2.15	0.0002
Non-MDI Population	1.00	—	—
Population with both Preventive and Disease Management Care Gaps (*N* = 858)			
MDI Population	0.94	0.62-1.41	NS
Non-MDI Population	1.00	—	—

[a]Population includes Medicare patients age ≥65 with 1+ care gaps at baseline. All care gap closure assessed at 30 days post index visit, except for FIT testing, mammography, annual DM exam, retinopathy exam, and smoking cessation which was assessed at 60 days post index visit. p-value from Logistic Regression Analysis. NS, not statistically significant at p value < 0.05.

implementation of MDI, it is critical to understand the financial costs and benefits of closing medical-related care gaps in the dental setting, especially for the Medicare population. These could include savings due to improved long-term health outcomes of patients whose care gaps are closed due to MDI.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because this data is proprietary information held by Kaiser Permanente Northwest. Questions regarding data access should be directed to david.m.mosen@kpchr.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kaiser Permanente Northwest IRB. Written informed consent for participation was not required for the study in accordance with institutional requirements.

AUTHOR CONTRIBUTIONS

All authors of the study have met authorship criteria established by the International Committee of Medical Journal Editors statement of Uniform Requirements for Manuscripts submitted to Biomedical Journals. In that regard, all of the co-authors are responsible for the reported research, participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted.

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Alzheimer's Disease and Oral-Systemic Health: Bidirectional Care Integration Improving Outcomes

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Dentistry is an effective healthcare field that can impact Alzheimer's disease through prevention and education. Every day dental providers use an arsenal of assessment protocols directly coinciding with modifiable Alzheimer's risk factors. An innovative way to help in the prevention of Alzheimer's disease is to utilize oral health professionals who reach the public in ways other health care providers may not. Bidirectional care integration is needed to stifle many systemic diseases and Alzheimer's disease is no different. Ultimately with collaborative care the patient reaps the benefits. Alzheimer's is associated with many etiologies and pathophysiological processes. These include cardiovascular health, smoking, sleep, inflammatory pathogens, and diabetes. In the United States, dental providers assess each of these factors daily and can be instrumental in educating patients on the influence of these factors for dementia prevention. Globally, by 2025, the number of people with Alzheimer's disease is expected to rise by at least 14%. Such increases will strain local and national health care systems, but for the US if Medicare were expanded to include dental services, many older adults could be spared needless suffering. The goal of this perspective article is to highlight existing practices being used in the field of dentistry that can easily be adapted to educate patients in preventive care and treat risk factors. It is the duty of healthcare professionals to explore all opportunities to stem the advance of this disease and by integrating oral and systemic health into transdisciplinary science, health care and policy may do just that.

Keywords: Alzheimer's disease, medicare, sleep apnea, smoking, dentistry, pathogens, diabetes, cardiovascular disease

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INTRODUCTION

Alzheimer's disease (AD) is a progressive mental deterioration that occurs in middle or old age due to the brain's degeneration [1]. Every 65 s, someone in the United States is diagnosed with Alzheimer's disease, the most common form of dementia, and it currently affects over 5.8 million people in the United States. The Alzheimer's Association projects by 2050 nearly 15 million people in the United States will receive an Alzheimer's diagnosis. The same report shows that a full half of primary care physicians feel unprepared to meet the demand of such a drastic increase [2]. In 2014, Rush University Medical Center analyzed death records nationally and found that most people who die from Alzheimer's have a recorded cause of death listed as respiratory or cardiac disease. When taking these numbers into account, AD would be elevated to the third leading cause of death in the United States [3].

Hundreds of billions of dollars in research and drug exploration have yielded a 99.6% drug failure rate [4]. While various drug developers are taking different approaches considering such near complete failure, many scientists and physicians are targeting prevention as the best strategy to reduce Alzheimer's cases [5–10]. In 2017, *The Lancet* Commission presented a report that stated more than one-third of global dementia cases may be preventable through addressing lifestyle factors that impact a person's risk [11]. The World Health Organization (WHO) agreed with this assessment and strongly recommended physical activity, quitting smoking, managing hypertension, and diabetes to reduce the risk of cognitive decline [12]. Disturbed sleeping patterns and periodontal disease have also been related to AD and accelerated cognitive decline rates [13–19].

The brain changes from Alzheimer's disease start at least a decade before symptoms show [20, 21], and as stated above, prevention is the best current defense against this disease. Prevention strategies should begin years before the typical onset presents, which is where dental providers can make the most significant contribution. Every day, dental professionals are performing vital tests, giving education on preventative measures, and prescribing medications in the line of treating and preventing dental health concerns that may also serve to reduce the risk of Alzheimer's. If dental professionals can use these routine tests to educate their patients and offer counseling on risk and preventative measures, more ways may be found to reduce the human suffering caused by AD. Even simply good oral health can have a positive effect on brain health [22]. This perspective focuses on the work that dental professionals regularly administer in the areas of cardiovascular health, smoking, sleep, inflammatory pathogens, and diabetes that can also serve in the prevention of Alzheimer's, with a special note on the benefit of Medicare spending in the dental field and Alzheimer's prevention.

HEALTH ISSUES AFFECTING ALZHEIMER'S DISEASE

Cardiovascular Health

Many factors related to cardiovascular health increase the risks of Alzheimer's [23, 24]. Midlife obesity, hypertension, and high cholesterol are all associated with an increased risk of dementia [25–27]. A study that followed Americans from 1987 to 2017 revealed that individuals with hypertension in midlife had a significant risk factor for cognitive decline [28]. In a 2014 study, Dr. Gottesman et al. found hypertension was associated with 39% greater odds of dementia [29]. Another study of over 500 people born the same week in 1946 measured blood pressure, cognitive assessments, and PET imaging at ages 36, 43, 53, 60–64, and 69 years. Results showed that elevated blood pressure in middle age resulted in drastic increases in dementia later in life, smaller brain volume, and increased blood vessel damage [30].

Discussion

Taking blood pressure is considered standard of care in dentistry. On every patient at every visit blood pressure is taken and recorded, which enables clinicians to see subtle increases that may indicate systemic issues. Dental providers see patients as often as four times more per year than their general practitioners. Panoramic radiographs are taken during regular assessments by most dental practices at initial visits, and every 3–5 years following. The radiographs allow practitioners to see cysts, tumors, wisdom teeth, the temporomandibular joint, and bone abnormalities, including bone loss from periodontal disease. The film can also detect any calcifications in the soft tissue area. Atherosclerotic lesions of the carotid artery occur at the bifurcation of the common carotid. When these lesions are calcified, they may present on panoramic radiographs as nodular calcifications or vertical radiopacities [31]. Often, these issues remain undetected, as they rarely produce symptoms. Ultimately, the interruption of blood flow to the brain causes a loss of neurological function and may lead to an ischemic or hemorrhagic stroke. Stroke is a strong, independent, and potentially modifiable risk factor for all-cause dementia [32]. People who have had a stroke have nearly double the risk of developing Alzheimer's disease [33]. Clinicians should be careful to evaluate panoramic radiographs in patients who have a history of cardiovascular disease, and other risk factors such as smoking, hypercholesteremia, being overweight or having diabetes. Calcifications are also associated with oral infections and increased mortality and clinicians should carefully assess panoramic radiographs to intercept calcified atherosclerotic lesions of the carotid artery [34]. By remaining vigilant while reviewing radiographs, dental professionals can help identify potential risk factors that may be early indicators of Alzheimer's.

Smoking

Smoking is linked to vascular problems, which is a contributor to Alzheimer's. This may be by way of strokes or smaller brain bleeds, but toxins in cigarette smoke increase oxidative stress and inflammation, which have been linked to Alzheimer's. A 2017 study found that a smoking habit increases the chance of dementia later in life [29]. Studies have found that smokers have reduced brain size, specifically in the cortex, which is responsible for many mental tasks including visual processing and complex abstract thinking [35]. Smoking is a leading cause of preventable death [36], so many smokers may actually die before they reach the age when dementia develops. Therefore, it is difficult for data to be conclusive as to how severely smoking is related to AD, but we know there is a strong correlation [37]. Fortunately, by quitting smoking, damage can at least be partially reversed [36].

Discussion

Smoking cessation programs within the dental practice are already being done, lending itself to individualized support. Dental practitioners have the availability to follow the 5 A's smoking cessation plan (ask, advise, assess, assist and arrange) developed by the US Public Health Service to enhance motivation for smokers to change their behavior [38]. Whether clinicians refer services, write a prescription, or perhaps even assess current smoking status by measuring exhaled carbon monoxide levels, they have the potential to change the lives of smoking patients. Through support, care, and education dental professionals can help to illustrate to patients the dangers of smoking concerning risk of AD.

Sleep

Sleep is critical to overall wellness [39, 40]. It helps to refresh the brain, clean out waste products [41], and replenishes nutrients. Impaired sleep effects the glymphatic system, the system that clears the brains waste products, and new research suggest that there may be a causal relationship between inadequate sleep and dementias [42]. Sleep cleans the hippocampus which facilitates consolidation of memories, which is a crucial step in being able to take in and process new information [43]. Getting proper amounts of sleep can help with most systemic ailments, from lowering blood pressure, reducing depression, obesity, regulating blood sugar, and strengthening the immune system. Proper sleep has been shown to increase amyloid clearance from the brain, and new research shows that people getting proper sleep make less amyloid [44–46]. Other studies have found that a lack of deep sleep is associated with higher tau levels, which forms toxic tangles inside brain cells and may be linked to Alzheimer's [47].

Sleep apnea, a condition that happens when the airway becomes blocked or collapses during the night, has been associated with numerous contributory factors for AD [48, 49]. According to the American Sleep Apnea Association, about 22 million Americans have sleep apnea [50]. A 2013 study found that older adults who experience fragmented sleep, such as that caused by sleep apnea, are more prone to develop Alzheimer's disease [13].

Discussion

Dentistry has become a force to help patients with sleep apnea Dental professional's contribution to patient care in this area should include assisting in diagnosing and to referring to other healthcare specialists, and to determining when dental therapies are of value, e.g., and even treating mild to moderate apnea with mandibular advancement devices [51, 52]. The collaboration between dentists and sleep physicians is growing stronger by the day. Being able to execute simple questionnaires like the STOP Bang and the Epworth Sleepiness Scale can help identify potential risk factors. Additionally, indicators of sleep disordered breathing, such as a scalloped tongue, large tonsils, a red beaten uvula, or grinding patterns [53], can be noted with a simple cursory look during an oral cancer exam. Two of the quickest and most simple assessments are the Malampatti score and tonsil grading that are incredible evaluators and teaching tools for the patient. Dental professionals are educators and pivotal in the discussion of risks, referrals, and treatment options of disordered sleep, which may help to lower patient's risk of developing Alzheimer's disease [54, 55].

Inflammatory Pathogens

Compelling active research regarding microbes, the immune system and the oral cavity and their interaction with inflammation keeps periodontal disease at the forefront of systemic discussions [56]. Many studies have shown that older people with periodontal disease may have an increased risk of Alzheimer's [57–59]. Inflammation causes neural damage from the cascade of events of the central nervous system starting with pro-inflammatory cytokines such as C-reactive proteins, tumor necrosis factor-a, interleukin-1 and interleukin-6 [60]. Periodontal pathogens such as Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, and even HSV1 (cold sores) may all be implicated in Alzheimer's [61–64].

Dr. Judith Miklossy has been studying spirochetes for 3 decades. She was one of the first to demonstrate spirochetes in brain matter. *In vivo* and *in vitro* spirochetes were able to reproduce the clinical, pathological and biological hallmarks of AD. These results fulfilled Hill's criteria and confirmed a causal relationship [65]. A 2021 report revealed *T. denticola* as a potential contributing factor, along with *P. gingivalis*, as risk factors for AD. The research group found that *T. denticola* had the ability to enter the brain and increased the expression of amyloid-β (the hallmark in AD), although the mechanism is unclear [66].

It has been reported that amyloid forms almost instantly around viruses and bacteria, and that infections, including mild ones that produce only minimal symptoms, fire up the immune system in the brain and leave a debris trail that is the hallmark for Alzheimer's [67, 68]. When a virus or bacterium sneaks past the blood-brain barrier, which becomes leaky with age, the brain's defense system is triggered. To combat the intruder, the brain makes amyloid to act as a sticky web to trap the intruder. The beta-amyloid is an antimicrobial peptide (basically, a protein) that the immune system creates to physically trap germs, so what is left is a webby plaque seen in the brains of those with Alzheimer's [69]. Some Alzheimer's researchers are convinced that microbes are causative in Alzheimer's [70, 71]. *P. gingivalis* is a high risk, red complex periodontal pathogen [72]. There is increasing evidence implicating the polymicrobial infection with *P. gingivalis* as playing a part in disease pathogenesis, not only from the low-grade inflammation but the actual translocation into the brain vasculature [64]. A link between Alzheimer's and *P. gingivalis* in the brain is consistent with this emerging model for microbes in the disease's etiology [58, 73–75].

Discussion

There is mounting evidence of periodontal disease impacting altering, systemic health negatively. There are independent associations between periodontal disease and a host of systemic diseases including but not limited to: diabetes, cardiovascular diseases, certain cancers, and cognitive diseases [76, 77]. The activities in health and disease within the gut, the brain and the oral cavity seem to have overlapping consequences. For example, individuals with chronic local inflammation due to periodontal disease have corresponding changes within the gut, to include a link to inflammatory bowel disease [78]. A growing body of clinical and experimental evidence suggests that gut microbiota may contribute to and influence brain disorders [79].

Treating patient's periodontal disease and preventing future events has long been a goal of dental professionals. The strong evidence that reducing oral inflammation, created by infections of the periodontia, contributes to a reduction in systemic inflammation, reinforces the concept that dental providers have a responsibility to help in treating a patient's total health, which in turn may reduce the possibility of many systemic diseases including Alzheimer's. We are the only licensed professionals with this capability, so it is essential to educate ourselves and our patients about Alzheimer's related risks and their periodontal health. Whether they are a causal agent, a contributory agent, or an exacerbator matters not, dentistry helps communities lower their risk. Our tools, from chairside pathogen testing to the use of ozone and lasers, not to be out done by education skills and behavior change strategies, can be put to use in ways to mitigate yet another disease.

Diabetes

Nearly 36% of all U.S. adults and 50% of those 60 years or older are estimated to have metabolic syndrome, a combination of health conditions such as obesity, high blood pressure, insulin resistance, type 2 diabetes, or a poor lipid profile [80]. The correlation between diabetes and risk for Alzheimer's has been the focus of numerous studies [81, 82]. Additionally, there is a new type of diabetes being studied, type 3, which is also strongly correlated with Alzheimer's [83]. People with type 2 diabetes may be twice as likely to develop Alzheimer's, and those with prediabetes or metabolic syndrome may have an increased risk for having predementia or mild cognitive impairment [84]. Those with high blood sugar, whether technically diabetic or not, have a faster cognitive decline rate than those with normal blood sugar [85].

Discussion

Oral health professionals have long been aware of the complications of hypoglycemia in patients with diabetes. Many oral health professionals scrutinize health histories, question patients, and check their blood glucose levels, yet there is a need to increase the monitoring of diabetes during dental visits. In 2018, the American Dental Association added CDT code D0411 for chairside HbA1c, and in 2019 code D0412 to check blood glucose levels. This was not put in place for the expectation to diagnose diabetes, but to help monitor patients during dental procedures. Chairside screening and referral may improve prediabetes and diabetes diagnosis. Point of care testing, specifically in dental practices, can play a vital role in the early detection of type 2 diabetes [86]. Many individuals may not seek diabetic testing due to fear. Dental practitioners often have strong, trusting relationships with patients that may help them feel more comfortable discussing health concerns, like diabetes and Alzheimer's. These are incredible opportunities for dental professionals to help in early detection.

Special Note on Medicare

Having access to dental care is difficult for many US populations especially the elderly and not having access is associated with cognitive decline [87]. It would be kinder and fiscally more responsible to extend Medicare benefits to dentistry if it lowers the cases of a disease projected to affect so many people in such a near future. In 2020, Alzheimer's and other dementias cost the nation ∼$305 and $206 billion in Medicare and Medicaid payments [2]. If dental care were added to Medicare, it may help to reduce the flood of cases. Unless a treatment to slow, stop or prevent this disease is developed, in 2050, Alzheimer's cost is projected to exceed $1.1 trillion. This dramatic rise includes more than 4-fold increases in government spending under Medicare and Medicaid, and in out-of-pocket spending [2].

Medicare beneficiaries with Alzheimer's regularly have other chronic conditions, such as heart disease, diabetes, and kidney disease, and require more skilled nursing, home health, and hospital stays per year than other older people [2]. Not only are there regulations as to whether dental professionals can even do services in a care facility depending on state governing bodies, but there are minimal state and federal guidelines regarding dental care. The inclusion of dental services in Medicare may help to combat the ravages of Alzheimer's disease and curtail the rapid rise in diagnosis rates.

CONCLUSION

Successful healthcare is not just the proper management of disease, but it includes strong prevention strategies. Something must be done to spread knowledge on preventive measures to help slow down the rate of Alzheimer's disease. The goal of this perspective piece is to provide examples for the need to bring dentistry into the fold of interdisciplinary approaches in healthcare. The utilization of *all* healthcare providers is essential along with universal education, partnerships, and healthcare coverage. Many of our communities are left behind due to access and cost and many professionals are not willing to serve those regions. Dental professionals focus on disease prevention, health promotion and often form long-term relationships with their patients. The nature of these relationships can help dental professionals notice subtle changes that may be indicators of a future Alzheimer's diagnosis, and preventative care and education can then be advised. New roles are emerging to help address specific treatment needs and access to dental care, but much more must be done. Many dental hygienists are open to not only expanding services into the underserved communities but working within other healthcare areas such as hospitals and physicians' offices. Including dental care coverage to Medicare would be advantageous but making needed changes will not be easy. Innovative collaborative efforts must be made, and dental professionals are uniquely situated to help roll back the tide of this horrible disease.

For further information you may be interested in attend consensus conferences addressing oral systemic health, collaboration and integration principles. Some examples include, but not limited to, The Santa Fe Group *Oral Health into Overall Health* https://santafegroup.org/events/ The American Academy of Oral Systemic Health *Collaboration Cures* https://www.aaosh.org/2021-scientific-session The Dental Integration Conference *A Time That's Come* https://www.dentalintegrationconference.com

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AOR conceived and presented the idea and wrote the perspective article based upon their opinion and data supporting that opinion.

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MINI REVIEW
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Multiple Idiopathic Cervical Root Resorption: A Challenge for a Transdisciplinary Medical-Dental Team

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The goal of this perspective article is to use multiple idiopathic cervical root resorption (MICRR) as a model to demonstrate the need for transdisciplinary collaborations, from basic science to treatment planning, to improve the quality of health care for all. This is not a review of the literature on the current state of MICRR. Tooth root resorption is a normal physiological process required for resorption and exfoliation of primary teeth; however, root resorption of adult teeth is largely pathological. MICRR is an aggressive form of external root resorption, which occurs near the cemento-enamel junction (CEJ). The cause of MICRR remains elusive, however, it is mediated primarily by osteoclasts/odontoclasts. Accumulating case studies and experiments in animal models have provided insights into defining the etiologies and pathophysiological mechanisms for MICRR, which include: systemic conditions and syndromes, inherited genetic variants affecting osteoclast/odontoclast activity, altered periodontal structures, drug-induced root resorption and rebound effects after cessation of anti-resorptive treatment, chemotherapy, exposure to pets or viral infections, and other factors such as inflammatory conditions or trauma. To determine the causative factors for MICRR, as well as other oral-dental conditions, at minimum, a comprehensive health history should be collected for all patients by dental care providers, discussed with other health care providers and appropriate collaborations established. The examples highlighted in this perspective emphasize the need for transdisciplinary research collaborations coupled with integrated management strategies between medicine and dentistry in order to identify cause(s) early and improve clinical outcomes.

Keywords: periodontal disease, root resorption, osteoclast, odontoclast, genetics, medications, bone resorption

INTRODUCTION

Using MICRR as a model, this perspective underscores the need for researchers and clinicians to adopt transdisciplinary approaches for defining the etiology of unknown oral-dental conditions. In this regard, please see the commentary and short video, 5–7 min, describing the procedure for doing an oral exam for non-dental clinicians published in JAMA, 2018 (1, 2).

While root resorption is a normal physiological process required for resorption and exfoliation of primary teeth (3), root resorption of adult teeth is largely pathological. Pathological root resorption can be broadly classified into internal (i.e., originating within the dental pulp) or external (i.e., attacking the outer root surface) processes, mediated by osteoclasts/odontoclasts (4–7). This perspective focuses on multiple idiopathic cervical root resorption (MICRR), an aggressive form of external root resorption that occurs near the cemento-enamel junction (CEJ) (**Figure 1**). The CEJ is the area where the crown transitions into root(s) and where gingival fibers attach to a healthy tooth root and surrounding alveolar bone. As we highlight below, there has been progress in identifying etiologies for MICRR, particularly genetic and medication-associated causes, prompting us to reconsider the term "idiopathic" once the cause has been identified.

Multiple Idiopathic Cervical Root Resorption: A Brief Introduction

MICRR affects multiple teeth within the dentition (13–16). MICRR lesions are often asymptomatic, non-carious, and lack overt gingival inflammation, increased pocket depth, or tooth mobility that are associated with classical cases of periodontal disease. Histologically, numerous resorptive areas are noted along root surfaces with evidence of osteoclasts/odontoclasts contained in Howship's lacunae (10, 16, 17). MICRR lesions are frequently aggressive in nature and resistant to interventions, ultimately resulting in tooth loss (10, 16, 17). Often, MICRR is detected as an incidental finding on radiographs or during routine dental examination. Fortunately, with enhanced tools and technologies over the last decade (18, 19), our understanding of MICRR etiology and its course has been improving, which will eventually result in refining clinical management and thus, better outcomes.

While idiopathic root resorption is considered a rare condition, it is one that many dentists encounter over years of practice. The effects are devastating, e.g., loss of dentition, a feeling of helplessness by clinicians and patients due to lack of effective prevention/treatment options, and poor esthetics and function driving patients into isolation, negatively impacting mental health and wellbeing. To date, the prevalence of MICRR remains unknown. Since the first case of MICRR described by Mueller and Rony (20), etiologies of MICRR have been largely speculative. Here, we provide an overview of the cellular and molecular mechanisms mediating root resorption, and provide examples of etiology, including systemic conditions and genetic factors, medications, viral infections, inflammatory conditions, environmental and other proposed causes for MICRR (**Table 1**) (55).

Cellular and Molecular Mechanisms of Root Resorption

Histological studies in humans and animals have unequivocally demonstrated that root resorption is mediated by osteoclasts/odontoclasts and is distinct from bacterial-mediated cariogenesis (5, 7, 10, 16, 17, 56). Yet the factors that activate osteoclasts/odontoclasts and recruit them to root surfaces rather than bone surfaces (noted in periodontitis) remain unknown. Bernhard Gottlieb in 1923 noted cases of periodontal disease that were not associated with marked inflammation but rather with perceived defective cementum formation (57–59). He observed that "cementum was the only tissue which connects tooth with the body," and if not formed correctly, would put individuals at risk for a type of periodontal disease (characterized by gingival recession or pocket formation), which he termed as "marginal cementopathia" (57, 58). Clinicians and researchers have revisited this concept, especially with increased knowledge about conditions that trigger clastic activity, including those associated with defective cementum formation (59, 60).

During initiation of cervical root resorption, the portal of entry is the cementum below the gingival epithelium, and resorption starts with localized destruction and/or removal of PDL (56). Response to PDL injury includes formation of a blood clot and inflammation, followed by granulation tissue and recruitment of macrophages to the affected area (56, 61). Impaired vasculature in the area leads to hypoxia, which promotes osteoclast differentiation and activity (62). As the osteoclastic/odontoclastic resorptive lesions expand toward the pulp space by destroying cementum, dentin, and enamel, several resorption channels and interconnections with PDL (portal of exits) are created, generating a 3D space (52, 56). In most cases, the advancing resorptive lesions are prevented from perforating into the pulp space by the pericanalar resorption resistant (PRSS) sheet (52, 56). This layer consists of predentin, dentin, and occasionally reparative bone-like tissue. In the final stages of the disease, repair and remodeling sometimes occurs through the activity of cementoblast/osteoblast-like cells, resulting in deposition of bone-like tissue into the resorption cavities (52, 56).

SYSTEMIC CONDITIONS AND GENETIC FACTORS

Systemic Conditions and Syndromes

Root resorption has been associated with systemic and syndromic conditions, including endocrine disorders. In some of these conditions, dysregulated resorption affects the skeleton, leading to reduced bone mineral density or osteolytic lesions. Examples of conditions associated with root resorption include: hypothyroidism (21), hyperparathyroidism (22, 23), systemic sclerosis (24), Gaucher's disease (25), hereditary hemorrhagic telangiectasia (26), Paget's disease of bone (27, 28), Goltz syndrome (29), Papillon–Lefévre syndrome (30), and Turner syndrome (31). To date, no studies have firmly established causality between these conditions and MICRR.

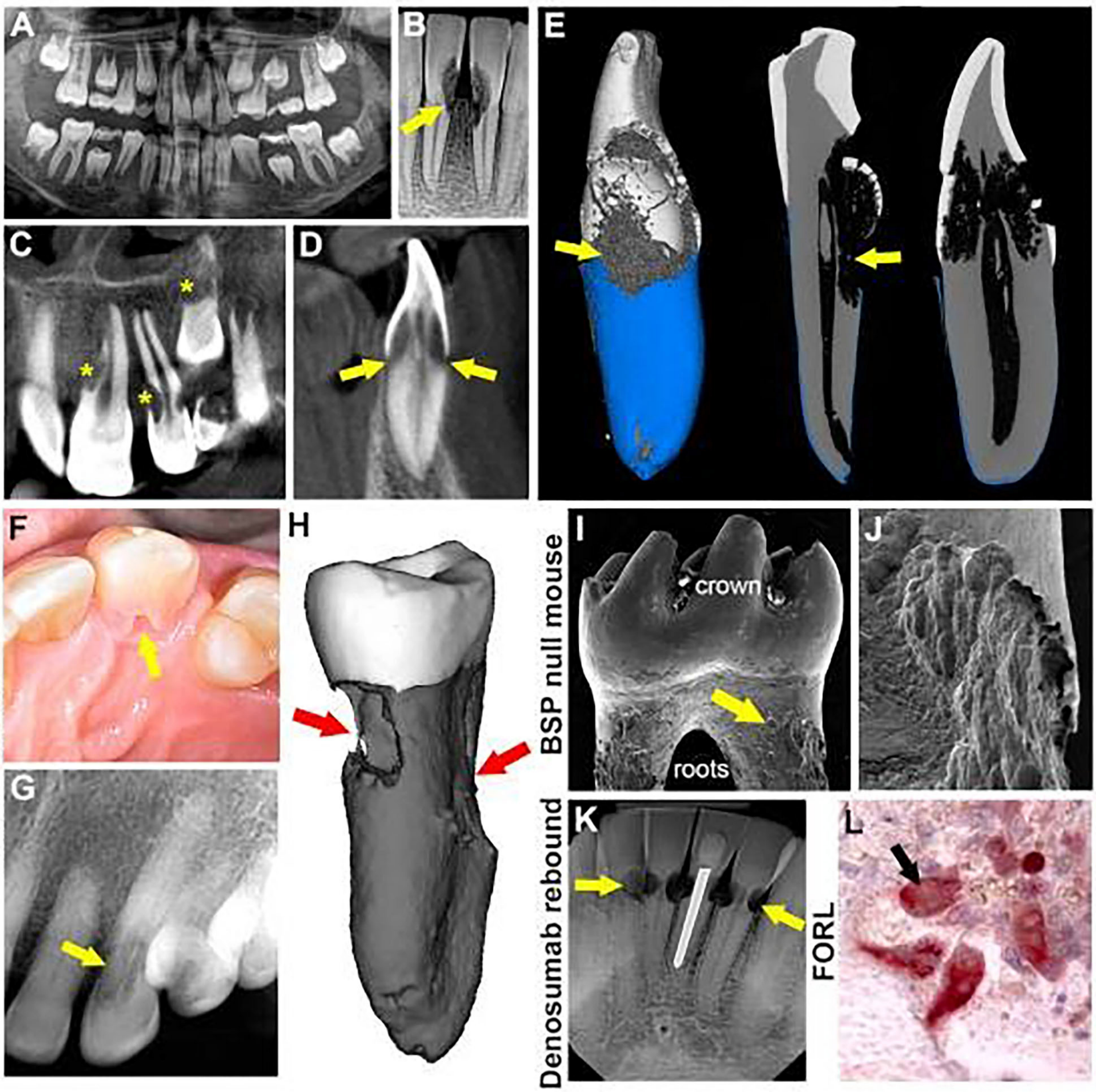

FIGURE 1 | Multiple etiologies of MICRR. **(A)** Panoramic radiograph of 8-year-old female with familial expansive osteolysis (FEO) associated with *TNFRSF11A* variant showing cervical root resorption of permanent maxillary and mandibular incisors (yellow arrows). **(B)** Periapical radiograph of the same patient with FEO, at 9-years-old, showing extent of external resorption (yellow arrows). **(C,D)** Cone beam computed tomography (CBCT) of the same patient at 9-years-old showing extensive resorption of permanent central and lateral incisors (yellow stars) and unerupted canine (yellow star and yellow arrows). **(E)** 3D micro-computed tomography (micro-CT) reconstruction of incisor of the same FEO patient at age 9, noting defective cementum formation and root resorption. **(F)** Intraoral photograph of an advanced resorption lesion (yellow arrow) on the palatal aspect of tooth from affected individual with an inherited *IRF8* variant. **(G)** Radiograph of the lesion (yellow arrow) shown in **(F)**. **(H)** Micro-CT reconstruction of an extracted tooth exhibiting extensive cervical resorption (red arrows). **(I)** Scanning electron microscopy (8) image of BSP null mouse molar showing abundant pitting (yellow arrows) at cervical root surfaces. **(J)** Higher magnification SEM of the tooth in panel I showing details of cervical root resorption in BSP null mouse molar. **(K)** Periapical radiograph of lower anterior teeth in 69-year-old patient, after discontinuation of denosumab, showing multiple areas of cervical root resorption (yellow areas). **(L)** Tartrate-resistant acid phosphatase (TRAP) stain of histology section showing multinucleated odontoclasts (red cells, black arrow) on root surfaces of a cat with feline odontoclastic resorption lesions (FORL). **(A–D)** reproduced with permission from Macaraeg et al. (9). **(F,G)** reproduced with permission from Neely et al. (10). **(I)** reproduced with permission from Foster et al. (11). **(K)** Copyright © 2020 American Academy of Pediatric Dentistry and reproduced with their permission (12).

TABLE 1 | Potential Risk Factors for multiple idiopathic cervical root resorption (MICRR).

Potential predisposing factors		Examples and references
Systemic conditions and genetic factors	Systemic diseases	Hypothyroidism (21), hyperparathyroidism (22, 23), Systemic sclerosis (24), Gaucher's disease (25), Hereditary hemorrhagic telangiectasia (26), Paget's disease of bone (27, 28)
	Syndromes	Goltz syndrome (29), Papillon–Lefe'vre syndrome (30), and Turner syndrome (31)
	Genetic mutations and altered osteoclast/odontoclast activity	*IRF8 (19)*, *TNFRSF11A* (9, 32, 33), *NFATC1*(unpublished data from our group)
	Genetic mutations and altered periodontium	*ALPL* (34, 35), *BSP* (11, 36)
Medication-induced root resorption	Anti-resorptives	Discontinuation of denosumab therapy (12), https://www.ehealthme.com/ds/prolia/tooth-resorption/ Administration of bisphosphonate therapy may prevent MICRR progression (37, 38)
	Chemotherapeutics	(39)
Pets and viral infections	FeHV-1	(5, 6, 14, 40–44)
	Herpes zoster	(45, 46)
Trauma	Fracture, luxation, replantation, transplantation	(47–51)
Environmental factors	Parafunctional habits	Bruxism, tongue thrusting (47, 49, 52)
	Previous orthodontic treatment	Fixed appliances, esthetic brackets, application of force > 20–26 g/cm^2 (47, 49, 53)
	Musical instruments	Wind instruments (54)

Altered Osteoclast/Odontoclast Activity

Familial expansile osteolysis (FEO; OMIM#174810) is caused by mutations in the *TNFRSF11A* gene (9, 63, 64), which encodes for receptor activator of nuclear factor κ-B (RANK), a receptor found on osteoclasts and their progenitors. Upon binding to RANK ligand (RANKL), RANK promotes osteoclastic formation/function. In FEO, *TNFRSF11A* mutations affecting its signaling peptide may result in constitutive activation independent of RANK ligand stimulation leading to uncontrolled osteoclast activity (63). Individuals with FEO often present with early-onset deafness, skeletal deformities, and premature loss of teeth (63–65). FEO has been associated with extensive resorption of cervical and apical areas of permanent teeth (32, 33). Recently, Hajishengallis and colleagues reported a case of FEO in a 10-year-old female with missing ossicles and MICRR (9). In addition to MICRR affecting at least 7 erupted permanent teeth, premature atypical root resorption of all primary teeth (started at age 5 and progressed with most of the roots resorbed by age 7) and resorption of an unerupted permanent canine was noted (**Figures 1A–D**). Genetic testing focusing on missing ossicles at the time of birth was inconclusive and the accelerated root resorption of primary teeth was not well-appreciated. However, when the aggressive root resorption involved permanent teeth, it prompted further endocrinology and genetic testing, which revealed decreased lumbar spine mineral density, high circulating alkaline phosphatase (66) levels, and identification of the *TNFRSF11A* mutation, which together led to the diagnosis of FEO.

MICRR in this case involved several anterior teeth (maxillary lateral incisors, left central incisor, unerupted left canine, and mandibular central incisors and left canine). Interestingly, cone-beam computed tomography scans of the resorptive defects suggested that the lesions started from a small portal of entry in the cementum and expanded below the bone level inside the tooth, sparing the pulp canal space. Unfortunately, two of the affected teeth (mandibular lower central incisors) showed increased sensitivity and required extraction. Micro-CT analysis of these teeth revealed defective formation of root cementum (**Figure 1E**). Other potential complications of FEO include progressive osteoclastic resorption that can lead to severe, painful, disabling deformities, and pathologic fractures of bones. Although the patient in this case showed only a possible mineralization disorder, she was placed on intravenous bisphosphonates for management of overall skeletal problems. Ten months later, her biochemical markers of the disease were reversed, and the root resorption lesions appeared stable. The transdisciplinary medical-dental collaboration between Children's Hospital of Philadelphia and University of Pennsylvania School of Dental Medicine generated sufficient diagnostic information to identify the cause of this young patient's condition, leading to appropriate and effective medical and dental treatment.

Genetic variants linked specifically with root resorption, but not overt systemic/syndromic manifestations, have been rare to date. A few reports suggest a genetic predisposition to MICRR based on hereditary patterns (17, 19, 67), and several reports noted MICRR in healthy individuals with apparently non-contributory medical histories (10, 13–16). Neely, Thumbigere-Math, and colleagues reported a familial pattern of MICRR with a 30-year follow-up (10, 17). To the best of our knowledge, this is the only report of inherited MICRR with an extended follow-up. The family included two generations with four MICRR-affected and four unaffected family members (10, 17). The 63-year-old proband presented with a history of MICRR affecting multiple teeth (**Figures 1F–H**). Over several decades, the resorptive lesions progressed with a total of 19 affected teeth, leading to extraction/exfoliation of 12 teeth. Additionally, the proband's two sons and one daughter developed MICRR during their fourth to sixth decades of life. All affected subjects were asymptomatic, lacked known predisposing factors, and reported a non-contributory medical history. Whole exome-sequencing identified a novel autosomal dominant heterozygous mutation [c.1219 G>A (G388S)] in the interferon regulatory factor 8 (*IRF8*) gene, which encodes a transcription factor that negatively regulates osteoclast differentiation (19). *In vitro* and *in vivo* functional analysis demonstrated that $IRF8^{G388S}$ mutation promoted increased osteoclastogenesis, thus providing a molecular basis for enhanced root resorption. Based on MICRR-associated variants in *TNFRSF11A* and *IRF8*, other variants targeting key regulatory steps in the osteoclast/odontoclast pathway might increase predisposition to root resorption. This concept has been borne out by studies using a transgenic mouse model where knockout of *Tnfrfsf11b* (osteoprotegerin), a decoy receptor for RANKL, promoted extensive molar root resorption (68).

Altered Periodontium as a Contributing Factor

Defective cementum formation has been suggested to predispose to periodontal breakdown, i.e., the concept of "periodontosis" by Gottlieb (58). Reduction or absence of acellular cementum at the cervical root surface theoretically exposes the root to resorption. Mutations in tissue-nonspecific alkaline phosphatase (TNAP), encoded by the *ALPL* gene, result in the inherited mineralization defect, hypophosphatasia (HPP; OMIM#146300, 241500, 241510) (69–71). Early exfoliation of deciduous teeth and loss of permanent teeth are pathognomonic signs of HPP due to defective cementogenesis. Abnormal root resorption in permanent teeth of some HPP patients has been reported (34, 35), possibly associated with cementum defects. Other inherited cementum defects in humans are rare, but genetically engineered mouse models serve as proof-of-principle examples. Mice deficient in bone sialoprotein (BSP), an extracellular matrix protein critical for cementum mineralization and function, exhibit a lack of acellular cementum and subsequent periodontal breakdown (11, 36). BSP null mice feature dramatic osteoclast/odontoclast mediated root resorption exclusively targeting the cervical regions of all molars (**Figures 1I,J**). The cementum defect and periodontal destruction in the absence of inflammation illustrate Gottlieb's periodontosis concept and suggest other inherited periodontal structural defects may promote cervical root resorption.

Inherited defects likely intersect with acquired or environmental factors to increase susceptibility to MICRR, possibly explaining delayed onset and diagnosis of root resorption in some cases. We emphasize that not all cases are associated with genetic etiologies, although increased understanding of genetic inputs in MICRR should prompt genetic testing when cases cannot be explained by local etiologic factors or systemic abnormalities.

MEDICATION-INDUCED ROOT RESORPTION

It is well-recognized that medications have side-effects that can adversely affect oral health. For example, certain medications used to treat epilepsy, hypertension, and heart disease, or immunosuppressants in organ transplant patients, are associated with gingival hyperplasia (72, 73). Several medications cause severe xerostomia (dry mouth) (74, 75). Yet other therapies cause severe oral mucositis requiring treatment alterations. The examples below underscore the importance of collecting detailed medication histories (e.g., prescribed treatments as well as mouth rinses, toothpastes, herbal products, and vitamins) in individuals exhibiting root resorption. Significantly, these situations serve to remind physicians to consider treatment effects on oral health and incorporate dental clinicians in monitoring overall health of patients.

Anti-resorptive Medications and Potential Rebound Effect Associated With MICRR

Anti-resorptive therapies are widely prescribed for treatment of osteoporosis and painful osteolytic manifestations of cancer. Several generations of bisphosphonates have served as key anti-resorptive agents for decades, while more recent therapies target regulators of osteoclast, osteocyte and osteoblast differentiation and function. Denosumab is a monoclonal anti-RANKL antibody that inhibits RANK-mediated activation of osteoclasts. Recently, Deeb et al. reported that a 69-year-old patient who discontinued denosumab after 5 years experienced MICRR affecting multiple teeth (**Figure 1K**), in conjunction with pain and sensitivity, but no alterations in attachment levels (12). A surge in osteoclastic activity may provide an explanation for occurrence and progression of MICRR, i.e., a rebound effect after discontinuing anti-resorptive therapy. After administration of denosumab, osteoclast activity rapidly declines and can drop by over 80% within weeks to months and remain at that level while denosumab treatment is continued (76). Once treatment is discontinued, antibody levels suddenly decline, resulting in transient increases in osteoclastic activity and bone turnover to levels above the starting range, before eventually returning to pretreatment levels (77). Although at this time there is insufficient evidence to support a causality between denosumab and MICRR, a website established to self-report cases of root resorption in patients treated with denosumab revealed 20 cases between 2013 and 2019, affecting predominantly females over 60 years taking denosumab for 2–5 years (https://www.ehealthme.com/ds/prolia/tooth-resorption/). Due to their antiresorptive effects on alveolar bone, systemic bisphosphonate use has been suggested to prevent progression of root resorption (37), and local delivery of bisphosphonates have been explored as potential approach for preventing root resorption of replanted teeth (38). While local use of bisphosphonates appears likely to serve as an effective interventional strategy in these contexts, caution should be taken due to the recent association of systemic anti-resorptives with MICRR, as well as the more established links with medication-related osteonecrosis of the jaw (MRONJ) (78–81).

Chemotherapy

Llavayol et. al reported that a 16-year-old female who received chemotherapy for ovarian cancer developed MICRR in 12 teeth, 9 years later (39). While the authors discarded other possible etiologies and hypothesized a correlation between chemotherapy and defective cementum and PDL, they were not able to establish the etiology. An alternative interpretation is that the medications affected mineral homeostasis, potentially activating osteoclast activity along with destruction of cementum and PDL.

PETS AND VIRAL INFECTIONS

Cats exhibit a high incidence of external root resorption, termed feline odontoclastic resorptive lesions (FORL), a disorder that strongly resembles MICRR in humans. The prevalence of FORL is around 29–60% (82, 83), and more commonly seen in domestic vs. wild cats, and often in females (84, 85). The etiology of FORL remains unknown, however, the mechanisms and progression of osteoclastic/odontoclastic root resorption appears similar to humans (**Figure 1L**) (86). Proposed risk factors include increasing age, diet low in magnesium/calcium and higher in vitamin D, and low frequency of teeth cleaning (84). FORL has been associated with Feline herpes virus 1 (FeHV-1), and it has been speculated that transmission of FeHV-1 to humans can initiate MICRR (5, 6, 40–44). Von Arx et al. reported four individuals with MICRR who had extended contact with cats and presented positive titers of neutralizing antibodies against FeHV-1 (40). Similarly, Wu and colleagues reported a case of MICRR in an individual who had contact with cats (14).

Other reports have described patients with herpes zoster/shingles who developed MICRR in corresponding areas of nerve innervation. Solomon et al. reported cervical root resorption in two teeth in a 31-year-old female with a positive history of herpes zoster infection in the corresponding division of the maxillary trigeminal nerve (45). Similarly, Ramchandani and Mellor reported MICRR in a 72-year-old female who presented with a 17 year earlier history of herpes zoster infection of the maxillary division of the trigeminal nerve (46).

AREAS OF NOTE

Many other examples based on case reports and anecdotal experiences from clinicians and patients are worth mentioning since they may trigger additional thoughts regarding mechanisms mediating purported root resorption. While most examples of MICRR are non-inflammatory, we would be remiss if we did not mention inflammatory conditions associated with root resorption, such as severe periodontal disease, where marked inflammation triggers factors causing both osteoclast-mediated bone and cementum resorption. Additionally, osteoclast inhibitors such as denosumab and bisphosphonates have been associated with an acute-phase response and the release of proinflammatory cytokines, possibly explaining another underlying mechanism between anti-resorptive medications and MICRR (87, 88).

Environmental factors are another area warranting consideration. Examples here relate to Gottlieb's findings discussed above that some types of periodontal disease were associated with perceived defective cementum formation rather than marked inflammation (57–59). Individuals with minor defects in cementogenesis, whether related to genetic factors or exposure to environment toxins during tooth development, when exposed to periodontal pathogens or other local factors may be more susceptible to MICRR. Answers to this proposed mechanism of MICRR will require coordination among transdisciplinary researchers and clinicians as well as patients. Other environmental factors include marked trauma to the oral region, which is known to mediate osteoclast/odontoclast root resorption, usually localized to the affected area. Other examples of environmental factors, but regionally specific vs. MICRR, include playing of wind instruments, parafunctional habits and previous orthodontic treatment, the latter usually limited to apical root resorption.

CONCLUSION

Several valuable points are to be gained from this perspective:

1. The need for transdisciplinary approaches to improve health outcomes.

   The goal of this perspective is to use MICRR as a model for portraying the need for transdisciplinary approaches in order to improve diagnosis and subsequent treatment of diseases/conditions, including the potential to identify medications that may affect oral health. The specific examples of MICRR provided here are used to demonstrate that oral conditions should be considered in the context of the whole body in order to move away from silos, which are unfortunately evident within the disciplines of dentistry and medicine. We must move toward integrated systems approaches for research and treatment.
2. MICRR is associated with multiple conditions.

   The complex etiology of MICRR presented here highlights situations where the condition seems to be selective to the dentition, where in other situations it may prove to be a sign i.e., pathognomonic, for the condition. Some groups might consider MICRR as a manifestation associated with multiple conditions involving dysregulation of osteoclast differentiation/activity as the "common denominator" or "central triggering issue," as opposed to a pathological entity that may have multiple etiologies. Other groups might consider MICRR as a pathological entity as not every individual affected by a myriad of etiologies (e.g., viral infection, use of medications, genetic disorders, etc.) exhibits signs of MICRR. Irrespective of the differing views, the examples provided in this perspective emphasize the need for transdisciplinary collaborations to improve our understanding of the characteristics of a given condition/disease.
3. MICRR remains a puzzle to solve.

   Further transdisciplinary research from basic science to clinical studies is needed to define the etiology of MICRR, understand mechanisms honing osteoclasts to tooth root surfaces vs. surrounding bone, and develop treatments to arrest osteoclast activity and help repair tooth root structures vs. extraction.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Longitudinal Observation of Outcomes and Patient Access to Integrated Care Following Point-of-Care Glycemic Screening in Community Health Center Dental Safety Net Clinics

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Introduction: Rates of diabetes/prediabetes continue to increase, with disparity populations disproportionately affected. Previous field trials promoted point-of-care (POC) glycemic screening in dental settings as an additional primary care setting to identify potentially at-risk individuals requiring integrated care intervention. The present study observed outcomes of POC hemoglobin A1c (HbA1c) screening at community health center (CHC) dental clinics (DC) and compliance with longitudinal integrated care management among at-risk patients attending dental appointments.

Materials and Methods: POC HbA1c screening utilizing Food and Drug Administration (FDA)-approved instrumentation in DC settings and periodontal evaluation of at-risk dental patients with no prior diagnosis of diabetes/prediabetes and no glycemic testing in the preceding 6 months were undertaken. Screening of patients attending dental appointments from October 24, 2017, through September 24, 2018, was implemented at four Wisconsin CHC-DCs serving populations with a high representation of disparity. Subjects meeting at-risk profiles underwent POC HbA1c screening. Individuals with measures in the diabetic/prediabetic ranges were advised to seek further medical evaluation and were re-contacted after 3 months to document compliance. Longitudinal capture of glycemic measures in electronic health records for up to 2 years was undertaken for a subset ($n = 44$) of subjects with available clinical, medical, and dental data. Longitudinal glycemic status and frequency of medical and dental access for follow-up care were monitored.

Results: Risk assessment identified 224/915 (24.5%) patients who met inclusion criteria following two levels of risk screening, with 127/224 (57%) qualifying for POC HbA1c screening. Among those tested, 62/127 (49%) exhibited hyperglycemic measures: 55 in the prediabetic range and seven in the diabetic range. Moderate-to-severe periodontitis was more prevalent in patients with prediabetes/diabetes than in individuals with measures in the normal range. Participant follow-up compliance at 3 months was 90%. Longitudinal follow-up documented high rates of consistent access (100 and 89%, respectively), to the integrated medical/DC environment over 24 months for individuals with hyperglycemic screening measures.

Conclusion: POC glycemic screening revealed elevated HbA1c measures in nearly half of at-risk CHC-DC patients. Strong compliance with integrated medical/dental management over a 24-month interval was observed, documenting good patient receptivity to POC screening in the dental setting and compliance with integrated care follow-up by at-risk patients.

Keywords: diabetes mellitus, prediabetic state, point-of-care testing, general practice, dental, glycated hemoglobin A, risk assessment, delivery of healthcare

BACKGROUND

Overview of Problem

The Centers for Disease Control and Prevention (CDC) projected that over 10.5% of individuals in the USA have diabetes mellitus (DM), with 21% undiagnosed [1]. Moreover, ∼34.5% of the US adult population has prediabetes, with >80% unaware of their glycemic status (CDC, 2020) [2]. Between 2015 and 2030, diabetes prevalence in the USA is projected to increase by 54%, annual diabetes-associated mortality by 38%, and annual overall cost associated with diabetes to exceed $620 billion [3]. These data project that diabetes remains on track for continued escalation of its epidemic status.

Similarly, recently updated projections of periodontal disease (PD) reported increasing prevalence, currently estimated in excess of 40%, with higher rates projected among the elderly and in association with race and ethnicity, projected by population-based screening [4]. Because recent systematic review and meta-analysis of the evidence base surrounding bidirectional associations between PD and diabetes continues to support potential interactions between these conditions [5], there is an increased need to expand and promote integration of inter-disciplinary efforts across primary dental and medical settings to identify and manage high-risk individuals.

Whereas, current US Preventive Services Task Force (USPSTF) guidelines recommends screening for type 2 DM (T2DM) for individuals with hypertension, aged 40–70 years who meet obesity status definitions [6], glycemic screening in the dental setting has remained controversial (reviewed by Glurich et al. [7]). Biological screening in the dental setting was not recommended at the time USPSTF guidelines were issued because diabetes is not managed in the dental domain and an adequate evidence base to support screening was lacking. However, alignment of recent key developments supports timeliness of re-evaluation of dental clinic (DC) settings as primary care settings where at-risk patients can be identified. These key developments include (a) epidemiological evidence of the burgeoning epidemic status of T2DM and PD cited above; (b) evidence demonstrating substantive prevalence of undiagnosed T2DM/prediabetes in the DC setting [8, 9]; (c) publication of an expert consensus report and clinical guidelines recommending integrated T2DM and PD management issued by 2018 Joint Workshop International Diabetes Federation and European Federation of Periodontology following systematic examination of the evidence [10]; (d) findings of systematic review of meta meta-analyses surrounding bidirectional relationships between T2DM and PD, which continue to support value in integrated interventional approaches to prevention and treatment [11]; and (e) updated guidelines and issuance of Current Dental Terminology (CDT) codes (2019) to support point-of-care (POC) glycemic assessment in dental settings to inform patient management [12].

Study Rationale

Implementation of POC hemoglobin A1c (HbA1c) screening across four community health center DCs (CHC-DC) in Wisconsin described herein was supported by a systematic review undertaken to examine outcomes of clinical and field trials published since 2007 exploring POC screening of patients attending dental visits [8]. Eligibility criteria for subjects enrolled in these field trials included the following: (1) no pre-existing diagnosis of T2DM/prediabetes, (2) no biological glycemic measure in a defined period, and (3) documentation that patients had known risk factors for diabetes [8]. These studies sought to estimate prevalence of undiagnosed T2DM/prediabetes in their dental patient population. Substantial rates of putative T2DM (1–14%) and prediabetes (19–90%) were detected across a range of dental practices with highest rates observed in dental practices serving a higher proportion of patients meeting disparity population definitions [13, 14]. However, studies that reported on re-evaluation of glycemic measures in the medical setting on patients testing into hyperglycemic ranges mainly did so only within 24–48 h following the POC screening test and failed to establish the true rate of diabetes diagnosis based on the prevailing clinical practice guidelines effective in the temporal window of these studies. These guidelines stated requirements for confirmatory glycemic measures in the diabetic range within 6 months. Longitudinal follow-up of further glycemic evaluation or concordance between the screening measures and further biological glycemic assessment across time was also not an objective of the field trials. Furthermore, instrumentation to conduct biological glycemic screening varied across studies and included glucometers not approved by the Food and Drug Administration (FDA) for global screening in 7/10 studies systematically reviewed [8]. Finally, the glycemic measure used to screen glycemic levels at POC also varied across studies with 7/10 employing HbA1c [8]. Findings of the systematic review underlined a need for appropriately designed protocols to support further assessment of the relative clinical value in conducting POC screening in the DC setting. Emphasis was placed on targeting of undiagnosed patients with risk factors for DM and no glycemic measures within a defined temporal window in order to evaluate the value of designating the DC setting as an additional interdisciplinary primary care setting.

Analysis of longitudinal patient engagement in integrated care delivery following POC screening was also of interest to CHC-DC operationalizing safety net operations. In lieu of population-based screening, targeted screening was posited to identify potentially undiagnosed individuals who require further medical assessment and appropriate follow-up in both the medical and dental settings. Notably, regression modeling of candidate variables contributing to diabetic risk by authors of previous field trials screening for undiagnosed hyperglycemia in DC settings identified PD prevalence and missing teeth as novel independent risk factors [13, 14]. Detection of T2DM/prediabetes risk, ideally at early stages, was targeted positing that intervention during early development could slow or prevent progression in activated patients and potentially reduce risk for onset of diabetic complications and chronicity of PD.

The focus of the current study was to implement POC HbA1c testing to detect rates of T2DM and prediabetes across patients of four CHC-DC in Wisconsin with targeted screening only of the subset of patients with risk factors for hyperglycemia and observe patient behavior relative to seeking medical–dental access if glycemic screening measures were elevated. The study design included questionnaire-based screening, in combination with Clinical Laboratory Improvement Act (CLIA)-waived HbA1c testing utilizing Federal FDA-approved instrumentation in the DC settings targeting only dental patients with high-risk profiles. Observational longitudinal follow-up was further planned to monitor patient compliance with triage and follow-up testing by medical providers 3 months post-screening. Finally, a subset of patients across three of four centers where data were accessible in the electronic health records (EHRs) was monitored for glycemic follow-up and evidence of periodontal evaluation within a minimum time frame of 1 year and up to 2 years post-POC screening in order to more accurately observe concordance of screening outcome, true biological status, and access to available integrated medical/dental care delivery models in CHC settings.

DESIGN AND METHODS

Study Design and Objectives

This observational community case study evaluated clinical utility of identifying the subset of eligible dental patients potentially at risk for T2DM/prediabetes in the context of scheduled dental visits at participating CHC-DC sites where a POC HbA1c screening protocol was implemented. Specifically, the study focused on the subset of individuals attending dental care appointments with no existing diagnosis or history of DM/prediabetes and no glycemic screening within the past 6 months to document glycemic status but who exhibit risk factors for diabetes and met inclusion criteria as outlined in the study flow diagram in **Figure 1**.

The study objectives included observational characterization of (1) undiagnosed dysglycemia prevalence detected; (2) tracking of compliance with triage to medical evaluation and follow-up; and (3) longitudinal tracking of individuals to observe access to medical and dental care for individuals found to be at high risk for T2DM/prediabetes following POC screening in the dental setting.

Population and Setting

This community case study was undertaken across three CHC-DC serving largely rural populations in Wisconsin including 2 of 10 CHC-DC operated by Family Health Center of Marshfield, Inc. (FHC-M) and Marshfield Clinic Health System (MCHS) in the following: (1) Marshfield, Wisconsin (WI); (2) Medford, WI; and (3) Bridge Community Dental Center serving the regional population of Wausau, WI. The fourth DC that enrolled patients was St. Elizabeth Ann Seton Dental Clinic, a walk-in clinic serving an urban population in Milwaukee, WI. Study enrollment was undertaken over 11 months from October 24, 2017, through September 24, 2018. Longitudinal follow-up was carried out for a minimum additional 12 to up to 24 months through October 1, 2019, on subjects with available data in order to observe patient longitudinal access for follow-up glycemic measures in the medical setting and periodontal assessments in the dental setting. All of the participating sites represent DCs designated as dental safety nets established largely in rural settings to serve disparity populations who otherwise have limited access to dental care [15]. Over 85% of patients seeking care at FHC-M dental centers alone are on Medicaid [16] and other CHCs similarly provide dental care to a high volume of the Medicaid population and to those with no dental insurance coverage largely due to poverty status. The majority of patients seen at St. Elizabeth Ann Seton Dental Clinic in Milwaukee, as a "walk-in" clinic, have no dental home. Their operations largely target provision of dental care to individuals experiencing acute dental conditions. While periodontal assessment and longitudinal tracking data on these patients were not available, patient enrollment at this fourth site was included mainly to explore rates of hyperglycemia in their patient population and gauge receptivity of clientele of this clinic to HbA1c screening in the dental setting.

Overview of Participant Screening Procedures

The study and all study forms were reviewed and approved by the Institutional Review Board of the MCHS. Participating DCs applied for and were issued CLIA waivers to support conduct of HbA1c screening in the dental setting using Siemens DCA Vantage HbA1c Analyzer (Siemens Healthineers, USA). This analyzer uses an immuno-assay to determine

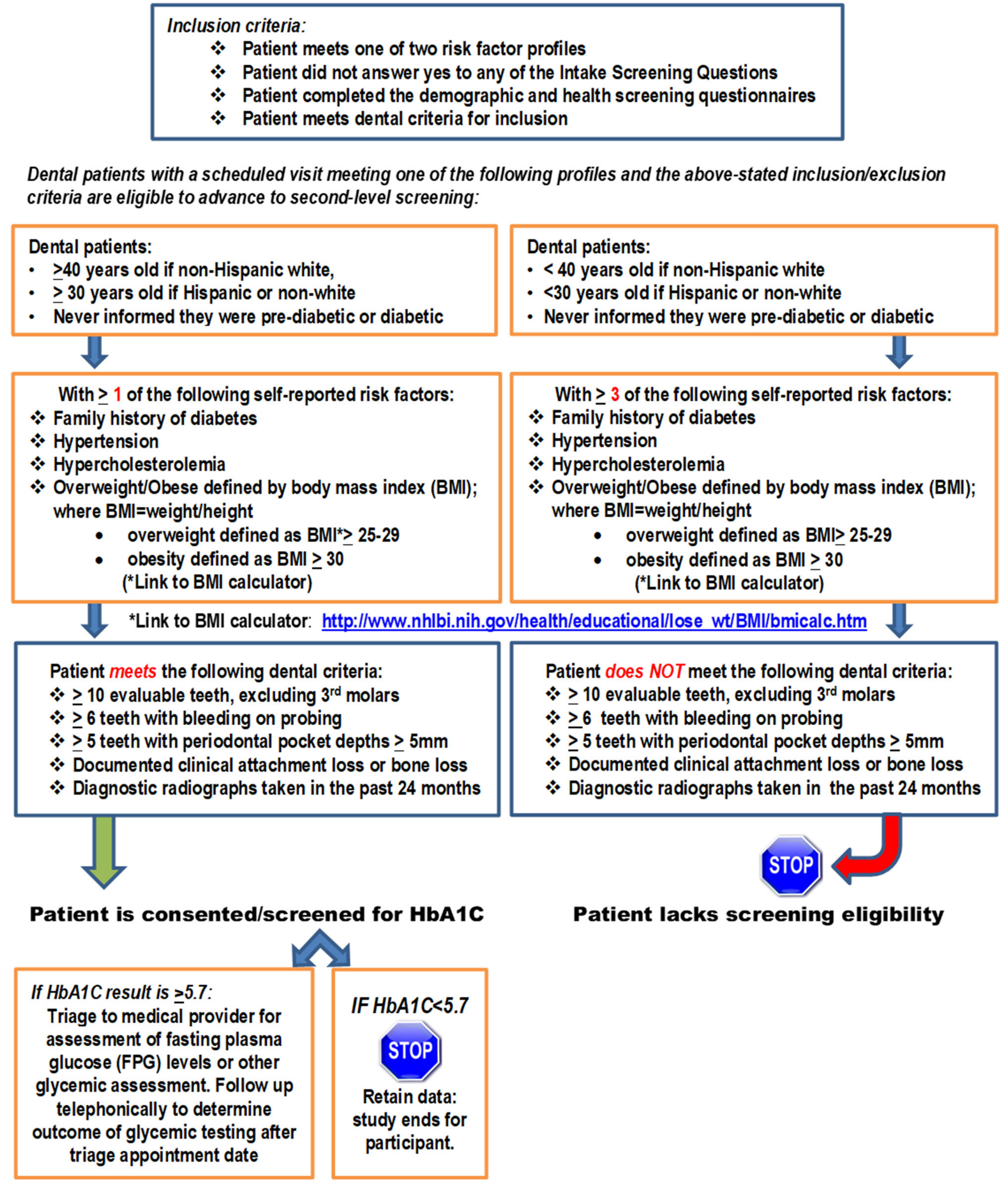

FIGURE 1 | Study flow diagram for study-eligible dental patients.

HbA1c measurement, has FDA approval for CLIA-waived POC HbA1c screening in the clinical setting, and reproduces results of the validated laboratory reference method HA 8160 cationic exchange high-performance liquid chromatography with high fidelity and accuracy [17]. The instrument was supplied to the study team through the 17VNPL DCA

Vantage Analyzer Placement Program [18]. All testing supplies, reagents, and normal/abnormal controls were purchased from the manufacturer.

Sample size estimates were based on targeting of 1,000 patients for initial screening to identify patients with undiagnosed diabetes/prediabetes based on rates reported in earlier field trials examining POC glycemic testing in the dental setting [8] and estimated patient census across the four sites. Enrollment of ∼200 undiagnosed cases was conservatively projected. Enrollment was terminated at 11 months following screening of 915 patients and enrollment of the study-eligible cohort ($n = 224$). Screening was accomplished in two steps. The *Intake Screening Questionnaire* consisting of nine questions was completed by all patients presenting at the participating dental centers to determine eligibility for POC HbA1c screening in the dental setting (Appendix 1). Those who answered "no" to all questions met eligibility criteria and gave written informed consent for enrollment in the study. Enrolled subjects next completed the demographic and comorbidity profile questionnaire (Appendix 2), which consisted of 12 questions, and the American Diabetes Association Diabetes risk test (https://www.diabetes.org/risk-test), which generated a risk score. The final screening step involved capillary collection of blood following a finger stick and analysis of the HbA1c measure by the Siemens DCA Vantage HbA1c Analyzer. Enrolled subjects with measures < 5.7% exited the study, while those with measures ≥ 5.7% were continued for longitudinal observational follow-up for at least 12 months. These subjects first received telephonic follow-up 3 months following HbA1c screening to determine whether they had complied with recommended triage to medical providers for further monitoring of their glycemic status. Follow-up included longitudinal tracking of glycemic measure outcomes or identification of a new prescription for medications associated with glycemic regulation in the medical setting and observation of periodontal assessments and/or other dental procedures in the dental setting. Patients also either underwent periodontal assessment at time of enrollment or had clinical assessments abstracted from the EHRs if they had been evaluated within 3 months of study enrollment. Assessment criteria included documentation of bone loss, attachment loss, and moderate-to-severe PD based on updated definitions of PD classification defined by the American Academy of Periodontology (AAP) Task Force [19]. **Figure 1** summarizes parameters applied to ensure stringency regarding documentation of PD. Patients were required to have a minimum of 10 evaluable teeth excluding third molars. Further requirements included documentation of the following: ≥6 with bleeding on probing, ≥5 teeth with periodontal pocket depth (PPD) ≥ 5 mm, and evidence of clinical attachment loss ≥ 3 mm or >16% (≥3-mm bone loss) based on diagnostic radiographs captured within the past 24 months as defined by AAP classification definitions [18]. Data on number of missing teeth were also collected.

Analytical Approach

Data were summarized to characterize participant characteristics and study outcomes relative to glycemic measures. HbA1c values defined by American Diabetes Association were used to classify normal range (<5.7%), prediabetic range (≥5.7–6.4%), and diabetic range (>6.4%) [20]. Outcomes of study subjects with measures ≥ 5.7% and rate of access to medical and dental care and glycemic measures captured in the EHR were also tracked over time to determine integrated care access. Due to small numbers of subjects with measures in the diabetic range, these patients were pooled with those in the prediabetic range for statistical comparisons Fisher's exact test was used for comparisons of categorical characteristics (e.g., gender), and the Wilcoxon rank sum test was used for comparisons of numerical characteristics (e.g., age).

TABLE 1 | Descriptive characteristics of screened cohort.

	Study eligible?	
	No ($n = 93$)	**Yes ($n = 127$)**
Mean age (years)	32.3 ± 9.5	51.1 ± 13.3
Male	30.1%	35.4%
White race	76.3%	68.5%
Hispanic	6.5%	19.7%
Hypertension	6.5%	35.4%
Hypercholesterolemia	2.2%	36.2%
Mean BMI	28.5 ± 8	30.9 ± 7.9
History of smoking	59.1%	49.6%

BMI, body mass index.

RESULTS

Population Characteristics

Across the four CHC-DC sites, a total of 915 patients were initially approached to identify 224 (24%) with no existing diagnosis of T2DM/prediabetes or glycemic evaluation in the past 6 months. Following exclusion of four individuals, 127/220 (58%) met criteria for potential risk for undiagnosed T2DM/prediabetes and underwent further screening and POC HbA1c testing. Characteristics of the screened cohort are summarized in **Table 1**. Screening for risk factors selected a cohort characterized by older age and higher frequency of Hispanic ethnicity.

Among study-eligible subjects ($n = 127$), 100% underwent POC HbA1c screening. Results of HbA1c shown in **Table 2** found that 62/127 (49%) of the subset of potentially at-risk patients had POC screening HbA1c values ≥ 5.7%, with 55/62 (89%) and 7/62 (11%), exhibiting measures in the prediabetic and diabetic ranges, respectively. Subjects with HbA1c measures above normal ranges were somewhat older and showed some differences in established risk factors, but our numbers in the diabetic range were too small ($n = 7$, with HbA1c > 6.4%) for definitive comparisons.

Observations Across Dental Variables

Among enrolled subjects, periodontal assessments within 3 months or at time of enrollment were captured for 100/127 (79%) of at-risk subjects who underwent POC HbA1c screening in dental settings. **Table 3** shows outcomes of the periodontal assessment stratified by glycemic status indicated by outcome of POC HbA1c screening measures, including percent of subjects with bone loss, attachment loss, and moderate-to-severe PD

TABLE 2 | Outcomes of POC HbA1c screening summarized by participant characteristics.

	Normal[#] (***n*** = **65**)	**Pre-DM**[##] (***n*** = **55**)	**DM**[###] (***n*** = **7**)	***P*-value**[a]
Mean age (years)	48.9 ± 13.3	53.5 ± 13.5	51.9 ± 9.5	0.035
Male	30.8%	34.5%	85.7%	0.273
White race	70.8%	65.5%	71.4%	0.703
Hispanic	18.5%	20.0%	28.6%	0.824
Hypertension	36.9%	30.9%	57.1%	0.853
Hypercholesterolemia	35.4%	34.5%	57.1%	0.856
Mean BMI	29.9 ± 8.5	31.8 ± 7.3	32.8 ± 6.0	0.091
History of smoking	58.5%	40.0%	42.9%	0.051

[a]Test result comparing normal to pre-DM pooled with DM. Percentage of participants meeting PD definitions is shown for each subset of patients classified by HbA1c screening outcomes reflecting glycemic status as defined by the American Diabetes Association: normal range[#] (<5.7%), prediabetic range[##] (≥5.7–6.4%), and diabetic range[###] (>6.4%) [19]. Data in this table were based on self-reported responses completed by eligible participants at time of enrollment in response to the questionnaires (see Appendices).
POC, point-of-care; HbA1c, hemoglobin A1c; DM, diabetes mellitus.

TABLE 3 | Dental measures as available for cohort with POC HbA1c screening data.

	Normal[#] (***n*** = **50**)	**Pre-DM**[##] (***n*** = **45**)	**DM**[###] (***n*** = **5**)	***P*-value**[a]
Attachment loss	76.6%	82.5%	100%	0.434
Bone loss	70.2%	85.7%	80.0%	0.136
Moderate/severe PD	31.1%	43.6%	80.0%	0.132
Mean number of missing teeth	5.4 ± 6.4	5.7 ± 6.0	3 ± 2.2	0.777
Mean bleeding on probing	5 ± 6.8	4.4 ± 5.3	11 ± 9.0	0.660

[a]Results of statistical evaluations comparing normal with pre-DM pooled with DM. Definitions of criteria used to define moderate-to-severe PD for study participants: patients were required to have a minimum of 10 evaluable teeth excluding third molars. Furthermore, documentation of the following parameters was required: ≥6 teeth with bleeding on probing, ≥5 teeth with periodontal pocket depths (PPDs) of ≥5 mm, evidence of clinical attachment loss ≥ 3 mm, or ≥16% (≥3 mm) bone loss based on diagnostic radiographs captured within the past 24 months, as defined by AAP classification definitions [18]. Data on number of missing teeth were also captured. Percentage of participants meeting PD definitions is shown for each subset of patients classified by HbA1c screening outcomes reflecting glycemic status as defined by the American Diabetes Association: normal range[#] (<5.7%); prediabetic range[##] (≥5.7–6.4%); and diabetic range[###] (>6.4%) [19].
POC, point of care; HbA1c, hemoglobin A1c; DM, diabetes mellitus; AAP, American Academy of Periodontology; PD, periodontal disease.

based on updated definitions of PD classification defined by the AAP Task Force [19]. Although the differences were not statistically significant, subjects with elevated HbA1c measures showed higher levels of PD than those with normal measures across all three periodontal parameters assessed.

Longitudinal Follow-Up

At 3 months, 90% of subjects who had undergone biological screening with HbA1c measures ≥ 5.7% participated in telephonic follow-up. At follow-up, 79% reported having attended or scheduled appointments with medical providers. Longitudinal follow-up for ≥12 months (range: >12–24 months) by monitoring glycemic measures and prescription data for pharmaceuticals targeting glycemic control was possible for 44/127 (35%) of subjects enrolled at FHC-M dental centers or the Bridge Community site, who also accessed medical care through MCHS. As shown in **Figure 2A**, mean glycemic measures determined in the medical setting in patients with HbA1c measures in the normal range captured at POC in the dental setting were lower than mean of measures for those subjects whose screening measure captured at POC in the dental setting was ≥5.7% (5.6 vs. 6.2%, respectively). A trend toward higher prevalence of missing teeth was also noted among those with POC HbA1c measures ≥ 5.7% (**Figure 2B**).

The integrated medical–dental EHR (iEHR) was screened from time of enrollment to up to 24 months to capture any new laboratory data indicating glycemic screening. During the 24 months of follow-up, 153 glucose measures across the 42 patients were documented in the iEHR (mean = 3.6 measures per patient; range: 1-16 measures). Comparing results of POC HbA1c measures at time of enrollment and at time of first follow-up glycemic measure (HbA1c or fasting plasma glucose), elevated glycemic status at screening was corroborated in 32/44 (73%) of subjects. Notably, fasting and random glucose measures were more routinely performed to monitor at-risk patients and were available for 42/44 patients. For two patients, only pharmaceutical exposures to medications indicating glycemic management were available for follow-up. Observation of glycemic data for >12 months (up to 24 months) was possible for 29/42 (69%) of subjects being followed up for whom laboratory values were available. Among 4/127 participants (3.1%), a new diagnosis of T2DM was validated based on confirmation of glycemic measures during longitudinal follow-up, assignment of new diagnostic code, and/or newly prescribed medications for glycemic control. Among the 23/44 patients with screening measures in the prediabetic range for whom longitudinal follow-up was possible, prediabetic/diabetic status was validated in 18/23 (78%) of subjects during longitudinal follow-up. An additional six patients who had exhibited high-normal values for POC HbA1c screening measures were found to have measures in the prediabetic range during follow-up.

A trend toward improved glycemic status over time was noted in 20% of subjects in response to pharmacological management and/or lifestyle changes. Patient access for dental management was also trackable for 80% of 44 patients with available data in the EHR. Among these patients, 88% underwent at least one periodontal examination during the 2-year observational follow-up window.

DISCUSSION

Findings Regarding Rate of Hyperglycemic Risk in the Community Health Center Dental Clinic Population

A growing evidence base continues to support that onset and progression of chronic systemic and oral diseases are driven by integrated pathophysiological processes and impact on health outcomes in a holistic manner. In this scenario, simultaneous

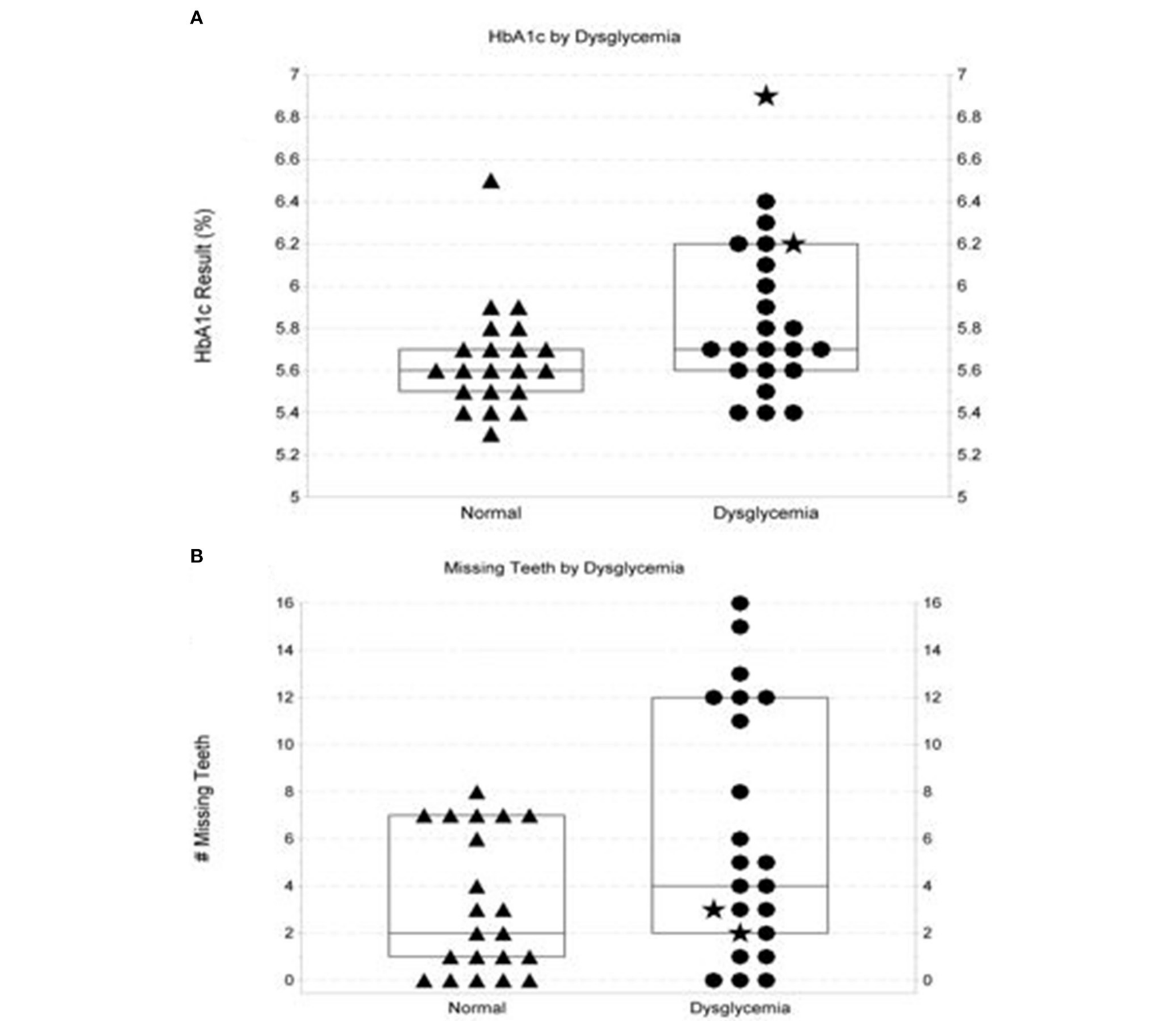

FIGURE 2 | Characteristics of at-risk dental patients with normo-glycemic point-of-care screening outcomes vs. those with outcomes in the pre-diabetic/diabetic range. **(A)** shows distribution of follow-up glycemic measures performed by a commercial laboratory in the medical setting on at-risk patients with normoglycemic vs. elevated glycemic measures when screened at point-of-care. Box plot in **(A)** show the median and interquartile range. Two patients screening in the diabetic range are denoted by ★. The figure shows a trend ($p = 0.054$) for more follow-up measures in hyperglycemic ranges (defined as HbA1c measures $\geq$ 5.7% or fasting plasma glucose measures $\geq$ 100 mg/dL. **(B)** illustrates observations surrounding numbers of missing teeth documented in at-risk patients with initial elevated HbA1c screening measures ($\geq$5.7%) vs. number of missing teeth in those with point-of-care HbA1c measures in the normoglycemic range (p-value = 0.094). Box plots in **(B)** show the median and interquartile range. Two patients screening in the diabetic range are denoted by ★.

exacerbation may occur with bidirectional contributions impacting both oral and systemic disease severity especially in the absence of effective integrated intervention. Increasingly, re-evaluation of our health-care delivery models has been advocated with emphasis on evolution of improved integrated medical–dental care delivery models supported by systematic examination to show evidence that such models are cost-effective and actually leverage improved patient outcomes [21]. In the absence of medical–dental integration across the entire spectrum of stakeholders, which may be further confounded by disparities in access experienced by some segments of the population, the potential for contribution to the epidemic escalation of diabetes and PD remains. The current study sought to examine whether one targeted intervention, namely, biological testing for glycemic status in the unconventional primary DC setting that provides health care to populations with overrepresentation of disparity populations, could activate patients to access care by providers practicing in an integrated care delivery environment. Among study-eligible, high-risk subjects with a low track record for glycemic monitoring attending dental visits at CHC-DC who underwent HbA1c screening at POC, the rate of hyperglycemia was 49%. Notably, as seen in **Table 1**, a higher percentage of study-eligible subjects reported comorbidities [hypertension, hypercholesterolemia, and body mass index (BMI) > 30] compared with the screened population whose risk profile did not meet eligibility requirements for POC screening, corroborating previously reported findings regarding high prevalence of multiple comorbidities among patients with diabetes [22]. Moreover, in the subpopulation with elevated glycemic screening measures where longitudinal follow-up was possible, screening results were corroborated for 78% of participants.

Outcomes of Longitudinal Follow-Up

This case study examined longitudinal follow-up in the longest temporal window reported to date (up to 2 years) following implementation of POC glycemic screening in four CHC dental primary care settings to determine impact on patient care-seeking behavior in health-care environments offering integrated care delivery access in the context of dental safety net operations. Implementation of biological screening for hyperglycemia at POC using FDA-approved glucometers in the subpopulation of appointed dental patients meeting high-risk profiles detected a 24% rate of at-risk individuals based on patient survey responses alone. Among this subset, 58% qualified for POC HbA1c screening in the dental primary care setting. Notably, differences surrounding periodontal prevalence in this relatively small study between patients screening in the normoglycemic and hyperglycemic were not statistically significant. Nonetheless, a trend toward higher rates of more advanced PD was noted among subjects with POC HbA1c measures in the prediabetic and diabetic ranges as compared with patients with normoglycemic measures as evidenced by percent of bone loss, attachment loss, and PD severity level across the glycemic strata. Telephonic follow-up at 3 months to monitor subjects' planned compliance with recommended triage for follow-up with a medical provider was possible for 90% of all study participants. Among these participants, all but one patient indicated compliance or planned follow-up. Notably, among the subset of participants where investigators could access data in the iEHR, semi-annual or annual glycemic assessments for up to 2 years post the date of POC screening were documented for 100% of subjects. Moreover, attendance for annual periodontal assessments up to 24 months post-POC testing was also documented for 80% of the subset. Taken together, longitudinal observation documented a change in patient behavior relative to accessing integrated care for glycemic and periodontal assessment, and a high level of patient activation following POC glycemic screening in the CHC-DC setting was observed.

Comparisons With Historical Field Trials Examining Point-of-Care Glycemic Testing in Community Health Center Dental Clinic Settings

In a field trial conducted by Genco et al. [23] that examined feasibility of POC glycemic screening across a range of dental settings, the authors similarly observed that compliance with triage for glycemic monitoring in the medical setting was highest in the CHCs compared with private dental practices (79 vs. 22% ($p = 0.001$). Furthermore, 85% compliance was noted in a CHC with an integrated care delivery model participating in their field trial [23]. Data from the current study corroborate initial findings reported by Genco et al. Notably, Greenberg et al. [24] also found higher rates of acceptance for triage to the medical setting by dental providers among patients attending DCs (86%) vs. private dental practices (76%). A systematic review examining the role of diabetic screening in the dental setting by various stakeholders similarly reported that five studies examining patient opinion surrounding acceptability of diabetic screening in the dental setting unanimously reported high rates of acceptability [25].

PD represents an early complication and harbinger of diabetes/prediabetes [9], emphasizing the need for cross-disciplinary integrated care delivery models. A 2015 study conducted in an outpatient clinic serving low- to mid-income population in Amsterdam treating patients with diabetes in a non-integrated setting conducted a trial targeting improved communication between medical and dental professionals. An alternative model explored in an additional study by these authors included provision of an oral health questionnaire completed by the dentist, and periodontal screening index (PSI) score was supplied to the physician during patient visits to inform patient management as an alternative approach to POC testing. Notably, among patients with moderate-to-high PSI scores, 65% had untreated PD. The study reported that moderate-to-high PSI was moderately more prevalent in 54% of the population with T2DM and in 57% of patients exhibiting obesity, but response rate for questionnaire completion was reported as 41% [26].

These data suggest that some populations may be more responsive to accessing integrated care delivery, although reasons for this are currently unclear and would require further investigation. Given that CHC-DC serve disparity populations with among the highest rates of PD and diabetes, data from the current study and other initial field trials suggest that the clientele of CHC-DC operating as safety nets are motivated to access integrated care delivery that offers affordable access to both medical and dental care for this population. Moreover, such populations are likely to derive the greatest level of benefit given the high prevalence of PD and diabetes documented among disparity populations. However, due to limited sample sizes of studies to date that have been able to observe integrated care access, studies in larger populations across more diverse populations are needed to further test this premise.

Study Limitations

Some study limitations are noteworthy. Longitudinal glycemic and dental follow-up was possible for approximately one third of 44/127 (35%) of study participants who underwent HbA1c screening and was not possible for an additional 35% of patients seen mainly for treatment of dental emergencies at the walk-in St. Elizabeth Ann Seton Dental Clinic in Milwaukee Wisconsin, which does not provide routine dental care to these patients or track their dental history. However, the walk-in St. Elizabeth Ann Seton Dental Clinic patients were responsive to study participation, and 20/44 (45%) of them indicated intent to comply with recommendation for medical follow-up. For the remaining 30% of patients, access to longitudinal follow-up data was not available, although these patients may have sought care in other health-care systems where EHR access was not possible. Whereas, glycemic evaluation for fasting or random glucose measure in the medical setting was available for 95% of patients, follow-up HbA1c measures were only available for 62% of participants. Finally, due to constraints in the sample size in which longitudinal follow-up was possible, further data modeling was precluded.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Marshfield Clinic Health Systems Internal Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IG contributed to study design, drafted the study protocol, data analysis, regulatory paperwork, implemented point-of-care glycemic testing and protocols, and drafted the manuscript. RB performed biostatistical analyses, informed statistical aspects of study design, and edited the manuscript. AP assisted with data management, data set preparation, data analysis, and reviewed manuscript. NS contributed to strategic design of all study objectives, final review, final editing of manuscript, and figure development. AS provided day-to-day oversight of study activities, tracked enrollment, quality checked data entry, developed reports, provided oversight of multi-site project management, fiscal oversight, and review the final manuscript. GN participated in study design relative to operational aspects occurring in the dental clinical setting, facilitated establishment and integration of point-of-care glycemic testing and research activities involving patient examinations into clinical operations, championed the study with dentists and hygienists, and participated in final editing of manuscript. AA initiated the study, obtained and oversaw funding for study support, provided study oversight, lead the study design and activities of the research team, prepared study reports, and participated in final editing of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/froh.2021.670355/full#supplementary-material

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Urban-Rural Disparities in Dental Services Utilization Among Adults in China's Megacities

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Objective: China's dental care system is bifurcated between urban and rural areas. However, very few studies have examined the dental services utilization inequities in China's megacities, particularly in these urban and rural areas. This study aims to examine the urban-rural disparities in dental services utilization among adults living in China's megacities based on the Andersen dental services utilization model.

Methods: This study used data from 4,049 residents aged 18–65 who participated in the "2019 New Era and Living Conditions in Megacities Survey." Multivariate logistic regressions were employed to examine the associations between place of residence and dental services utilization for individuals from ten megacities in China. Predisposing variables (age, gender, marital status, living arrangement, and education), enabling variables (socioeconomic status, occupational status, income, insurance coverage, health attitude, and health behavior), and need variables (self-rated health, oral health status, gum bleeding) were controlled for.

Results: The mean age of the 4,049 adults was 45.2 (standard deviation = 13.0), and 30.4% (n = 1,232) had no dental visits at all. Adults who resided in urban areas were more likely to use dental services [odds ratio (OR) = 1.57, 95% confidence interval (CI) = 1.30 to 1.91] than those residing in rural areas after controlling for key covariates. Factors associated with higher odds of visiting dentists include having a higher income (OR = 1.44, $P < 0.001$), higher education level (OR = 1.53, $P = 0.042$), being covered by insurance for urban residents/employees (OR = 1.49, $P = 0.031$), having a positive attitude toward healthy diets (OR = 1.43, $P < 0.001$), attending regular physical examination (OR = 1.66, $P < 0.001$), having more tooth loss (OR = 1.05, $P < 0.001$), and having frequent gum bleeding (OR = 2.29, $P < 0.001$).

Conclusion: The findings confirm that place of residence is associated with dental services utilization while adjusting for key covariates. Despite rapid economic development in China, many adults had never visited dentists at all. More efforts should be taken to encourage widespread dental care, such as providing more dental coverage and better access to dental care services.

Keywords: urban-rural, oral health, dental care use, dental visit, Chinese

INTRODUCTION

Oral health problems and disorders are common among adults in the Chinese population. According to the 4th National Oral Health Epidemiology Survey conducted between 2015 and 2016 in China, the prevalence of dental caries is more than 90.0% for adults between the ages of 35 and 74 years old [1]. Furthermore, the prevalence of periodontitis among middle-aged adults ranging from 35 to 44 years old is 52.8% [2]. Such oral health diseases and problems are associated with a lack of dental services utilization [3–5]. Moreover, the use of dental care services among the Chinese population is very low compared to those in developed countries [6–10]. Due to its direct association with the persistence of oral health issues, it is important to identify factors associated with dental services utilization in China. The knowledge generated in this area would provide a better understanding of service utilization patterns, assist in designing a cost-effective dental care system and promote policy change in the future.

Despite China's significant economic development in the past three decades, large disparities in income, infrastructure, and social services between urban and rural areas remain. For example, the ratio of urban to rural income was 1.86 in 1985, and it increased to 2.56 in 2019 [11]. According to the Chinese Health Statistics Yearbook of 2018, urban areas had 535 hospitals specializing in dental treatments in 2017; in contrast, rural areas only had 154 dental hospitals. People living in urban areas are more likely to have higher levels of income and education than their rural counterparts, as well as have retirement pensions [12, 13]. Additionally, rural residents encounter barriers in obtaining basic public services and welfare, such as the healthcare system and social security coverage [14]. Such urban-rural disparities impose a significant barrier that hinders individuals residing in rural areas from accessing dental care; studies have generally reported a lower use of dental care services in rural areas [8, 15–17]. Due to the unbalanced development across urban and rural areas, dental health resources, including the dental department and dental workforce, are insufficient and distributed unevenly between the two areas [18]. Although there are no national statistics on the dental care expenses in China, some estimates suggest that 85% of dental care cost is paid out-of-pocket [18, 19]. Rural residents are more likely to postpone dental appointments due to the inaccessibility of dental services and their inability to pay out-of-pocket dental care expenses [7].

The urban-rural divide also exists in megacities that exhibit a higher development level than other areas of China [20]. A megacity is defined as containing over five million residents [21], and under this definition there were 16 megacities in China in 2019 [22]. Unlike developed countries, all of China's megacities are metropolitan regions that include urban, peri-urban and rural land, and all have rural populations within the city boundaries. Because their development level is higher than other parts of China, the urban-rural divide in China's megacities has significantly narrowed with respect to income, education level, housing, and social welfare programs since 1990 [20, 23, 24]. However, the reduced urban-rural income divide does not significantly diminish the urban-rural disparities in healthcare service allocation and distribution [25]. Understanding the dental services utilization in China's megacities is of particular importance because of their mega-sized populations, rapid economic development, and millions of rural migrants without urban household registration status [20]. Nonetheless, very few studies have been conducted on dental services utilization among adults in China's megacities.

This study aimed to address the knowledge gap by examining how dental service utilization was associated with place of residence among adult populations in China's megacities. Based on existing literature on dental services use [6–10], we hypothesized that dental services utilization would be associated with urban area residence after controlling for key covariates.

METHODS

Samples and Data Collection

This study used the data from the "2019 New Era and Living Conditions in Megacities Survey (NELCMS)." This survey is a cross-sectional observational study using a multi-stage, stratified sampling design and focuses on policy issues related to social structure and social mobility among adults in China's megacities. It was conducted in ten megacities in China, including the most economically developed megacities characterized by a Gross Domestic Product (GDP) per capita higher than 134,000 RMB (equivalent to 19,619 U.S. dollars). Namely, the megacities surveyed were Beijing, Shanghai, Guangzhou, Shenzhen, Tianjin, Hangzhou, Chongqing, Chengdu, Wuhan, and Changsha. The questionnaire consists of two volumes, including 418 items. The main contents included the following aspects: demographic characteristics, work and social security, socioeconomic status, living and household conditions, activities of daily living assessment, and health status and behavior habits.

Using the probability-proportional-to-size sampling method, researchers selected participants through four stages: city, community, household, and individual. Forty communities were randomly selected from each city. Twenty-five households were randomly selected from the housing registration database obtained from each community. One individual was randomly selected from each household. The study was approved by the Ethics Committee of Shanghai University (ECSHU 2020–096).

Inclusion criteria for participation were: (a) self-identified as Chinese and able to communicate in Mandarin; (b) full-time residence in this city for more than 6 months in the past year; (c) age between 18 and 65; (d) capable of answering interview questions. In this survey, questionnaires included Volume A and Volume B. Volume A is the core interview that focuses on social mobility and social structure. Volume B covers individuals' health-related questions, such as health status, health insurance, and health care utilization. Participants were randomly selected to complete either Volume A or Volume B. To address the study aim, only participants who completed Volume B were selected.

In full accordance with ethical principles, well-trained interviewers collected the data during in-home interviews in Mandarin. The informed consent was obtained prior to the data collection. The interviews lasted about 45–60 min. To ensure that the questionnaire was reliable and valid, we conducted a pilot

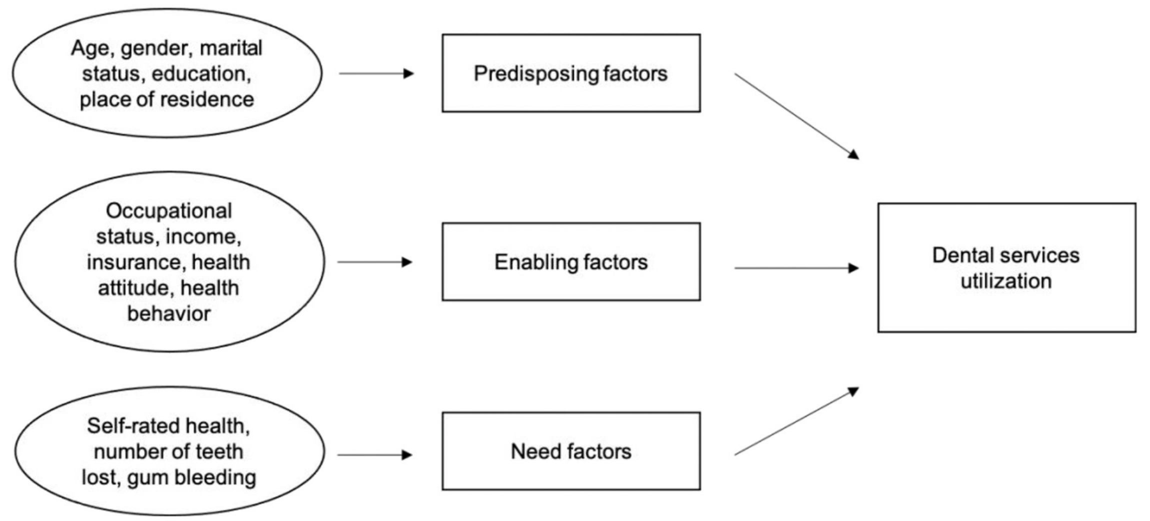

FIGURE 1 | Modified andersen dental services utilization model.

study on 50 adults. Based on their feedback and suggestions, the questionnaire was revised and finalized before the formal data collection. From July 2019 to August 2019, the research team collected data from a total of 5,000 participants who filled out Volume B of the questionnaire. After excluding 815 participants with missing values on the individual's and father's International Socio-Economic Index of Occupational Status (ISEI) and 136 participants with missing values on the study variables, the final analytical sample consisted of 4,049 respondents.

Measures

Dependent and Independent Variables

The dependent variable in our analysis is dental services utilization. The survey asked, "how often do you visit a dentist for dental care?" The responses are the frequency of dental visits (0 = never, 1 = rarely, 2 = less than once every two years, 3 = at least once every 2 years, 4 = at least once a year, 5 = twice a year). Dental care utilization in China is at a very low level; a national survey in 2015–2016 found that 78.6% of adults aged 35–44 and 79.3% of older adults aged 65–74 had not used dental care services in the past 12 months [17]. We therefore dichotomized the responses into 1 = "never" and 0 = "otherwise." The independent variable, place of residence, was dichotomized into 1 = urban or 0 = rural.

Covariates

This study applies the Andersen Healthcare Utilization Model (**Figure 1**) [26, 27] to guide the selection of variables. According to this model, people's use of dental services over a given period is a function of predisposing factors, enabling factors, and need factors.

Predisposing Factors

Demographic information includes age (18–25, 26–30, ..., 61–65 years old, nine categories ranging from 18 to 65), gender (0 = female, 1 = male), marital status (1 = married or living with partner, 0 = otherwise), and education (0 = illiterate/elementary school, 1 = middle/high/vocational school, 3 = 3 years college or more).

Enabling Factors

Early-life and current socioeconomic status include the father's and individual's occupational status determined by the International Socio-Economic Index of Occupational Status (ISEI) developed by Ganzeboom et. al. [28], and individual's annual income (0 = < 78,000 RMB, 1 = ≥ 78,000 RMB). To facilitate interpretation of findings, ISEI were dichotomized into 2 groups [0 = < 54 (low), 1 = ≥ 54 (high)]. Health insurance coverage consists of 0 = no health insurance, 1 = New Cooperative Medical Scheme for rural residents, 2 = Urban Residents Basic Medical Insurance, 3 = Urban Employees Basic Medical Insurance, and 4 = other insurance (mostly commercial insurance). In addition, we measured the respondents' health attitude by asking whether they are concerned about eating a healthy diet. The response was coded as 0 = no, and 1 = yes. Health behaviors were measured by the regularity of attending physical exams (having physical exam once a year, 0 = no, 1 = yes).

Need Factors

Self-rated health was measured by nine questions acquired from the Self-Rated Health Measurement Scale [29]. Each item was scored on a scale of 0–10, with higher values representing better self-rated health. The potential range of the scale is 0 to 90. The Cronbach's alpha for the measure was 0.833, which showed a high internal consistency. Oral health status was determined by self-reported tooth loss (the number of missing teeth), and self-reported gum bleeding (0 = never/hardly, 1 = occasionally/frequently/always).

Statistical Analysis

Post-stratification individual-level sampling weights were used to adjust for differences in the individual-by-household-by-community-by-city distribution between the sample and the general population in the ten megacities in the study [30]. We defined city as sampling unit ($n = 10$), and neighborhood as strata ($n = 40$). All analyses presented in **Tables 1**, **2** and **Figure 2** were adjusted for sampling weight.

We first used descriptive statistics, including proportions and 95% confidence intervals (CIs), to consider the complex sampling and sampling weights. Bivariate analyses were conducted using Chi-Square tests to estimate urban-rural disparities in dental visits. Multivariate stepwise logistic regressions were conducted, according to the Andersen Healthcare Utilization Model [27] and previous literature [16, 31]. We only included the place of residence in the first step (Model 1). In the second step, we entered predisposing factors, including age, gender, marital status, and education. Next, we added enabling factors, which consisted of the father's and individual's occupational class, income, insurance, health attitude, and health behavior (Model 3). In the final Model 4, we added need factors, including self-rated health and oral health status of the participants.

We used margins post estimation to examine whether the urban-rural disparities in dental services utilization were associated with a change in age after controlling for other covariates [32, 33]. We used STATA (Version 15.0) for all statistical analyses. A P-value ≤ 0.05 was considered significant.

RESULTS

The sample characteristics are summarized in **Table 1**. In the weighted analytical sample, 28.23% of urban residents and 17.58 % of rural residents had at least one dental visit per year. In addition, 637 (23.82%) urban residents and 595 (43.27%) rural residents never had any dental visits.

Bivariate analyses did not find urban-rural differences in the distributions of gender, age, and marital status. However, in comparison to residents in urban areas, those in rural areas were less likely to have dental visits [76.18% (urban) vs. 56.73% (rural)]. Rural residents had lower income, lower levels of education, and lower levels of father's and individual's occupational status. Additionally, rural residents were less concerned about eating a healthy diet and less likely to have regular physical exams compared with their urban counterparts. No significant urban-rural difference was found in self-rated health and oral health status.

Table 2 presents the results from the stepwise logistic regression models on visiting a dentist for Chinese adults in megacities. Place of residence had a significant association with dental visits in Model 1 (including the variable on place of residence only) [Odds Ratio (OR) = 2.44, 95% CI = 2.10 to 2.85].

In Model 2, male adults were less likely to visit a dentist (OR = 0.81, 95% CI = 0.69 to 0.95). Education beyond three-year college was significantly associated with dental visits (OR = 2.17, 95% CI = 1.57 to 2.99).

Individuals with a higher level of socioeconomic status (i.e., education, income, and occupational status) were more likely to visit a dentist ($P < 0.05$) (Model 3). Additionally, in comparison with those who did not have insurance, residents with the New Cooperative Medical Scheme (health insurance for rural residents) had similar odds of visiting a dentist. Individuals who were more concerned about a healthy diet and had regular physical examinations were more likely to visit a dentist.

Among need variables, self-rated health was not related to dental visits. In the fully specified model (Model 4), the odds of visiting a dentist were 57.3% higher for urban residents than their rural counterparts (OR = 1.57, 95% CI = 1.30 to 1.91). Moreover, individuals with fewer remaining teeth (OR = 1.05, 95% CI = 1.02 to 1.09) and gum bleeding symptoms were more likely to visit a dentist (OR = 2.29, 95% CI = 1.95 to 2.68).

Adjusting for other covariates (demographics, socioeconomic status, health attitude and behavior, self-rated health, and oral health status), **Figure 2** shows the margins post estimation of predicted probability of visiting a dentist across age groups and by place of residence. Overall, rural residents were less likely to use dental care compared with their urban counterparts in all age groups.

DISCUSSION

This study has provided a better understanding of dental services utilization in megacities by demonstrating that place of residence was associated with dental services utilization while adjusting for key covariates. Data from ten megacities in China were employed, and the individuals' socioeconomic conditions, health insurance, health attitude and behaviors, and oral health status were found to be significant explanatory variables. In addition, the urban-rural disparities in dental services utilization remained regardless of age.

Never visiting a dentist is a common phenomenon among the adult population in China. Our study showed that 30.4% of the respondents had never experienced a dental visit. Furthermore, a study conducted in China using national data found the rates of not visiting a dentist in the past 12 months were relatively high−78.6% for adults aged 35 to 44, and 79.3% for older adults aged 65 to 74 [17]. According to the data from the National Health and Nutrition Examination Survey (NHANES) conducted in the U.S. from 2011 to 2014, 33.8% of adults aged over 30 reported not having a dental visit in the past 12 months [6]. Our study shows that even in these highly economically developed megacities in China, the rate of dental visits is much lower than those in developed or high-income countries [9, 10].

Urban-rural disparities are reflected by the predisposing factors. Affordability of dental service could be another significant reason for the limited dental visits, particularly among residents from rural areas. This is consistent with a study conducted in 14 European countries among older adults that found older adults with lower income were less likely to seek dental care [9]. Our study found that the type of health insurance possessed by an individual strongly associated with dental services utilization. Although the Chinese government has

TABLE 1 | Sample characteristics ($N = 4,049$, weighted).

	Total sample	Residents with dental visits ($N = 2,817$)		Residents with no dental visits ($N = 1,232$)	
	$N = 4,049$	Urban ($N = 2,037$)	Rural ($N = 780$)	Urban ($N = 637$)	Rural ($N = 595$)
	%/Mean (SD)	%/Mean (SD)	%/Mean (SD)	%/Mean (SD)	%/Mean (SD)
PREDISPOSING VARIABLES					
Gender					
Male	46.6	44.1	46.0	51.8	50.3
Age					
18–25	6.3	5.2	8.6	4.4	9.1
26–30	10.7	9.6	14.3	8.3	12.3
31–35	11.8	10.9	12.9	12.4	12.9
36–40	10.8	11.3	11.0	10.6	8.8
41–45	10.3	10.3	10.1	9.0	12.4
46–50	12.0	11.9	12.0	10.7	13.8
51–55	9.7	8.3	10.9	10.6	11.8
56–60	10.8	11.9	7.1	12.5	9.7
61–65	17.6	20.6	13.1	21.5	9.2
Marital status					
Married/living with partner	80.1	79.6	79.7	79.4	83.3
Education					
Illiterate/elementary school	8.7	3.7	14.3	6.4	20.6
Middle/high/vocational school	50.6	43.9	56.1	54.6	62.1
3 years college or more	40.7	52.4	29.6	39.0	17.3
ENABLING VARIABLES					
Father's occupational status (ISEI)					
High (≥54)	31.1	40.3	16.8	36.3	13.1
Individual's occupational status (ISEI)					
High (≥54)	33.3	44.2	24.2	28.4	13.4
Income					
High (≥78,000)	32.2	37.9	31.6	29.7	16.1
Insurance					
No health insurance	8.5	5.6	10.2	10.4	14.0
New Cooperative Medical Scheme	11.1	1.2	25.4	2.2	35.4
Urban Resident Basic Medical Insurance	22.0	23.9	18.9	24.6	16.8
Urban Employee Basic Medical Insurance	51.7	60.6	40.7	56.2	30.8
Other medical insurance	6.7	8.7	4.8	6.6	3.0
Regular physical exam					
Yes	60.7	72.5	54.5	55.0	34.4
Care about eating a healthy diet					
Yes	56.9	64.5	54.9	50.9	40.0
NEED VARIABLES					
Self-rated health					
SRHMS (range:0–90)	61.5 (12.7)	61.0 (12.4)	61.2 (12.4)	61.8 (13.2)	63.1 (13.2)
Tooth loss					
Number of missing teeth (range:0-28)	1.5 (3.3)	1.7 (3.4)	1.5 (2.8)	1.3 (3.4)	1.0 (3.0)
Gum bleeding					
Yes (occasionally/frequently/always)	50.9	56.1	59.1	37.4	36.6

SD, standard deviation; ISEI, international socio-economic index of occupational status; SRHMS, self-rated health measurement scale.

TABLE 2 | Multivariate logistic regression models of having dental services utilization at least once (*N* =4,049, weighted).

	Model 1		Model 2		Model 3		Model 4	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Place of residence (Ref. Rural)								
Urban	2.442***	2.095–2.845	1.731***	1.460–2.052	1.566***	1.299–1.889	1.573***	1.296–1.908
PREDISPOSING VARIABLES								
Gender (Ref. Female)								
Male			0.810**	0.691–0.949	0.773**	0.657–0.909	0.777**	0.658–0.918
Age (Ref. 18–25)								
26–30			1.079	0.726–1.603	1.006	0.680–1.488	0.976	0.658–1.448
31–35			0.909	0.604–1.367	0.855	0.571–1.281	0.819	0.545–1.230
36–40			1.232	0.812–1.871	1.160	0.767–1.756	1.068	0.702–1.625
41–45			1.196	0.780–1.833	1.101	0.719–1.684	1.053	0.688–1.611
46–50			1.359	0.891–2.072	1.270	0.837–1.927	1.146	0.752–1.745
51–55			1.243	0.797–1.936	1.209	0.780–1.873	1.044	0.669–1.631
56–60			1.206	0.784–1.855	1.181	0.771–1.807	0.969	0.627–1.498
61–65			1.504	0.992–2.279	1.485	0.986–2.236	1.185	0.777–1.806
Marital status (Ref. Otherwise)								
Married/living with partner			0.861	0.686–1.081	0.848	0.676–1.064	0.859	0.682–1.081
Education (Ref. Illiterate/elementary school)								
Middle/high/vocational school			1.301	0.988–1.713	1.203	0.910–1.590	1.225	0.913–1.643
3 years college or more			2.165***	1.567–2.993	1.537*	1.082–2.182	1.529*	1.061–2.205
ENABLING VARIABLES								
Father's ISEI (Ref. Low)								
High					1.010	0.844–1.209	1.014	0.844–1.218
Individual's ISEI (Ref. Low)								
High					1.422***	1.167–1.732	1.490***	1.222–1.817
Income (Ref. Low)								
High					1.382**	1.131–1.689	1.438***	1.175–1.760
Insurance (Ref. No health insurance)								
New Cooperative Medical Scheme					1.070	0.765–1.498	1.098	0.775–1.554
Urban Resident Basic Medical Insurance					1.474*	1.094–1.986	1.570**	1.154–2.135
Urban Employee Basic Medical Insurance					1.335*	1.011–1.763	1.383*	1.040–1.838
Other medical insurance					1.608*	1.053–2.455	1.763*	1.147–2.708
Regular physical exam (Ref. Low)								
Yes					1.669***	1.410–1.977	1.661***	1.399–1.972
Care about eating a healthy diet (Ref. No)								
Yes					1.457***	1.238–1.716	1.429***	1.209–1.689
NEED VARIABLES								
Self–rated health (SRHMS)							0.901	0.766–1.059
Tooth loss (Number of missing teeth)							1.053**	1.017–1.092
Gum bleeding (Ref. No)								
Yes (occasionally/frequently/always)							2.286***	1.948–2.682

*OR, odds ratio; CI, confidence interval. Significance level: *p < 0.05, **p < 0.01, ***p < 0.001. ISEI, international socio-economic index of occupational status; SRHMS, self-rated health measurement scale.*

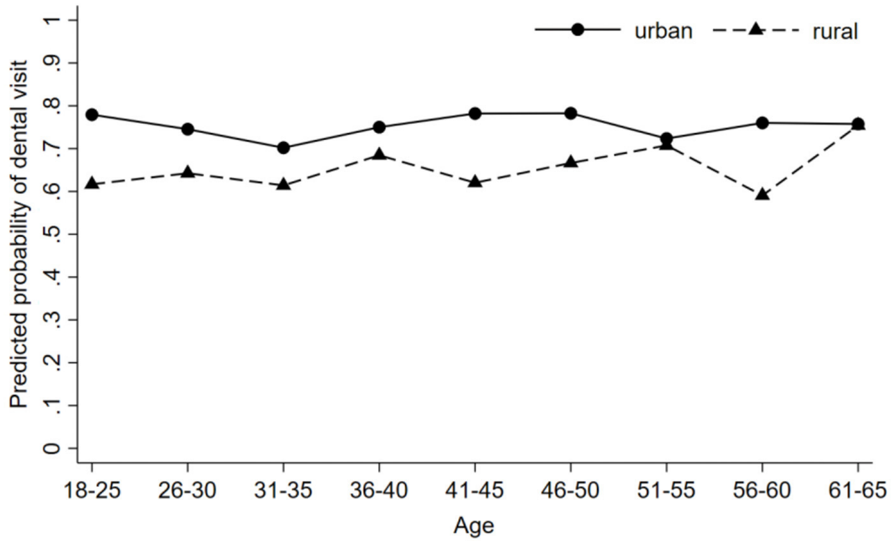

FIGURE 2 | Disparities in predicted probability of having dental visit by place of residence (urban vs. rural) with 95% confidence intervals (N = 4,049, weighted). All estimations include gender, marital status, education, attending the regular physical exam, care about eating a healthy diet, father's occupational status, individual's occupational status, income, insurance, self-rated health, tooth loss, and gum bleeding as covariates.

provided universal basic medical coverage since 2009 [34], no health insurance covers the expenses for preventative oral health services in China. There are still various out-of-pocket costs for dental visits, depending on the type of insurance. Compared with the Urban Resident Basic Medical Insurance (URBMI) and Urban Employee Basic Medical Insurance (UEBMI) for urban residents, the New Cooperative Medical Scheme (NCMS) for rural residents has less medical coverage. The NCMS also has complicated and ambiguous reimbursement procedures [14, 34, 35]. The NCSM covers only partial medical expenses and no dental treatment expenses [36]. This can be reflected in our study, as having NCSM did not increase the odds for dental visits. Thus, expanding dental services with a lower amount of out-of-pocket cost for adults could be a strategy to increase dental services utilization.

Within the enabling factors domain, the present study found that concerning about eating a healthy diet was significantly related to dental services utilization, consistent with previous studies [16, 31]. The Chinese population has a long tradition of attributing oral diseases to the food taken [37]. Oral health literacy has an important role in addressing oral health problems because it is associated with oral health behaviors (e.g., use of dental floss, regular toothbrushing) [38] and oral health-seeking behavior [39]. Similarly, having regular physical exams can reflect individuals' health literacy and health conscientiousness [40]. Adults living in urban areas have easier access to regular physical exams and are more likely to seek dental care. Studies have also indicated that oral health belief was associated with increased dental service use [4, 37]. Although a "National Love your Teeth Day" (September 20th) has been designated by the Chinese government to increase public awareness of oral health since 1989 [41], additional efforts are warranted to enhance public knowledge of oral diseases and problems and the importance of preventive dental visits.

Regarding the need factors for dental care, studies conducted in developed countries revealed that compromised oral health status was negatively associated with preventive dental services utilization [9]. Opposite from these previous findings, our study found that poorer oral health was positively associated with dental visits in China's megacities. Presumably, this contradictory finding could be attributed to the different approaches China and developed countries take in addressing oral health. Chinese dental visits are treatment-oriented and driven by severe dental symptoms, which means that people do not seek dental care unless they feel unbearable toothaches or experience severe periodontal symptoms [7]. On the other hand, in developed countries it is common to have regular dental visits that are prevention-oriented, such as tooth cleaning, dental check-ups, or examination [6]. Another factor could be that cultural attitudes toward oral health are different. Wu et al. [42] suggested that perceptions of oral health and oral health beliefs are embedded in social and cultural contexts. Most Chinese people tend to utilize traditional remedies such as drinking green tea and taking Vitamin C rather than seeking professional dental services for treatments [43].

The strengths of this study reside in its focus on the comparisons between urban and rural residents in China's megacities. This is one of the first studies devoted to revealing urban-rural disparities in dental services utilization among adult populations in China's megacities. This study is also unique in investigating whether the urban-rural disparities vary by age. In China, very few studies have been conducted on inequalities in dental services utilization. Moreover, the data were collected from ten megacities that can represent many regions of the urban areas in China.

There are a few limitations in this study that need to be acknowledged. First, this survey does not contain information on reasons for dental visits (preventive, treatment, or emergency visits), nor the time frame of each individual's dental visits. Second, respondents' health attitude was measured by asking whether they are concerned about eating a healthy diet. The absence of relevant information on oral health attitude is a limitation. Third, given the nature of the cross-sectional data, the possibilities of establishing a causal relationship between dental service utilization and the explanatory variables are precluded. Fourth, data in this study were derived from respondents' self-reports, which may lead to recall bias. Future studies should consider using objective measures of clinical oral examinations and including other factors that might influence an individual's dental services utilization, such as oral health literacy, personal health choices, and psychosocial factors. Furthermore, intervention strategies and related dental policies are warranted to ensure equitable access to and quality of dental services utilization in China.

CONCLUSIONS

This study has extended literature by showing that place of residence is associated with dental services utilization while controlling for key confounding factors using data from ten megacities in China. Despite rapid economic development in China, some adults had never visited a dentist, even in the most economically developed megacities. More efforts should be implemented to improve dental care use by providing more dental care coverage and better access to dental care services.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Shanghai University (ECSHU 2020-096). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XgQ contributed to the acquisition, analysis and interpretation of data, and draft of the article. XnQ contributed to the acquisition, analysis and interpretation of data and draft of the article. BW contributed to the conceptualization and design of the study, interpretation of the results, and draft of the article. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Dentists as Primary Care Providers: Expert Opinion on Predoctoral Competencies

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Dentistry and medicine traditionally practice as separate professions despite sharing goals for optimal patient health. Many US residents experience both poor oral and general health, with difficulty accessing care. More efficient collaboration between these professions could enhance health. The COVID-19 pandemic disclosed further disparities while underscoring concerns that physician supply is inadequate for population needs. Hence, enhancing healthcare provider education to better meet the public's health needs is critical. The proposed titles "Oral Physician" or "Oral Health Primary Care Provider" (OP-PCP) acknowledge dentist's capacity to diagnose and manage diseases of the orofacial complex and provide some basic primary healthcare. The US Surgeon General's National Prevention Council and others recommend such models. Medical and dental education already overlap considerably, thus it is plausible that dental graduates could be trained as OP-PCPs to provide primary healthcare such as basic screening and preventive services within existing dental education standards. In 2018, 23 dental and medical educators participated in an expert-opinion elicitation process to review educational competencies for this model. They demonstrated consensus on educational expansion and agreed that the proposed OP-PCP model could work within existing US Commission on Dental Accreditation (CODA) standards for predoctoral education. However, there were broader opinions on scope of practice details. Existing CODA standards could allow interested dental programs to educate OP-PCPs as a highly-skilled workforce assisting with care of medically-complex patients and to helping to reduce health disparities. Next steps include broader stakeholder discussion of OC-PCP competencies and applied studies including patient outcome assessments.

Keywords: oral physician, primary care dentist, dental student, oral health primary care provider (OP-PCP), oral-systemic, interprofessional education/care (IPE/IPC), dental education, dentistry

INTRODUCTION

Definition of the Problem

Many Americans experience poor health and lack adequate access to care. This is especially true for underserved populations such as low-income and minority groups. Dentistry and medicine practice as separate professions despite their shared missions to optimize their patients' health. Yet more efficient interprofessional collaboration could broaden access to oral and general healthcare, potentially reducing disparities and costs (1–4). Dental team disease screening could save between $42.4 million and $102.6 million in U.S. healthcare costs annually (5). The U.S. Surgeon General's National Prevention Council and others support the use of dentists in primary care roles (6–8). Meanwhile, concerns about lack of an adequate physician supply in the US have only increased during the COVID-19 pandemic.

This paper was submitted in response to a Frontiers in Dental Medicine challenge to "contribute to the development of evidence-based, cost-effective disease prevention and healthcare strategies applicable across diverse populations" on integrating oral and systemic health (9). It evaluates new dental education competency statements for training dentists to provide primary care tasks. To make this curriculum more cost-effective, it proposes to deliver this education during predoctoral education, within existing Commission on Dental Education (CODA) Standards (10). Hence, this educational action step augments recently published aspects of dental and medical integration related to the challenge (3, 4, 11–15).

Oral Health Primary Care Provider

"Oral Physician" or "Oral Health Primary Care Provider" (OP-PCP) are potential titles acknowledging general dentist's prospective expanded roles in basic primary healthcare (16–18). The American Dental Association (ADA) refers to dentists as "doctors who specialize in oral health" (19). The OP-PCP would be an enhanced dental practitioner functioning as part of an interprofessional healthcare team, connected virtually or in-person (20).

When dentists perform a thorough examination of dental patients, they typically assess the patient's blood pressure, and review medical, pharmaceutical, and psychosocial histories. They examine the oral cavity and head and neck, looking for oral diseases ranging from gingivitis to oral cancer. Dentists may detect signs and symptoms of other diseases beyond the oral cavity such as diabetes (21–24), cardiovascular disease (25–27), substance abuse (28, 29), eating disorders (30, 31) and child abuse or intimate partner violence (32–34), among others (35).

At the same time, an increasingly complex patient population requires dentists to become more sophisticated providers with greater knowledge of systemic conditions, and to be familiar with emerging approaches such as precision healthcare, salivary diagnostics, and new medical therapeutics (12). It is within the current legal scope of practice for dentists to diagnose and manage oral manifestations of systemic diseases, and to detect and help prevent systemic manifestations of oral diseases (14, 26, 36).

Appropriately trained dentists could build on these procedures to include some basic primary care in an integrated oral health practice, as described by Myers-Wright and Lamster (1). Expansion of primary screening within dental practice has been shown to be acceptable to the public. For example, random blood glucose testing in the dental office was well accepted by American patients and clinicians (21). Saudi Arabian patients accepted screening for hypertension and diabetes from dentists (37). In response to the pandemic, viral screening and immunizations became part of dentistry's scope of practice in many states (38).

The establishment of OP-PCPs within dentistry could shift dentistry's primary focus from restoring patient's oral health to maintaining their overall health. They could spend more time examining, diagnosing, and counseling patients and less time performing interceptive procedures. As leaders of dental teams, they can selectively delegate care to dental hygienists, expanded function dental assistants, or dental therapists as permitted by law (5, 20) and this could free their time to accommodate this expanded scope. Referral of more complex procedures to specialists makes room for more prevention in their practices an option (20).

Recent Changes and Timelines

The COVID-19 pandemic caused major disruptions in higher education, creating financial and logistical challenges for dental and other health professional schools. As schools struggled to provide adequate patient experiences while maintaining infrastructure and meeting other requirements, challenges led to innovation.

At the University of Washington (UW), the advent of the pandemic coincided with the construction of a new interprofessional health sciences education building, sparking new interprofessional bonds. The Health Sciences deans designed the building together to foster shared education and began planning a merged core curriculum in which dentistry is an equal partner with the other health professions. With the pandemic, scope of dental practice was already changing at the policy level. In Washington, dentists were permitted to prescribe or administer coronavirus screening (39). UW School of Dentistry successfully proposed that the state allow dentists, dental students, and dental hygienists to administer COVID-19 vaccines (40). Subsequently all UW health professions schools attended hands-on vaccination trainings together (with some dentist-trainers).

Immunization and disease testing by dentists are not new concepts. In 2005, Illinois Public Act 49-409 gave dentists status as "emergency dental responders" (Illinois Public Act 99-0025 changed this term to "dental responders") who could provide emergency medical care, triage, and immunizations during a disaster if appropriately certified (41). Illinois dentists were authorized to provide influenza vaccines in 2016 (41) and Oregon has permitted dentists to vaccinate patients since 2019 (42). The US Public Readiness and Emergency Preparedness (PREP) Act extended COVID-19 vaccinator status to all US dentists, dental students, and dental hygienists in 2021 (43). Similarly, the pandemic led to approval and expansion of telehealth services, including certain tele dentistry services.

Beyond vaccination, the broader concept of training pre- and/or postdoctoral students in additional skills for primary care has received national attention within the profession. The American Dental Education Association's (ADEA) 2021 Annual Session featured a Chair of the Board Symposium entitled *A Two-way Street: Primary Care and Oral Health Integration Training* with speakers from Harvard's Center for Integration of Primary Care and Oral Health. A key takeaway was that "the integration of oral health and primary care won't happen overnight, but it won't happen at all if we do nothing" (44). Previous ADEA panel sessions have examined curricular innovations to foster integrated mastery of biomedical concepts (45).

CODA determines the minimum competency standards that graduating dentists must meet but does not dictate how dental schools teach skills or measure competency (10). Thus, as long as it meets existing CODA Standards, an accredited predoctoral dental education program may require its graduates to demonstrate competency in standards that exceed this national benchmark–such as assuring competency in expanded roles in basic, primary healthcare. The intention of this project was to evaluate the feasibility of developing a new curriculum to provide such training in pre-doctoral dental programs, beginning at the level of expert opinion, the base of the evidence-based pyramid (46).

Purpose

The purpose of this study was to gain expert opinion about whether a pre-doctoral dental program could train its dental graduates as OP-PCP to competently provide primary healthcare in a specific set of proposed professional activities while the program remained in compliance with existing dental competency standards of the Commission on Dental Accreditation (CODA).

METHODS

Study Design

This expert opinion elicitation process (47) was a component of an Institutional Action Project for the Executive Leadership in Academic Medicine (ELAM) program at Drexel University by one author (SG). The study was deemed exempt from the institutional review board (IRB) human subject research review at UW.

Participants

The expert opinion elicitation took place between January and May 2018, engaging a convenience sample of educators in healthcare professions. The participant pool was structured to provide diversity by including different academic positions, areas of expertise, sex, and geographic location. Most participants were invited while attending the annual session of ADEA, where the chair-elect of the Section on Academic Affairs/Academic Deans (SG) was able to meet educational leaders face-to-face, explain the project, and request their participation. Some participants were added before and after the meeting to provide more range in expertise and teaching positions. Those who agreed to participate could respond in their preference of format: by email *via* questionnaire or discussion (SG), or through a verbal discussion (SG) by telephone or in-person.

Questionnaire Development

Sources representing expectations for dental and interprofessional competency were initially examined to create a list of professional skills an OP-PCP would need: *Standards of the Commission on Dental Accreditation* (10), *American Dental Education Association (ADEA) Competencies for the New General Dentist* (48), and *Interprofessional Education Collaborative (IPEC) Core Competencies for Interprofessional Collaborative Practice* (49). The competency statements in these three documents were grouped by content similarities. This revealed skills that an OP-PCP might need, which might not be covered or stressed in current dental education.

Each skill that a dental program could adopt to train OP-PCPs was restated in order to describe the level of competency proposed for new OP-PCP graduates. For some new skills, several alternative competency statements were proposed to determine how far the experts felt scope of practice should extend. All skills were examined to see whether they corresponded to any existing CODA standards. Then they were framed in a questionnaire, reviewed by study collaborators, and adjusted for content and clarity. In the final questionnaire, each respondent indicated whether they agreed with each proposed OP-PCP competency statement and optionally provided comments.

Data Analysis

As the intent was to collect qualitative data for a convenience sample of experts, the data were viewed at response distributions without statistical testing. These response distributions were categorized by two investigators as "agree/yes," "disagree/no," or "conditionally agree" (supported by comments). For questions requiring professional knowledge of clinical procedures (correlating with CODA Standard 24), only clinicians' responses were included. The investigators categorized comments into one of three groups: editorial directions for rewording or rewriting the proposal; affirmative statements, in which the respondent expressed enthusiasm; and conceptual/contextual observations or questions. The investigators (LM and SG) discussed any disparate categorizations to finalize this classification.

RESULTS

All proposed OP-PCP competency statements corresponded with existing CODA standards. These statements, grouped with their related CODA Standards, are presented in **Tables 1**, **2**, separating Standard 2-24 from the others. Respondents proposed three additional OP-PCP competency statements that also corresponded with existing CODA standards.

The convenience sample of experts captured distributions by sex, US location, professional field, academic role, and survey method (**Table 3**). No statistically significant differences were found among the characteristics when assessed by sex, professional field, or academic role (data not shown).

TABLE 1 | CODA Standards (CS) except CODA 2-24, and related Proposed Competency Statements (PCS) for Oral Physician - Oral Health Primary Care Provider (OP-PCP).

STD number	CODA Standard (CS) and Proposed Competency Statements (PCS)
CS 2-10	**Graduates must be competent in the use of critical thinking and problem-solving, including their use in the comprehensive care of patients, scientific inquiry and research methodology.**
PCS 2-10-1	OP-PCP graduates must be competent in performing clinical case reviews individually and in interprofessional healthcare teams.
CS 2-11	**Graduates must demonstrate the ability to self-assess, including the development of professional competencies and the demonstration of professional values and capacities associated with self-directed, lifelong learning.**
PCS 2-11-1	OP-PCP graduates must be competent in routinely self-assessing progress toward overall competency and individual competencies, considering needs for interprofessional as well as oral health knowledge.
PCS 2-11-2	OP-PCP graduates must be competent in educating others about health, including clinicians from other health professions, using critical thinking and feedback techniques.
CS 2-14	**In-depth information on abnormal biological conditions must be provided to support a high level of understanding of the etiology, epidemiology, differential diagnosis, pathogenesis, prevention, treatment and prognosis of oral and oral-related disorders.**
PCS 2-14	OP-PCP graduates must be competent to identify the etiology, epidemiology, differential diagnosis, pathogenesis, prevention, treatment and prognosis of oral, orofacial, and major systemic diseases that present in clinical care.
CS 2-15	**Graduates must be competent in the application of biomedical science knowledge in the delivery of patient care.**
PCS 2-15-1	OP-PCP graduates must be competent in describing a plan to regularly update their knowledge of advances and changes in modern biomedical sciences that apply to their clinical practice.
PCS 2-15-2	OP-PCP graduates must be competent in establishing a plan to regularly review "best practice" standards with their clinical team, including oral health standards with the general health team, and all relevant health standards with the oral health team.
CS 2-16	**Graduates must be competent in the application of the fundamental principles of behavioral sciences as they pertain to patient-centered approaches for promoting, improving and maintaining oral health.**
PCS 2-16-1	OP-PCP graduates must be competent in the use of effective techniques to discuss sensitive or embarrassing topics with patients, in delivering difficult news in a respectful manner, and in communicating with patients who are angry, fearful, sad, or otherwise highly emotional.
PCS 2-16-2	OP-PCP graduates must be competent in the use of nutritional counseling to promote, improve, and maintain oral and systemic health.
PCS 2-16-3	OP-PCP graduates must be competent in the use of evidence-based methods, including referral, to help patients rid themselves of unhealthy habits or disorders including those related to food intake, habits, substance abuse, and addictions.
CS 2-17	**Graduates must be competent in managing a diverse patient population and have the interpersonal and communications skills to function successfully in a multicultural work environment.**
PCS 2-17-1	OP-PCP graduates must be competent in communicating and collaborating with patients, families, interprofessional team members, and the public in a respectful and responsible manner to communicate health information and to make healthcare decisions.
PCS 2-17-2	OP-PCP graduates must be competent in working together with local communities, subpopulations, and other members of the interprofessional team to develop, deliver, and evaluate patient/ population-centered care and population health programs and policies that are safe, timely, efficient, effective, and equitable.
CS 2-18	**Graduates must be competent in applying legal and regulatory concepts related to the provision and/or support of oral healthcare services.**
PCS 2-18-1	OP-PCP graduates must be competent in describing the boundaries between dental and medical licensure.
PCS 2-18-2	OP-PCP graduates must be competent in delegating professional responsibilities according to each oral health team member's individual competencies and licensure.
PCS 2-18-3	OP-PCP graduates must be competent in identifying when a patient problem requires consultation with or referral to a member of a different health profession.
CS 2-19	**Graduates must be competent in applying the basic principles and philosophies of practice management, models of oral healthcare delivery, and how to function successfully as the leader of the oral healthcare team.**
PCS 2-19-1	OP-PCP graduates must be competent in accessing and documenting patient information in medical and dental records.
PCS 2-19-2	OP-PCP graduates must be competent in describing how to use medical and dental billing to receive compensation for patient care, as allowed by the laws of the state.
CS 2-20	**Graduates must be competent in communicating and collaborating with other members of the healthcare team to facilitate the provision of healthcare.**
PCS 2-20-1	OP-PCP graduates must be competent in comparing and contrasting the scope of licensure, roles, and responsibilities of the dentist working as a primary care provider with that of the medical doctor, the physician assistant, the nurse, the nurse practitioner, and the pharmacist.
PCS 2-20-2	OP-PCP graduates must be competent in participating in an interprofessional team approach that integrates oral health for the promotion and maintenance of overall health, and the prevention and treatment of disease.
PCS 2-20-3	OP-PCP graduates must be competent in accessing and documenting patient care and communications in medical or dental health records in an organized, accurate, and complete manner.
PCS 2-20-4	OP-PCP graduates must be competent in performing and documenting clear and concise referrals and consultations with other health professionals and follow up in a timely manner.
PCS 2-20-5	OP-PCP graduates must be competent in negotiating consensus on a shared plan of treatment with the other members of the interprofessional healthcare team.

(Continued)

TABLE 1 | Continued

STD number	CODA Standard (CS) and Proposed Competency Statements (PCS)
CS 2-21	**Graduates must be competent in the application of the principles of ethical decision making and professional responsibility.**
PCS 2-21-1	OP-PCP graduates must be competent in describing the ADA ethical principles and applying them to patient cases involving interprofessional healthcare.
CS 2-22	**Graduates must be competent to access, critically appraise, apply, and communicate scientific and lay literature as it relates to providing evidence-based patient care.**
PCS 2-22-1	OP-PCP graduates must be competent in deciding whether new evidence-based advances in biomedical science are pertinent to oral healthcare in their practice, and if they are, creating "best practice" standards which members of their interprofessional health team can use.
PCS 2-22-2	OP-PCP graduates must be competent in explaining evidence-based oral healthcare decisions and policies to their patients and interprofessional colleagues in terms they can understand.
CS 2-23	**Graduates must be competent in providing oral healthcare within the scope of general dentistry to patients in all stages of life.**
PCS 2-23-1	OP-PCP graduates must be competent in assessing the systemic and oral health of infant, child, adolescent, adult, pregnant, and geriatric patients.
PCS 2-23-2	OP-PCP graduates must be competent in provision of appropriate preventive counseling and referrals for the systemic health needs of infant, child, adolescent, adult, pregnant, and geriatric patients.
CS 2-25	**Graduates must be competent in assessing the treatment needs of patients with special needs.**
PCS 2-25	OP-PCP graduates must be competent in assessing the unique care, communication, psychosocial and diagnostic considerations, and treatment needs of patients of any ability, gender, sex, or age, within the scope of general dentistry.
PCS 2-25-1	OP-PCP graduates must be competent in explaining how patients' lives have been shaped by both biologic and psychosocial factors and identify aspects of the patient's abilities and needs that require special consideration by the oral and/or general health team.
PCS 2-25-2	OP-PCP graduates must be competent in identifying and following legal guidelines for reporting neglect and/or abuse of people with intellectual and/or developmental disabilities, special physical health needs, children, elders, and other vulnerable people.
PCS 2-25-3	OP-PCP graduates must be competent in providing a safe and comfortable clinical atmosphere for all patients.
PCS 2-25-4	OP-PCP graduates must be competent in serving patients with special health and/ or psychosocial needs and considerations as the oral health expert on the healthcare team.
CS 2-26	**Dental education programs must make available opportunities and encourage students to engage in service learning experiences and/or community-based learning experiences.**
PCS 2-26	OP-PCP graduates must be competent in serving on the healthcare team in a community-based setting as a primary care dentist or as a general dentist, in order to appropriately assess and address the healthcare needs of patients, and to promote and advance the health of populations.
PCS 2-26-1	OP-PCP graduates must be competent in functioning as a team member in a primary care setting, adapting to the role of dentist or primary care dentist as patient, community, and clinic needs dictate.

Distribution of support for the proposed OP-PCP competency statements showed general acceptance by the experts (**Figure 1**). Diversity of opinion occurred in some proposals associated with CODA Standard 2–24. The broadest range of opinion was seen with alternative competency statements proposed within Standard 2-24-A-1. Respondents considered how far they recommended OP-PCPs should develop skills in patient assessment, especially concerning use of an otoscope (2-24-A-1g) or stethoscope (2-24-A-1i, k, and n), assessing the abdomen (2_24-A-1n and o) or limbs (2-24-A-1n), or performing a peripheral neurologic examination (2-24-A-1q).

Respondents provided 261 comments. Fifty percent were editorial directions, including recommendations for wordsmithing or combining the proposal with another or grouping it with a different CODA standard. Twenty six percent were affirmative statements, agreeing with the proposal. Twenty four percent were conceptual/contextual observations or questions. This third group of comments revealed lack of uniformity in current dental education. Some commentators said certain suggested skills are already being taught and assessed at some dental schools, while others commented that those same skills are unrealistic to teach or impossible to assess. Respondents mentioned obstacles such as scope of practice, lack of time in the curriculum, and challenges in achieving appropriate levels of competency.

Illustrative and notable comment examples particularly occurred regarding 2.24. Proposal 2.24A.1 suggests various elements of an expanded physical examination. One expert commented on their agreement with the entire list, "This will be a big part of training." Another agreed that OP-PCPs should learn to examine the abdomen and commented: "Yes, any relation to having swallowed crown etc.,?" A third's comment on examining the limbs was: "Yes, visual, only if exposed," meaning that the OP-PCP should not, for example, pull up a patient's sleeves or pant legs to examine their patient's arms or legs for dermatologic features supporting a diagnosis of lichen planus or lupus erythematosus.

Proposal 2.24D.1 is that OP-PCP be competent to *provide health promotion and disease prevention plans, strategies, and interventions for oral diseases and for common major systemic diseases*. Comments included, "I am not sure about breadth here either," "I agree with all except interventions for major systemic diseases. This is where referral comes in," and "As written–implies responsibility to treat primarily major systemic

TABLE 2 | CODA Standard (CS) 2-24 only, and related Proposed Competency Statements (PCS) for Oral Physician – Oral Health Primary Care Provider (OP-PCP).

STD number	CODA Standard (CS) and Proposed Competency Statements (PCS)
CS 2-24	**At a minimum, graduates must be competent in providing oral healthcare within the scope of general dentistry, as defined by the school, including:**
CS 2-24 PART A	**… patient assessment, diagnosis, comprehensive treatment planning, prognosis, and informed consent**
PCS 2-24A-1	OP-PCP graduates must be competent in gathering information about the patient and their health including: a. Expanded patient interview b. Generally assess patient status c. Assess of mental status (orientation x 4) d. Assess weight + BMI e. Review medical + dental health records f. Examine skin of face + neck g. Examine head, neck, nose, eyes, ears, throat, + neck *with* the use of specialized equipment (i.e. otoscope) h. Examine head, neck, nose, eyes, ears, throat, + neck *without* the use of specialized equipment i. Assess respiration *with* stethoscope j. Assess respiration *without* stethoscope k. Assess heart *with* stethoscope l. Assess heart *without* stethoscope m. No assessment of abdomen n. Assess abdomen *with* palpation, *with* stethoscope o. Assess abdomen *with* palpation, *without* stethoscope p. Assess limbs q. Peripheral neurologic examination
PCS 2-24A-2	OP-PCP graduates must be competent in selecting, obtaining, and interpreting appropriate clinical tests, blood tests, and diagnostic imaging including salivary testing and assessment, glucose testing, A1C testing, and others as appropriate, including rapid testing for HIV with referral for confirmation and appropriate behavior counseling.
PCS 2-24A-3	OP-PCP graduates must be competent in screening and providing basic counseling and referral for diseases and conditions such as (but not necessarily limited to) these examples listed below: *Blood and Immune:* allergic diseases; anemias; benign and malignant vascular tumors; bleeding disorders; HIV and other immune deficiencies; Kaposi sarcoma; leukemia; lymphoma; neutropenia; polycythemia; others. *Cardiovascular:* angina; arrhythmia; carotid artery calcification; dyslipidemia; hypertension; MI; stroke; transient ischemic attack; others. *Endocrine:* adrenal disease; diabetes mellitus (Perform chairside glucose, a1c); multiple endocrine neoplasia; polycystic ovarian syndrome; obesity; parathyroid pathology; thyroid pathology; Turner syndrome; others. *Genetic and Developmental:* inherited diseases and syndromes, especially those with craniofacial manifestations. *Genitourinary/Breast:* benign prostatic hyperplasia; breast health; candidiasis; family planning; herpes; HPV infection; kidney failure; kidney disease; prenatal care; prostate cancer; renal osteodystrophy; sexually transmitted infections of the oral cavity; urinary frequency; urinary tract infection; others. *Gastrointestinal:* atrophic gastritis; Barrett's esophagus; celiac disease; dysphagia; Gardner syndrome; GERD; inflammatory bowel diseases; others. *Hepatobiliary:* gallstones; hepatitis; jaundice; liver failure; pancreatitis; others. *Musculoskeletal:* bone fractures; bone tumors; muscle tumors; muscular dystrophy; osteogenesis imperfecta; osteopetrosis; osteoporosis; Paget disease; syndromes; others. *Nervous system:* cranial nerve defects; dementia; multiple sclerosis; nerve sheath tumors; neurodegenerative diseases; sensory disorders; syndromes; others. *Psychiatric:* anxiety and depression; cognitive disorders; eating disorders; psychiatric disorders; substance use disorders; suicidal ideation; others. *Respiratory:* asthma; COPD; lung malignancy; oropharyngeal and pharyngeal malignancy; sinonasal polyps; sinusitis; sleep apnea; others. *Dermatologic:* acne; actinic damage; allergic conditions; esthetics; rosacea; skin cancers; syndromes; vesiculobullous diseases; others. *Social:* food insecurity; gender identity dysphoria; homelessness; sexual, physical, self, or emotional abuse; others.
CS 2-24 PART B	**… screening and risk assessment for head and neck cancer**
PCS 2-24B-1	OP-PCP graduates must be competent in selecting and applying diagnostic tests for oral conditions.
PCS 2-24B-2	OP-PCP graduates must be competent in selecting, performing, and submitting simple oral biopsies.
PCS 2-24B-3	OP-PCP graduates must be competent in working with the oncology team to prevent and manage the oral complications of cancer treatment, including chemotherapy, immunotherapy, and radiotherapy.

(Continued)

TABLE 2 | Continued

STD number	CODA Standard (CS) and Proposed Competency Statements (PCS)
CS 2-24 PART C	**… recognizing the complexity of patient treatment and identifying when referral is indicated**
PCS 2-24C-1	OP-PCP graduates must be competent in using a systematic approach to identify a potential systemic condition and identify when consultation or referral is appropriate.
CS 2-24 PART D	**… health promotion and disease prevention**
PCS 2-24D-1	OP-PCP graduates must be competent in providing health promotion and disease prevention plans, strategies, and interventions for oral diseases and for common major systemic diseases.
PCS 2-24D-2	OP-PCP graduates must be competent in providing basic nutritional, safety, and other lifestyle counseling, including administration of vaccinations where permitted by law.
PCS 2-24D-3	OP-PCP graduates must be competent in screening and providing interventions and prevention for patients with addictions and drug dependency, including alcohol, nicotine, and opioids. This includes recommendations regarding availability of opioid reversal agents.
PCS 2-24D-4	OP-PCP graduates must be competent in assessing the patient's medication profile to achieve medication optimization, including consultation with pharmacists, and refer for adjustment of medications not prescribed by dentists.
PCS 2-24D-5	OP-PCP graduates must be competent in detecting and managing patient abuse and neglect, and contributing to prevention efforts.
PCS 2-24D-6	OP-PCP graduates must be competent in functioning effectively as a medical team member in disaster relief efforts.
CS 2-24 PART E	**… local anesthesia, and pain and anxiety control, including consideration of the impact of prescribing practices and substance use disorder**
PCS 2-24E-1	OP-PCP graduates must be competent in diagnosis, prevention, and management of substance use disorder, including that which may arise in association with prescribing practices.

diseases–practicing medicine under current laws." Similarly, 2.24D.4 proposes that OP-PCP be competent to *assess the patient's medication profile to achieve medication optimization, including consultation with pharmacists, and refer for adjustment of medications not prescribed by dentists*. One expert's reaction was, "Too far outside scope." 2.24D.6 proposes that OP-PCP be competent to *function effectively as a medical team member in disaster relief efforts*. One expert commented, "Already should be doing this." Another commented "Must define the role. They cannot do emergency amputations, for example, ☺ [sic]. Need to define this carefully."

Proposal 2.24B.3 for OP-PCP competency is to *work with the oncology team to prevent and manage the oral complications of cancer treatment, including chemotherapy, immunotherapy, and radiotherapy*. One comment hinted at potential for antagonism between specialists and those choosing expanded scope of practice for OP-PCPs: "This is now overlapping with the specialty of Oral Medicine."

DISCUSSION

Expert opinion indicated proposed OP-PCP training is rooted in existing ADEA, CODA, and IPEC competencies, especially interprofessional practice. Experts supported teaching and assessing these skills within the existing framework of pre-doctoral dental education, and felt it was realistic to do so to the "competency" level. They agreed OP-PCPs would require extra education in critical thinking, patient assessment, diagnosis and treatment planning, prevention and health promotion, medical management of conditions already within the scope of dental care, and in certain primary care medical tasks. The respondent's comments, made in 2018, demonstrated a lack of agreement on some details related to scope of practice.

But factors beyond expert opinion are also influencing the practice of dentistry and the shape of dental education. Changes wrought by the pandemic and the evolving recognition of oral-systemic interactions (3, 50) support increased interest in expanding the role of dentists. A growing emphasis on IPE and integration of oral health into primary care is evident in curriculum development, specific funding programs, and other efforts (51–55). Ongoing changes in dentistry and dental education are in keeping with these OP-PCP competency statement proposals: 2.20.2, *participate in an interprofessional team approach that integrates oral health for the promotion and maintenance of overall health, and the prevention and treatment of disease*; 2.24D.2, *perform basic nutritional, safety, and other lifestyle counseling, including administration of vaccinations where permitted by law*; and 2.24D.6, *function effectively as medical team members in disaster relief efforts.*

Barriers to Change: Market Factors

Difficulty obtaining compensation for medical screening and counseling could potentially discourage dentists from primary care despite the obvious benefits to patient's health. Medical insurance coding is different from the claims coding used in dental insurance (56). The range of allowable diagnoses and procedures that can be billed to medical insurance is limited (57). Even if dentists could potentially bill medical insurance for some services, they and their staff are usually not trained to do so. Without compensation, dentists could not feasibly screen for hypertension, diabetes, obesity, missed vaccinations, and other timely primary care tasks. Therefore, Proposal 2-19-2 is that *OP-PCP graduates must be competent in describing how to use medical and dental billing to receive compensation for patient care, as allowed by the laws of the state*. Medical insurers would also need to be willing to compensate them for these additional services.

TABLE 3 | Characteristics of respondents.

Characteristics of respondents	*N*	Percentage
Total	**23**	**100%**
Sex		
Female	12	52.2%
Male	11	47.8%
Geographic location		
US East Coast	5	21.7%
Mid-US	9	39.1%
US West Coast	8	34.8%
Non-North American	1	4.3%
Professional Field		
Dentistry	18	78.2%
Anesthesiology	1	4.3%
Dental Hygiene	1	4.3%
Dental Public Health	2	8.7%
General Practice Dentist	4	17.4%
Oral Medicine w/wo Oral Radiology	4	17.4%
Oral Pathology w/wo Pediatric Dentistry	5	21.7%
Pediatric Dentistry	1	4.3%
Non-Dentistry	5	21.7%
Medicine (GI, Internal Med, Pediatrics, Psych)	4	17.4%
Educational Psychology	1	4.3%
Academic Role		
Administrator	14	60.9%
Faculty Member	9	39.1%
Survey Method		
Written Form	11	47.8%
Email Contact	7	30.4%
Verbal Interview	5	21.7%

Integrated dental and medical systems may provide the ideal setting for the OP-PCP (14, 54, 58–61). Large systems can institute value-based care models that incentivize desired changes; such models already occur in the dental marketplace. The rise of dental service organizations can also facilitate value-based changes, and their acquisition by larger health insurers. Larger health systems can feature interoperable electronic health records (E.H.R.) which improve collaboration and communication, reduce discrepancies and misunderstandings, and facilitate medical billing for dental care (62). Proposals 2-20-1, 2-20-2, 2-20-3, 2-20-4, and 2-20-5 describe competencies an OP-PCP must have to function successfully in such an integrated care setting.

Barriers to Change: Professional Identity

The self-identity of dentists is a barrier to change, whether by a new label or changing dentist's roles without re-branding them (63, 64). The increasing medical complexity of patients and broad calls for action to address systemic conditions such as hypertension (65) and diabetes (66) point to issues in which dentists could play a larger role. Nevertheless, dentistry retains a relative emphasis on technical skills (evident in the lengthy

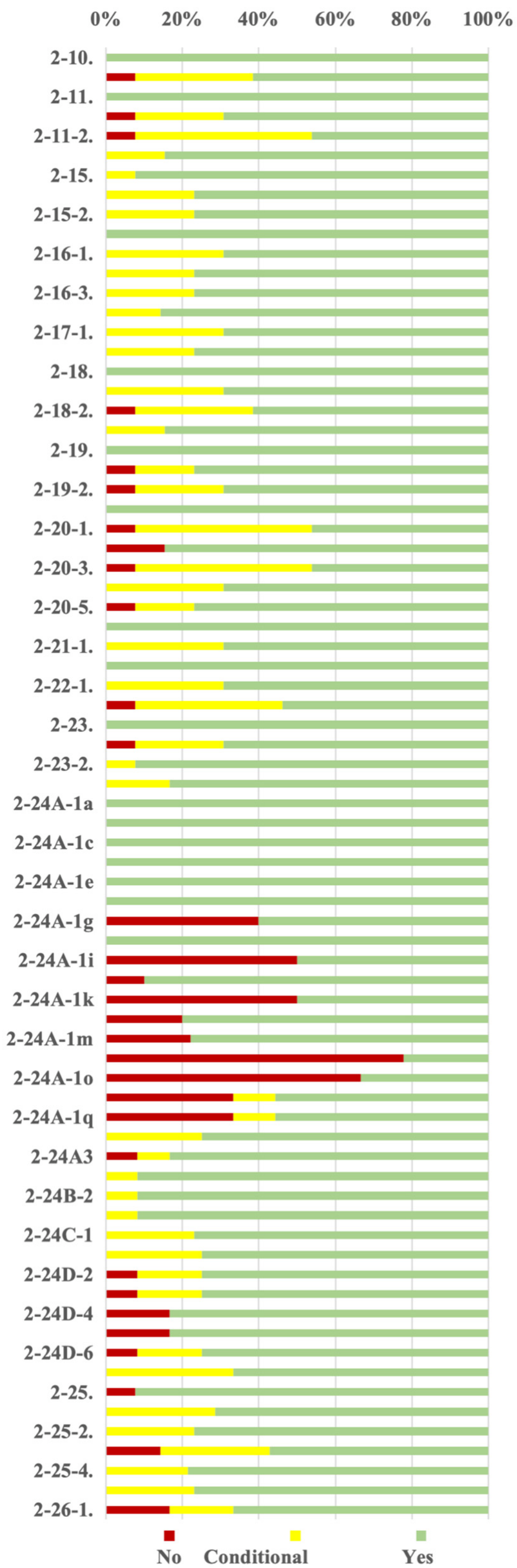

FIGURE 1 | Distribution of support for Proposed Competency Statements (PCS) for OP-PCP related to CODA Predoctoral Standards 2–10 to 2–26 [-separate file].

CODA Standard 2-24). Reluctance to cut any traditional skills to make way for new ones is likely.

It may be more difficult to convince dental students of the value of OP-PCPs than it would be to convince their patients (21, 36, 67, 68). Students enter school with expectations about being a dentist that don't include "primary care" tasks. They may say to themselves, "If I wanted to do that, I would have gone to medical school" (63, 64). Over the years, ADEA student surveys have shown that the top reasons students choose dentistry are personal dental experiences (54%), the influence of a family member or friend who is a dentist (38%) and the influence of their family dentist (33%) (69). Current models of dental practice, which have been slow to change, set expectations for students. However, recent events described already could influence a change in public and student expectations.

Barriers to Change: Cost of Dental Education

Given the high costs of dental education (reflected in tuition and high student debt), funding new programs will always be challenging. Dental school clinics operate primarily to train students and require a high faculty-to-student ratio. This model is less fiscally efficient than medical training that is embedded within hospitals and other clinical practice sites.

Dental schools are also typically safety net providers. While Medicaid covers pediatric dental care, adult dental benefits under Medicaid vary substantially between states, some states lacking them entirely. When money is tight, states often discontinue adult dental benefits. Traditional Medicare has no general dental benefit and Medicare Advantage Plans vary in coverage. Dental residencies with significant hospital-based training such as oral surgery or pediatric dentistry receive Graduate Medical Education (GME) funding but that money goes primarily to the hospitals, not the hospitals (70).

Students may be reluctant to participate in OP-PCP training if it would require additional time in dental school because 83% of dental students graduate with educational debt, averaging $304,824 in 2020 (71). Therefore, this proposal adapts predoctoral education within existing length of training. IPE could also advance this goal. If medical, dental, and nursing students all learned blood pressure measurement together, they would have greater confidence in each other's skills as future health professionals. Among others, Proposal 2-11-2, *educate others about health, including clinicians from other health professions, using critical thinking and feedback techniques* promotes this collaboration.

Barriers to Change: Scope of Practice

State laws govern the scope of practice of dentistry and other health professions. Changes in law allow healthcare practitioners, including faculty and students under their supervision, to perform tasks such as vaccinations and point of care diagnostic testing and counseling for systemic diseases (19).

For an expanded scope of dental practice to be successfully implemented, the profession would need to clearly define the desired scope of practice for the OP-PCP and achieve consensus on that definition. As Mathews [(72) Mathews 2010] mentions, this requires buy-in from all specialties. It would also be more likely to succeed if the change were supported by medical colleagues and those in other health professions. Such a conversation needs to begin somewhere, and the proposals presented to the experts in this project were aimed to begin such a discussion. Standard 2–24, the group of competency statements that lists specific clinical procedures, sparked the greatest diversity of opinion among the experts, as it was designed to do. Examples of comments provided by the experts, shared in the results, illustrate the need for further discussion and consensus on the scope of practice. Issues to be addressed include boundaries with dental specialties and other healthcare professions. Graduates would need to be cognizant of those limits, hence Proposal 2-18-1 is that *OP-PCP graduates must be competent in describing the boundaries between dental and medical licensure.*

Of relevance, historical changes that allowed advanced practice registered nurses (APRNs) and nurse practitioners (NP) in several states to be recognized as primary care providers are instructive. Such changes occurred in Massachusetts through legislation that recognized NPs as primary care providers (73). In Hawai'i, APRNs successfully introduced legislation to remove "barriers to full utilization of APRNs as primary healthcare providers with global signature authority and with prescriptive authority for controlled substances, medical equipment and therapeutic regimens in accordance with their scope of practice" (72). Key factors for a successful collaborative initiative were a comprehensive approach including all APRN specialties; key political champions who grasped the healthcare issues; the excellent reputation of APRNs; continuous communication and willingness to compromise on issues; and the support of nursing educators (72).

Limitations

This assessment is limited in its very nature, by design. Baseline expert opinion is challenging to acquire, especially using a grassroots, unfunded mechanism, yet it is valid to elicit opinions from a group of experts at the beginning of a bold new educational endeavor. The convenience sample is not generalizable to "population" but represents a valuable range of opinions. The expert opinion participant group had representation from females, males, deans, faculty members, and experts with geographic dispersion. The group included various ADA recognized dental specialty areas (74) whose definitions emphasize focus on patients or populations as opposed to procedures or specific anatomy.

Limitations of expert opinion are multifold. Foremost is the reliance on opinion versus synthesis of peer-reviewed scientific evidence. A high level of consensus was achieved in this one-round process, lending prima facie credibility to the findings. Nevertheless, this expert opinion assessment's function is simply to provide a starting point from which to define competencies for the OP-PCP, as demonstrated in similar processes in other professions (75). Further independent work based on this study is needed to progress toward finalizing OP-PCP educational competencies.

Next Steps

To become competent OP-PCPs, dental students would need authentic clinical experiences (76). Thus IPE must extend beyond didactic, simulation, and project-based learning, to include immersion in authentic collaborative clinical care settings where dentists function as OP-PCP (76–78).

Dental educators would need appropriate knowledge, skills, and attitudes to teach potential OP-PCPs. Many dental specialists in oral medicine, oral pathology, and oral surgery already have this expertise. Collaboration with other health professions education programs could help meet this need. Video teleconferencing could allow for more efficient faculty development across sites (76, 77).

Pilot projects could tackle key questions related to the modified curriculum's effectiveness and financial viability. Endpoints should include outcome measures that are student-centered (i.e., pass rates on national licensure examinations or alumni surveys), patient-centered (i.e., satisfaction of patients treated by these students), clinic-centered (i.e., satisfaction of health professionals who work with these students), finance-centered (i.e., differences in their clinical productivity as well as added training costs), and eventually community-centered (for example, improved healthcare outcomes in populations treated by these students and graduates).

CONCLUSIONS

No previous efforts have defined additional spheres of competency that should be required for dentists to function as OP-PCPs. These initial findings by 23 experts provide a platform for further discussion and action among dental and medical educators, policymakers, funders, health systems, patient groups and others. The healthcare system could gain high-quality capacity by using dentists as primary care providers within the scope of dental licensure to improve oral and overall health outcomes and achieve health equity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

SG conceived and designed the study and wrote the first draft of the competency statements and questionnaire. JB and WM reviewed the study design. LK, WM, PB, and CM-K reviewed the competency statements and questionnaire. SG recruited participants and collected comments. LK organized the database and analysis. SG and LK wrote the introduction, methods, results, and conclusions. SG, LK, and WM wrote the abstract. WM, PB, JB, and CM-K wrote sections of the discussion. LK, WM, and SG contributed to manuscript revision. All authors read and approved the submitted version.

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Input From Practice: Reshaping Dental Education for Integrated Patient Care

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Among the primary challenges in advancing the practice of integrated primary dental and medical health care is the appropriate educational and clinical preparation of a dental workforce that can function and flourish within integrated care environments. Most dental schools teach to traditional concepts and standards of dental care delivery which may be inconsistent with those of integrated care and could deter the entry and retention of graduates in contemporary, non-traditional practice models. To better understand how the dental school curriculum should be modified to accommodate integrative care models, a number of patient care organizations actively engaged in dental-medical integration were site visited to gain insight into the readiness of newer graduates, with emphasis on the US DMD/DDS graduate, to function in integrated practice. Leaders, practicing clinicians and staff were interviewed and common observations and themes were documented. This manuscript will focus on those educational components that integrated care organizations identify as absent or inadequate in current dentist education which must be addressed to meet the unique expectations and requirements of integrated patient care. These changes appear pivotal in the preparation of a dental clinician workforce that is respectful and receptive to new practice concepts, adaptative to new practice models, and competent in new care delivery systems.

Keywords: integration, dentistry, medicine, health systems, interprofessional education, dental education

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INTRODUCTION

Predoctoral (i.e., pre-DMD/DDS degree) dental education programs in the United States are in a perpetual mode of revision and adjustment as they attempt to respond to evolving change in society's needs and the practice of general dentistry [1–3]. Although these changes tend to emerge gradually, they are nevertheless real and compel dental schools to reconsider the knowledge, skills, abilities and values, collectively termed "competencies," required by new dental graduates [4]. There are many examples of change in dental practice: shifts in care emphasis from a repair/restoration focus to prevention and early interceptive treatment; growth in multi-provider group and corporate-affiliated practice; increased focus on the social determinants of health; employment of evidence-based decision making in treatment planning; and greater attention on the relationship of oral and overall systemic health. The emergence of new models of care delivery is linked to many of these drivers of change and is perhaps best exemplified in the growth of integrated dental-medical care practice [5].

Some of the changes pursued by dental schools have been self-inspired but many have been prompted by the advocacy of thought leaders and national dental organizations to instill necessary updates in prevailing dental accreditation standards [6–8]. In response to professional and community input, the Commission on Dental Education (CODA) has introduced a number of new standards over the past several decades which, in turn, have prompted dental schools to modify curriculum, clinical practices and community interaction [9]. Several newer standards were informed by the embryogenesis of integrated dental-medical care and the opinion held by many in the profession that its continued development in both traditional and non-traditional models of practice could significantly improve health care outcomes [10, 11]. The following are examples of modified or new accreditation standards that refer to those competencies considered essential in integrated care delivery:

- Standard 2-15: *Graduates must be competent in the application of biomedical science knowledge in the delivery of patient* care[1].
- Standard 2-19: *Graduates must be competent in applying the basic principles and philosophies of practice management, models of oral health care delivery and how to function successfully as the leader of the oral health care team.*
- Standard 2-20: *Graduates must be competent in communicating and collaborating with other members of the healthcare team to facilitate the provision of healthcare*[2].

These and other accreditation standards and intent statements have led to the adoption of new educational approaches in US dental schools. One major initiative has been the development of interprofessional education (IPE) activities wherein dental students at timepoints within the typical four-year DMD/DDS curriculum are brought together in learning experiences with students from the other health professions including but not limited to medicine, nursing and pharmacy [12–14]. The objective is that these students learn together, better understand the relationship with and scope of other health professions, develop interprofessional communication skills and, optimally, co-participate in the coordinated care of patients [15]. Beginning in 2009, several health professions education organizations including the American Dental Education Association (ADEA) began to formally organize around these initiatives leading to the creation of the Interprofessional Education Collaborative, or IPEC, which currently includes 21 national health profession associations. In 2011, the first IPEC competencies were adopted [16], expanding in 2016 to four core competencies described by IPEC as essential for students in the health professions to succeed in interprofessional collaborative practice [17].

Beyond these particular changes, recommendations continue to be voiced on how dental schools can best respond to changes in the needs of society and the emergence of new healthcare systems and models of practice [4]. Schools have been moderately successful in analyzing their success in the implementation of curricular revisions but much less so on the impact of these responses on the preparedness of new graduates to function and succeed within new models of dental care especially those characterized by high levels of interprofessional interaction such as that observed in integrated dental-medical practice [18, 19].

Consequently, this project was undertaken to gain input from leaders of dental care entities with high levels of integrated care activity about the readiness of new DMD/DDS graduates for this unique form of practice.

METHODS

Study Construct

During 2018-2019, the American Dental Education Association (ADEA), under the direction of its Chair of the Board of Directors, initiated the project with the goal to gain a better understanding about how US dental education institutions were currently preparing graduates for integrated care practice and possible areas where improvement in curriculum and/or clinical training was necessary [20]. As an initial step, the authors sought to identify dental practices and health care organizations that were actively engaged in a meaningful level of integrated care activity. The SAMHSA-HRSA Center for Integrated Health Solutions (CIHS) framework for levels of integrated health care [21] served as a reference to assess level of integrated care. Potential practices were identified by conducting literature searches of peer- reviewed publications and abstracts and by scanning conferences proceedings, meeting presentations, professional monographs and marketing materials. Entities appearing to have a moderate-to-high degree of integrated care activity and approaching CIHS's Levels 4-6 of collaboration/integration were targeted (i.e., Level 4- Close collaboration onsite with some systems integration; Level 5- Close collaboration approaching integrated practice; Level 6- Full collaboration in a transformed/merged integrated practice). In total, thirteen entities were identified and then contacted directly for further review. Two entities did not respond, one expressed a low level of interest in the project and three others were considered to have a relatively small amount of integrated activity. Based on initial response and interest in the project, seven entities remained and agreed to participate.

Each practice organization was site visited over a period of 1–2 days by one of the authors (RLMN) and included interactions with directors, care providers and support staff.

In the case of multi-site practices, a representative number of satellite locations were visited along with the primary site of care delivery. Structured questions (**Table 1**) were proposed to the chief administrative leaders. Interviews with clinical providers and auxiliary staff were less formal and more conversational in nature.

[1]Each CODA standard is accompanied by an Intent Statement(s). The Intent Statement within standard 2-15 is that the graduate can "*…integrate new medical knowledge and therapies relative to oral health care*".

[2]An Intent Statement within standard 2-20 is that students should "*... have educational experiences, particularly clinical experiences, that involve working with other healthcare professional students and practitioners. Students should have educational experiences in which they coordinate patient care with the healthcare system relative to dentistry*".

TABLE 1 | Interview guide for integrated care practice leaders.

1. Describe (in common language) the key characteristics of your oral health care delivery approach/model and how it differs from a traditional (large) group dental practice?
2. Was your organization integrated from its inception? If so, what factors drove that integration? If not, when did your organization or group become interested in integration or greater connectivity with the larger health system and why? What were your key drivers? Who were your key "connected" health partners?
3. How are you connected to your other healthcare colleagues, and how do functionally communicate with them?
4. In terms of your initial goals, at what phase are you in your integration efforts?
5. At your current and unique phase of integration or connectivity, what do you see as the major, unique advantages of your delivery approach?
6. How have your integration efforts benefited your patients?
7. How have your integration efforts benefited the dental providers and staff?
8. How have your integration efforts benefited your other health care colleagues?
9. Are the competencies/skills needed by dentists in this system different than that needed in a traditional group practice? If so, what must dental providers bring to your practice approach in order to be successful within it?
10. How can dental academic institutions better prepare their graduates to be successful in organizations such as yours?
11. What advice can you provide to dental schools or academic health centers considering a more integrated approach in their clinical endeavors?

The focus of the interviews and interactions was to determine how the participants viewed the preparedness of recent dental school graduates, specifically dentists, for professional activity within an active, integrated care environment, and where gaps in the educational process were evident. "Recent graduate" was defined as a dentist graduating from a US DMD/DDS degree program within the past 5 years. The site visit also served to assess the level of integrated dental-medical care by the selected entity.

The seven care groups visited included two large managed care/HMO type organizations, a multi-site hospital/federally qualified health center (FQHC) care entity, a hospital-based system with a general practice residency program serving as its chief dental care arm, a benefits organization with an expanding care delivery network, and two large, multi-provider dental group practice. Sites spanned the Northeast, Midwest and Western region of the country. One site proved to have rather minimal integrated care activity, one declined to have its interview reports published, and two sites showed some integrated activity but substantially less than that of the three sites eventually selected as the key informants for the ADEA Association Report.

The three entities selected for reporting were Permanente Dental Associates (PDA) in Portland Oregon, Marshfield Clinic Health System in Marshfield, Wisconsin and HealthPartners in Minneapolis, Minnesota. The organizational construct, care philosophies and other characteristics of these three organizations are fully described in previous publications [22–24]. Following the site visits with these entities, summary notes taken by (RLMN) were shared with those interviewed to confirm accuracy. Using an inductive approach, responses to interview questions were grouped into common themes for further consideration. Conclusions and recommendations relative to new dentist preparedness and other aspects pertinent to dental education were then drafted, shared and finalized. A full description of these interviews and recommendations has been previously reported in a five-part Special Report in the Journal of Dental Education [22–26].

RESULTS/DISCUSSION

General Observations

In the initial scan of engaged sites, only a limited number were found to have meaningful and sustained integrative care activities with medical units or other health professions providers. A number of practices or organizations reporting integrated care were found to be practicing it at very low functional levels. Some were still in the planning stages while others were at the very early stages of implementation. This finding suggests that the dental profession is still very much at the embryonic stage of integrated practice. The apparently low number of active, functional sites poses certain limitations and challenges to dental education.

As the project got underway, several large multi-provider dental practices falling into the general description of dental service organizations, or DSOs, began reporting on increased engagement in integrated dental- medical care. At least one DSO practice reported that it had moved to better support its integration efforts through conversion of its dental electronic health record (EHR) to a fully integrated, nationally recognized EHR used by a large number of US hospitals and medical care networks [27]. Unfortunately, the current project was not able to include these organizations and their engagement could potentially have expanded the site visit pool and the diversity of perspectives gained.

Perspectives and Recommendations From the Field

The following is a summary of the most common findings and suggestions gained through site visits at the three organizations described above and reported in greater detail in a special report of the Journal of Dental Education [22–26].

Interprofessional Education Must Be Improved Through Reinforcing Clinical Experiences

Organization leaders reported little difference in the preparedness of recent dental school graduates for integrated care practice compared to providers joining their organizations who graduated much earlier or who were engaged in prior traditional practice ("Recent graduate" was defined as a graduate of a dental school within the previous 5 years, between 2013 and 2018). This perspective was unanticipated as more recent graduates were expected to have had greater exposure to aspects of interprofessional education during their dental school training. Those interviewed were aware that dental schools had increased their emphasis on IPE in response to new accreditation standards and increased educational emphasis on IPE over the last decade. In general, they failed to see how that experience was translating into a different type of new provider or one more prepared for integrated care. Concern was expressed that IPE might be occurring in what one leader described as an "educational silo" [28], not strongly linked with active patient care and reinforcing clinical experiences, more formally termed interprofessional collaborative care (IPCC).

Based on the considerable investment that many schools have made in IPE, these comments should evoke reaction within the educational community. While the goals and objectives of IPE extend far beyond readying graduates for specific care environments, preparedness for delivery of integrated care represents a unique opportunity to measure IPE's impact in the form of a practical outcome. A strong recommendation from those interviewed in this project was that the IPE experience in dental schools not occur too distant or detached from the clinical practicum and that a good proportion of IPE should be embedded within clinical experiences where a measure of interprofessional collaborative care (IPCC) is practiced. This may be difficult for many schools with traditional intramural clinical operations, not part of an academic health center construct or not affiliated with other health professional schools or care units. Even for the approximate two-thirds of dental schools that are part of academic health centers, many have found it difficult to introduce and blend collaborative care activities with other health professions on campus. In some cases, it may be more feasible for dental schools to seek out extramural clinical sites where collaborative integrated care is active and could be modeled. One major limitation as previously noted is the relative paucity of dental settings where integrated care is active and institutionally supported.

Hospital- or Medically-Focused Residency Training Improves Preparedness

A correlate recommendation from those interviewed was that new providers with interest in integrated care practice should pursue advanced training of at least 1 year in a hospital-based general practice or pediatric dentistry residency program, representing the two chief elements of primary dental care. Graduates of general practice residency (GPR) programs that are closely aligned with hospital or medical operations and which provide coordinated care for inpatient populations were viewed as distinguishable from other new dental providers. The respondents felt that this was likely the result of the professional interactions between dentistry, medicine and the other health professions required within these types of programs. Not surprisingly, all three organizations had moved to placing substantial emphasis on a GPR experience as part of new provider recruitment. One organization felt that graduates of a particular US dental school were much better prepared for their brand of integrated practice; this particular school places senior students in extended community health center rotations and in several different locations nationally during the majority of the fourth year of their DMD/DDS education. This organization felt that these experiences exposed students to the dynamics of oral health inequities, health care disparities, economic/social/cultural determinants of health, and the treatment of acute dental disease, all which were an important part of their operational mantra. A general recommendation was that dental schools should sustain, if not expand, the amount of clinical time spent at community-based sites and, if possible, at FQHCs where medical and dental units support an integrative care philosophy and approach.

Maintain a Strong Curricular Experience in the Medical Sciences but Ensure an Applied, Practical Focus

The interviews identified a concern that dental schools were downscaling their basic and applied medical science curriculum in favor of competing curricular interests. The following examples were articulated: schools providing students with earlier clinical experience by transferring curricular time traditionally devoted to medical science instruction to the clinical practicum; a greater proportion of the available curriculum now devoted to exposure to and instruction in new chairside and laboratory technologies with focus on dental procedures; a fast-tracking of students through the core medical curriculum to meet the standards set by national boards but insufficient to provide the depth of knowledge needed for application in patient care; within the medical training of dental students insufficient emphasis placed on the discreet number of systemic conditions and diseases closely linked with oral health and provision of dental care. Some interviewed suggested that the dentist should be trained to the same level as primary care physicians relative to the limited number of medical conditions dominant within primary care and that consume the majority of integrated care communication and co-therapy planning such as diabetes, hypertension, and asthma. There was a perception that new dental providers have superficial knowledge across a wide range of medical conditions yet inappropriate depth and application ability in these common conditions. A prevailing opinion was that the foundational and applied medical curriculum within dental education must remain strong with emphasis on the possible unique role of dentists in the co-management of common medical conditions and the effective closure of gaps in disease prevention and health promotion strategies. The design of this type of curriculum requires effective communication between leaders of dental and other health professional schools and the coordinated participation of the entire dental faculty spanning generalist to specialist.

Invest in Integrated Electronic Health Records Allowing Communication Between Dental Medicine and the Other Health Professions

The issue of improving upon methods of professional communication was the strongest recommendation from our participants. It was strongly recommended that dental schools move toward participation in electronic health records (EHRs) shared with the medical community including hospitals and physician networks [29, 30]. The functional divide created by dental medicine and primary care medicine working from separate, unconnected EHRs was felt to be dramatically detrimental overall, placing dental practice in isolation from the surrounding and changing healthcare world. Optimism was expressed that several US dental schools recently moved away from dentistry-only EHRs to more broadly used health care platforms. While an expensive and challenging endeavor, this change was seen as essential if integrated care is to grow and new dental providers are prepared to be actively engaged. Of note, the three organizations surveyed here each employ a unifying EHR with integrated medical and dental components.

Provide Practical Experience in the Use of Health Analytic Tools

Contributors stressed the importance of the modern dental care provider being versed in the use of health analytic tools. These tools are often supported by contemporary, integrated EHRs, yet another reason for student exposure to such records. It was anticipated that providers will be more motivated to pursue innovative care strategies if they can witness the results of these efforts in improved quality care metrics. One example was the demonstrated ability by one organization to close gaps in certain medical preventive care protocols by the engagement of the dental team [22]. Those interviewed expressed that dental providers must feel comfortable and confident in accessing these analytic tools and in interpreting the data.

Educate Students About New Dental Practice and Compensation Models

Questions were raised about the efficiency of dental schools in providing practice management concepts that vary from the traditional, prevailing fee-for-service, independent contractor model of dental practice. As integrated medical-dental care is further pursued, and as the dental profession shifts from a repair/restore emphasis to a more prevention/early disease interception mode, it is probable that other business models of practice will emerge. For example, it is predicted that group practices will likely grow in size and number [31] and more third-party plans will incorporate value-based reimbursement approaches. Within these changes, our interviewees predicted that outcomes-focused, incentive-based formulas tightly linked to the ability of the dental provider to practice in diverse teams that include non-dental professionals will capture a larger part of the compensation landscape. Dental students must be exposed to these concepts so that as new graduates they can understand their relative strengths and weaknesses and make informed decisions on the type of practice that best matches their preferences and shifts in future dental care.

Stress the Power and Art of Effective Interprofessional Communication

A common thread across these interviews was the critical importance the individual provider to effectively communicate with all members of the care team in order to flourish in a more integrative model of care. There was a position that most schools could still improve upon training in both intraprofessional (i.e., within the dental team proper) and interprofessional communication. In a number of the practices visited, auxiliary personnel including dental hygienists, licensed practical nurses (LPNs) and medical assistants (MAs) performed a large portion of the integrated care effort including identification of medical/dental risk, gaps in care, and in the clinical provision of services such as blood pressure monitoring, blood draws and vaccine administration. The importance of effective communication between the supervising

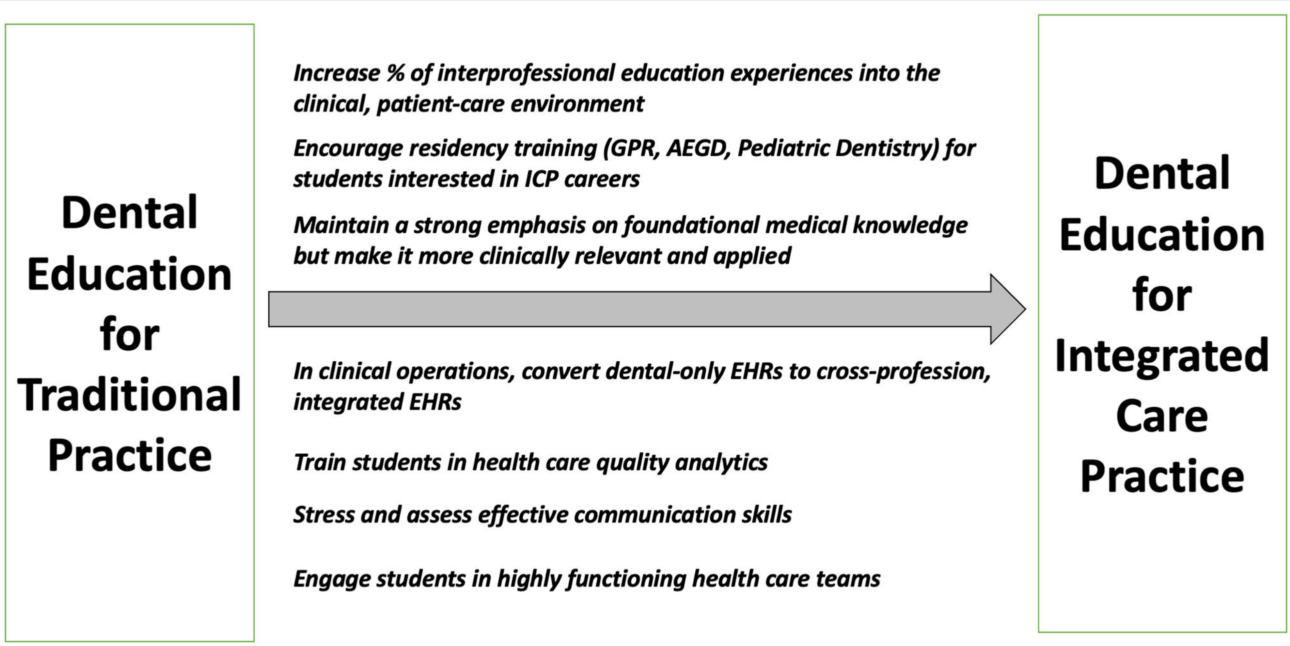

FIGURE 1 | Integrated care practice leader recommendations for improvement in the education and preparedness of dentists for future practice.

dentist and auxiliary staff is essential, as is the necessary interprofessional communication with correlate members of the primary care medical team. It was advised that increased efforts be made to prepare dental students to consistently and accurately use contemporary medical terminology to ensure the effective and safe transfer of information across the integrated team.

Engage Students in Highly Functioning, Intraprofessional and Interprofessional Teams, and Incentivize Effective Teamwork

An overwhelming recommendation from the interviews was that dental curricula further advance the concept of team-based care as essential to traditional and contemporary forms of practice. Students must be exposed to dynamic team environments where they practice as authentic members of a team in the care of patients. While simulated environments may be useful in this task, exposure to working examples of active teamwork was deemed critical. It was recognized, however, that identification of these examples may be difficult but must be pursued. Again, dental schools may need to move outside their intramural systems of care and explore external, community- based models to achieve this goal.

CONCLUSION

The recommendations emanating from this interview survey with leaders of integrated care practices (summarized in **Figure 1**) suggest that despite efforts to adequately prepare graduates for interprofessional collaborative care, improvements are necessary. Institutional responses to recent accreditation standards and national initiatives such as those emphasizing interprofessional education have undoubtedly had an impact but perhaps not to the extent envisioned. The dental education community should consider the presented recommendations and continue to advocate for advancement of current programs and continual refinement in the guidelines and principles upon which future program development is propelled. This report suggests that interprofessional education must move to the forefront and that greater efforts be undertaken to identify examples of integrated practice in the community where interprofessional, collaborative care is actively and effectively modeled.

These recommendations may present additional challenge for dental education as it attempts to respond to and address the many diverse drivers and indicators for change in the dental curriculum. Several of these recommendations will not align easily or fluidly with other shifts currently being witnessed or suggested (see Fontana). For example, devoting more curricular time to applied medical science and interprofessional collaborative care could be viewed as incongruent with expansion and earlier introduction of clinical care hours devoted to traditional care and greater immersion in new dental technologies. Experimentation with collaborative team models where appropriate compensation strategies have not yet been developed may be deemed inconsistent with the urgency to create more sustainable intramural clinical care systems and improved net clinical revenues. Investments in expensive universal EHRs will undoubtedly prove difficult as dental institutions attempt to curtail or reduce the rising cost of dental education. Despite these challenges, the promise and possibilities found within integrated dental-medical care demands that it be given high priority in dental education [3, 32]. New strategies will most likely require non-traditional approaches, innovation and significant adjustment in the current educational model, and in particular, the clinical practicum [33]. Therein lies the challenge for today's dental schools and leaders in dental education.

DATA AVAILABILITY STATEMENT

The datasets generated in this article are not readily available because the dataset consists of narratives and notes collected from key informant site visits. Permission from the contributors was not attained for further distribution. Requests to access the datasets should be directed to macneil@uchc.edu.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Designing Oral Health Curriculum That Facilitates Greater Integration of Oral Health Into Overall Health

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For several decades, health professions education has been transforming; pedagogical constructs such as active learning, recorded lectures, electronic assessment, asynchronous content delivery, and interprofessional education and practice. However, the typical oral health curriculum has need for further transformation to ensure graduates' ability to function in an integrated health system. There is significant literature outlining associations between oral health and overall health, therefore, it is paramount that oral health learners develop skills to collaborate in an integrated model. Satcher, in 2000, outlined the gravity of oral health inequities and the importance of oral health. He said, "Too little time is devoted to oral health and disease topics in the education of non-dental health professional." However, on the contrary typical oral health curriculum provide knowledge acquisition of topics related to overall health but isn't specifically designed to guide integrated care. In order to increase integrated care, groups like the Interprofessional Education Collaborative (IPEC) have developed competencies for interprofessional education and collaborative practice that guides the training of health professionals. One way to improve integration is accreditation standards that guide transformation as well incorporate IPEC competencies. Having competencies is important to prepare learners to function in clinics like Kaiser Permanente's medical-dental integration model that rely upon teams and teamwork and clarity of roles and responsibilities. This manuscript outlines principle of oral health curriculum that facilitate graduates ability to work in an integrated health system and how that contributes to the improvement overall health of patients.

Keywords: interprofessional education, collaborative practice, oral health, integrated care, curriculum

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BACKGROUND

In the 1800s, Horace H. Hayden and Chapin A. Harris founded the Baltimore College of Dental Surgery and established the first educational program to educate and train dentists with the understanding that it was important to create interdisciplinary connections between medicine and dentistry. In 1926, William J. Gies wrote, "Owing to failure of both physicians and dentists to recognize the fact that the primary objectives of dentistry and of medicine are identical-to keep people well (1)." However, despite this charge from Gies, throughout much of the twentieth century, the majority of dental institutions trained providers with minimal interdisciplinary integration. At the beginning of the twenty first century, the oral health status of Americans was brought to the forefront by the Surgeon General's report, *Oral Health in America: A Report of the Surgeon*

General, which cast a brighter light on the inequities in oral health, particularly within the pediatric population. The report states that "*oral health is essential to the general health and well-being of all Americans.*" Consequently, in the twenty first century, oral health professionals should be seen as an essential part of the healthcare team with the express intent of improving patient health outcomes, and a contemporary curriculum should prepare oral health graduates with the ability to function in an integrated health system.

More than two decades ago, stakeholders, such as The Institute of Medicine Report (2), the Macy Study (3), and the American Dental Education Association (ADEA) (4, 5), have advocated for systematic curricular change in dental education. These recommendations, in part, were driven by the fact that the predominate curriculum in the twentieth century was a two-by-two model, with biomedical science taught within the first 2 years and clinical experiences in the second 2 years, with minimal integration of biomedical and behavioral science and limited preparation to be a collaborative member of an interdisciplinary healthcare team. A significant portion of curricular change was shepherded by the Commission on Change and Innovation of ADEA in conjunction with dental institutions. Dental institutions embraced competency-based education, problem-based learning, community-based dental education, a reduction in departmental siloes, and community-based dental experiences, to name a few (6). In addition, the transformation of health professions education contributed to pedagogical constructs, such as active learning, recorded lectures, electronic assessment, asynchronous content delivery, and interprofessional education (IPE) and practice (IPP) (7–9). Several dental schools incorporated these elements into their curriculum, and some have completely redesigned their curriculum (10, 11). However, gaps in the oral health curricula, such IPE activities that improve collaborative skills, knowledge, and attitudes, and limited experiential interprofessional experiences, constrain the ability for oral health providers to function in an integrated health system. This review outlines modifications for the oral health curriculum that can facilitate the ability of graduates to work in an integrated health system and contribute to the improvement of patient healthcare outcomes.

DESIGNING CURRICULUM FOR INTEGRATION OF ORAL HEALTH AND SYSTEMIC HEALTH

It is important to acknowledge that the dental curriculum in US dental schools has fundamentally strong components that prepare graduates with a licensure-ready status. By integrating biomedical, behavioral, and clinical science didactic contents with simulated clinical- and patient-based clinical experiences, students are efficiently prepared to enter the healthcare workforce. This 4 year equivalent model has successfully produced practice ready providers, and the following recommendations are intended to be designed within a 4 year model.

One of the shortcomings of the traditional model is the siloed approach to delivering content. Additionally, this siloed approach delivered biomedical content in the first 2 years and potentially contributed to a belief by some learners that the biomedical sciences could be disconnected from the clinical care of oral diseases. Furthermore, the National Board of Dental Examination administered a two-part examination, which reemphasized the separation of biomedical science content from the clinical sciences. However, the Joint Commission recently discontinued the examination in the separated format and has ushered in an integrated biomedical, behavioral, and clinical sciences format. The twenty first century contemporary curriculum should be delivered in a manner that emphasizes the concept that the mouth is connected to the body and that oral diseases have associations with systemic diseases. This type of curriculum will deliver biomedical, behavioral, and clinical sciences content in an integrated format throughout the 4 year curriculum.

Haden et al. (6) surveyed the academic and associate deans of dental schools about curriculum format and reported that schools believed future curriculum should be arranged around themes, not disciplinary boundaries, with a blending of basic and clinical sciences. This may necessitate having foundation or primer courses to deliver essential knowledge prior to these integrated sessions, which would facilitate the retention of knowledge and reinforce the need for integrated care of patients. This curriculum format would require that some biomedical science, in some format, be presented later in the curriculum to reinforce the relationship of biomedical and behavioral science to the clinical care of patients. A few examples of this type of integration have been described in the literature, although many programs have introduced some integrations without documenting them in the published literature (10, 11). An example of this is the integrated case-based seminar at the University of Minnesota School of Dentistry, which is a team-taught course with faculty from multiple disciplines. One clinical faculty in conjunction with a biomedical or behavioral science faculty develops a case. This course is delivered after the biomedical courses have been completed and just before entering the clinic to reinforce the need for integrated care.

Curriculum revisions should be a transformative process that leads to substantive modifications that provide oral health professionals the ability to work in an integrated health system, collaborating with other health professionals and improving patient outcomes (12, 13). The association between systemic and oral health is well-documented in literature (14–16). Schenkein and Loos (15) noted that there was a statistically significant association between an increased risk of cardiovascular diseases and elevated levels of circulating inflammatory mediators that are commonly associated with periodontal disease. Jeffcoat et al. (16), in a retrospective analysis of linked medical and dental insurance records, reported that there was a statistically significant reduction in treatment cost for pregnant women who received treatment for their clinically diagnosed periodontal disease compared to those who were untreated or undertreated. Lamster and Myers-Wright (13), suggested that oral health practice was changing and that "oral healthcare providers need to be comfortable treating these older, medically complex patients, which includes an understanding of how chronic diseases affect a person's ability to tolerate dental care and the linkages between chronic disease and oral disease". Curriculum transformation must continue to train graduates to prevent, diagnose, and treat oral diseases and prepare them to contribute to the improvement of overall health (12). Such a curriculum would better prepare graduates to contribute to the improvement of overall health by identifying hypertension, providing smoking cessation plans for patients, identifying undiagnosed diabetes, contribute to the management of sleep apnea, screen for osteoporosis, and assist the management of obesity (17). An ideal curriculum would be structured in such a manner that it facilitates the oral health provider as an integral member of a team that functions to improve healthcare and patient outcomes.

INTERPROFESSIONAL EDUCATION

While IPE has been a part of the conversation in healthcare since the 1970s, significant momentum was gained in 2016 by the assembly of an expert panel of representatives from health professional schools who convened to develop a set of competencies for interprofessional collaborative practice (ICP) (18, 19). Currently, dental education has competencies for two oral health professionals: the general dentist and the entry-level dental hygienist (20, 21). In addition, individual institutions oftentimes supplement these with institutionally specific core competencies that mimic these two documents to meet institutional goals. The competencies of the Interprofessional Education Collaboration (IPEC) provide guidelines that prepare health professional learners to provide patient and family-centered care and team-based care that is "community and population oriented; process oriented; linked to learning activities, educational strategies, and behavioral assessments that are developmentally appropriate for the learner: able to be integrated across the learning continuum; sensitive to the systems context and applicable across professions…" (19). A recent systematic review reported IPE activities as an effective tool for improving a learner's "attitude toward interdisciplinary teamwork, communication, shared problem-solving, and knowledge and skills in preparation for collaboration with other members of interdisciplinary teams." Casa-Levine (22), reported that dental hygiene faculty and administrators had high regard for IPE and that it could enhance patient care and help hygiene learners be more effective team members. The incorporation of IPEC competencies with didactic and experiential interprofessional content into the dental and dental hygiene curriculum is a way to improve the abilities of learners to work as team members with other health professionals.

The 2010 survey of the dental curriculum reported that most dental institutions were increasing community-based clinical experience (CBCE) as a significant aspect of their curriculum, with 46% having completed the process, 33% in progress, and 19% having a 3 year priority (6). Additional studies have identified that CBCE has an impact on improving access to care, providing supplemental experiences, and enhancing the ability of a student to work with diverse populations (23, 24). A recent editorial discussed an initiative that created a nurse-led community-based model of IPE and the lessons learned, but fundamentally, it highlights how partnering with community partners provided students with hands-on experience in how social determinants of health impact patients and how their care impacts vulnerable populations (25). One participant school was a collaboration between a school of dentistry and a nursing school, where students increased their self-reported interprofessional competencies (26). When designing oral health professional curriculum, consideration should include interprofessional experiences that improve the ability of dentists and dental hygienists to be full members of the health team, improving the overall health of a patient and positively impacting a community with limited access.

ACCREDITATION

One of the critical areas in driving curricular change is the role that regulatory and accrediting agencies play in institutions implementing an innovative or pedagogical transformation.

In 2014, the Health Resource and Services Administration (HRSA) and the United States Department of Health and Human Services assembled an expert panel to develop a set of interprofessional oral health competencies for all primary care health providers (3, 27). One response to this call was the establishment of a validated set of competencies for nurse practitioners (28). Oral health was specifically identified within this updated nurse practitioner curriculum and was suggested to be a core competency element. To this end, nurse-practitioner programs are integrating oral health into primary care and are positioned to help reduce oral health inequities.

In 2019, the National Center on Interprofessional Education facilitated a consensus conference of 25 accreditors, titled the Health Professions Accreditors Collaborative (HPAC), and one outcome of this was a guidance document (29). In addition, the Accreditation Council on Graduate Medical Education convened a similar national collaborative of 35 national organizations, called the National Collaborative for Improving Clinical Learning Environments (NCICLE), who have released recommendations for interprofessional clinical learning environments (30). The National Center on Interprofessional Education has partnered with NCICLE to develop a model of using design thinking with these recommendations (Brandt B, Personal Communications, June 8, 2021). These initiatives by accrediting agencies will continue to be instrumental in guiding curricular transformation that will ultimately produce providers who contribute to improving patient outcomes. These examples highlight the important role of accrediting agencies and other stakeholders in the transformation of health professional education and downstream patient care and outcomes.

OPPORTUNITIES FOR PARTNERSHIPS

One of the potential outcomes for ICP is the benefits for the patient, which is captured in the elements of the triple aim. A recent article describes how pharmacists created an interprofessional collaboration with a local public health department to provide medication therapy management services (31). As a part of routine medical care, pharmacists provided a comprehensive review of medications for patients and found 719 medication errors and improved patient compliance. The dental office and dental public health and Federally Qualified Health Center (FQHC) clinics would also provide an excellent opportunity to interact with patients needing similar services. To that end, if similar programs were designed within dental school clinics, it could prepare oral health students with the skills to be team members in similar collaborations. A recent study evaluated the feasibility of providing medication therapy management in a dental school clinic and reported identifying patients with several chronic conditions: 64% had hypertension, 34% had diabetes, and 10.5% reported smoking cigarettes and identified drug therapy problems, of which "needs additional drug therapy" was the most common (32). Therefore, creating more collaborations with pharmacy and dentistry, in both the dental education clinics and community clinics, is a potential opportunity to help lower patient cost and improve patient health.

Studies have evaluated the perspective of learners; in a nursing and pharmacy collaboration, a pretest and a posttest revealed that both learner types improved scores on the interdisciplinary Education Perception Scale and the Care Decisions evaluation tools. More specifically, there was an increased awareness of the role of each learner in the management of pain (33).

One study recruited first-year pediatric nurse practitioners to participate in an interdisciplinary oral health educational intervention and demonstrated that the interprofessional experiences resulted in nurse practitioners being more knowledgeable about oral health and more confident in providing oral health counseling (34).

CURRENT KNOWLEDGE ON IMPACT OF INTERPROFESSIONAL EDUCATION

Reeves et al. (35), in a Cochrane review explained about how IPE affects professional practice and healthcare outcomes. The study updated findings from a 2008 study that evaluated how the use of IPE improves collaboration of healthcare professionals and patient care outcomes (36). The 2008 study resulted in six studies that met the criterion, and the 2013 update included nine additional studies that met the criterion. The results demonstrated that seven studies had positive healthcare processes and patient outcomes, four studies had positive and neutral, and four studies reported no effects from IPE. It is important to note that these studies were performed in different clinical practice types and different IPE interventions.

Dyesset al. (37) evaluated the impact of IPE on health professional students. The study eligibility required for three or more healthcare professional learner types to participate in an IPE activity and for didactic coursework to be included. Seven studies were selected that met the search criterion and demonstrated that IPE improved the attitudes of learners toward interdisciplinary teamwork, communication, shared problem-solving, and gaining knowledge and skills that prepared them to work on a collaborative interdisciplinary healthcare team.

Spaulding et al. (38) performed a systematic review to assess the impact of IPE on changing the attitudes and perceptions of learners, the acquisition of knowledge about the role of other healthcare professions, the development of collaborative skills, and the changes in perceived or actual collaborative behavior. This review studied IPE interventions aimed at learners in health and social disciplines, such as physicians, pharmacists, nurses, psychologists, physical therapists, occupational therapists, dieticians, and social workers. The intervention was defined as any activity with two or more learners engaged in an interactive learning experience designed for the explicit purpose of improving interprofessional collaboration or improving the health and well-being of patients and clients. The findings demonstrated that IPE was effective in improving the attitudes of learners and professionals toward other disciplines and the value of a team-based approach to improving patient outcomes.

SUMMARY

During the first two decades of the twenty first century, dental education has made strides in improving their curriculum. In order to continually advance the education of oral health professionals, there must be ongoing revisions. Oral health professionals are essential members of the health team, and curriculum revisions should ensure that graduates are prepared to function at the highest level of their scope and that scope can be expanded to include the improvement of overall health. A curriculum should be developed that integrates biomedical, behavioral, and clinical sciences throughout the entire program. In addition, a strong IPE program will prepare learners to work with other health professionals. One way to facilitate this integration would be to develop experiences that guide transformation and the incorporation of IPEC competencies. Additionally, the resources and policy change created by accrediting agencies are invaluable to the transformation of health professional education. Having competencies is important to prepare learners to function in clinics like the medical–dental integration model of Kaiser Permanente, which relies upon teams and teamwork and the clarity of roles and responsibilities. Training health professionals in an interprofessional manner requires shifts in the curriculum to graduate providers with the skills to function in a collaborative environment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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A Framework to Foster Oral Health Literacy and Oral/General Health Integration

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Science and technology advances have led to remarkable progress in understanding, managing, and preventing disease and promoting human health. This phenomenon has created new challenges for health literacy and the integration of oral and general health. We adapted the 2004 Institute of Medicine health literacy framework to highlight the intimate connection between oral health literacy and the successful integration of oral and general health. In doing so we acknowledge the roles of culture and society, educational systems and health systems as overlapping intervention points for effecting change. We believe personal and organizational health literacy not only have the power to meet the challenges of an ever- evolving society and environment, but are essential to achieving oral and general health integration. The new "Oral Health Literacy and Health Integration Framework" recognizes the complexity of efforts needed to achieve an equitable health system that includes oral health, while acknowledging that the partnership of health literacy with integration is critical. The Framework was designed to stimulate systems-thinking and systems-oriented approaches. Its interconnected structure is intended to inspire discussion, drive policy and practice actions and guide research and intervention development.

Keywords: health literacy, organizational health literacy, oral health, oral health literacy, health systems integration, health care services

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INTRODUCTION

As a field of study, health literacy, including oral health literacy, grew out of the recognition that the very advances in science and technology that have led to remarkable progress in understanding human health and disease are often lost on the public. Consumers who read health information and patients who leave doctor visits often fail to understand what has been said and what they should do in response. Some of this failure is a result of poor communication by the provider. As the National Academies' Institute of Medicine report noted in 2004, "Nearly half of all American adults—90 million people—have difficulty understanding and acting upon health information" (1). This report highlighted one of the first definitions of health literacy: *The degree to which individuals have the capacity to obtain, process, and understand* basic *health information and services needed to make appropriate health decisions*" (2). Oral health literacy underscores the need to understand basic oral health information in order to make appropriate health decisions, many of which may have overall health implications (3).

In parallel with health literacy has grown a movement to integrate oral and general health in research, education, and clinical care. Their separation, the product of history and tradition, has led many to believe that oral health is less important and outside the realm of general health. But science has long proven otherwise (4–7). Reams of data demonstrate that what happens in the mouth affects, and is affected by, what happens elsewhere in the body. The association between periodontal disease and diabetes was recognized decades ago and the evidence linking oral disease with increased risk for certain cancers, and heart and lung disease is strong (8, 9). Former U.S. Surgeon General C. Everett Koop summed it well saying, "You are not healthy without good oral health" (10).

In this paper we explore the relationship between oral health literacy and oral/general health integration showing that the two are inextricably linked. Achieving oral health literacy enhances the prospects of successful integration and in combination contributes to improved health outcomes, improved quality of care, and cost reductions (3). Together, they work toward reducing health disparities, especially glaring in the health of poor and minority groups, and thus achieving greater health equity. As stated in the Healthy People 2030 overarching goal; *Achieving health and well-being requires eliminating health disparities, achieving health equity, and attaining health literacy* (11).

Our analysis examines factors common to health literacy and integration that, for better or worse, influence them and suggests ways to overcome barriers and move forward. Specifically, we propose that investments in health literacy can open new avenues for advancing progress in developing a stronger health delivery system, improved public health, and enhanced health equity.

A NEW URGENCY

The first decades of the century marked substantive health literacy research and a succession of meetings and publications on health literacy, and oral health literacy in particular. These efforts revealed health literacy associated health outcomes due to personal, provider and health systems factors (1, 12). National action plans and toolkits offered guidance on the interface between health literacy and health outcomes (13, 14). Meanwhile, advocates decried the negative impact on the health of the public and ever-rising costs, due to the lack of understanding of the causes and ways to prevent disease, conflicting and complex health information messages, and poor communication between providers and patients. Then came the year 2020.

The COVID-19 pandemic laid bare the extent of health care inequities in America the limitations in public health infrastructure, and the poor design of our health care delivery systems. An avalanche of information from multiple media platforms created massive confusion from conflicting messages from senior leaders and agencies, conspiracy theories, misinformation, and the lack of a unified national approach (15, 16). In addition, we experienced blatant structural racism, social injustice, and civic unrest. These events continue to cause stress, anxiety, and confusion among the population as a whole and within the health care environment. Specific to oral health, this experience has revealed major oral health inequities, challenged dental care services and the dental care workforce, and revealed the fragmentation in our health care and education systems (17–19). The provision of clear communication to individuals, families, providers, organizations, and jurisdictions was challenged, underscoring the urgency to take action to address the issues. It is clear that improving the health of the U.S. population, which is critical to economic stability and advancement, requires a combination of health practices and policies that emphasize the importance of good health, including oral health, for the entire population.

The groundwork for how next to proceed as society weathers the pandemic storm has been laid out in the earlier events of the decades, mostly under the auspices of the National Academies of Science, Engineering and Medicine's Roundtable on Health Literacy and the Department of Health and Human Services (14, 20). These references include the federal government publications of health priorities and recommendations for each decade, currently ***Healthy People 2030*** (21, 22).

A significant outcome of health literacy research and these national assessments led to changes in the definition of health literacy. The revisions broaden the scope and responsibilities from a focus solely on individuals to a *systems* approach. Healthy People 2030 includes new definitions (**Box 1**) for personal (individual) and organizational health literacy, providing more specificity than the earlier definitions (23).

BOX 1 | New Health Literacy Definitions: Healthy People 2030.

Personal health literacy is the degree to which individuals have the ability, to find, understand, and use information and services to inform health-related decisions and actions for themselves and others.

Organizational health literacy is the degree to which organizations equitably enable individuals to find, understand, and use information and services to inform health-related decisions and actions for themselves and others.

The combination of personal (individual) and organizational health literacy definitions reinforces the need for integration of all health promotion, health care information, and services (both oral and general health). Both definitions highlight the importance of acting on the information to inform health-related decisions and actions, not only for themselves, but also for others. Relevant to integration, the reference to individuals encompasses more than the lay public (individuals, families, communities) and includes health care providers, policy makers, administrators of health and health care programs, and those responsible for developing and disseminating health information. The organizational definition further recognizes the role entities that create health information and those that provide health services play in contributing to health literacy and the importance of their doing so "equitably." This definition also acknowledges that health literacy is dependent on the context (where, when, how, and by and to whom) and serves as the basis for the discussion

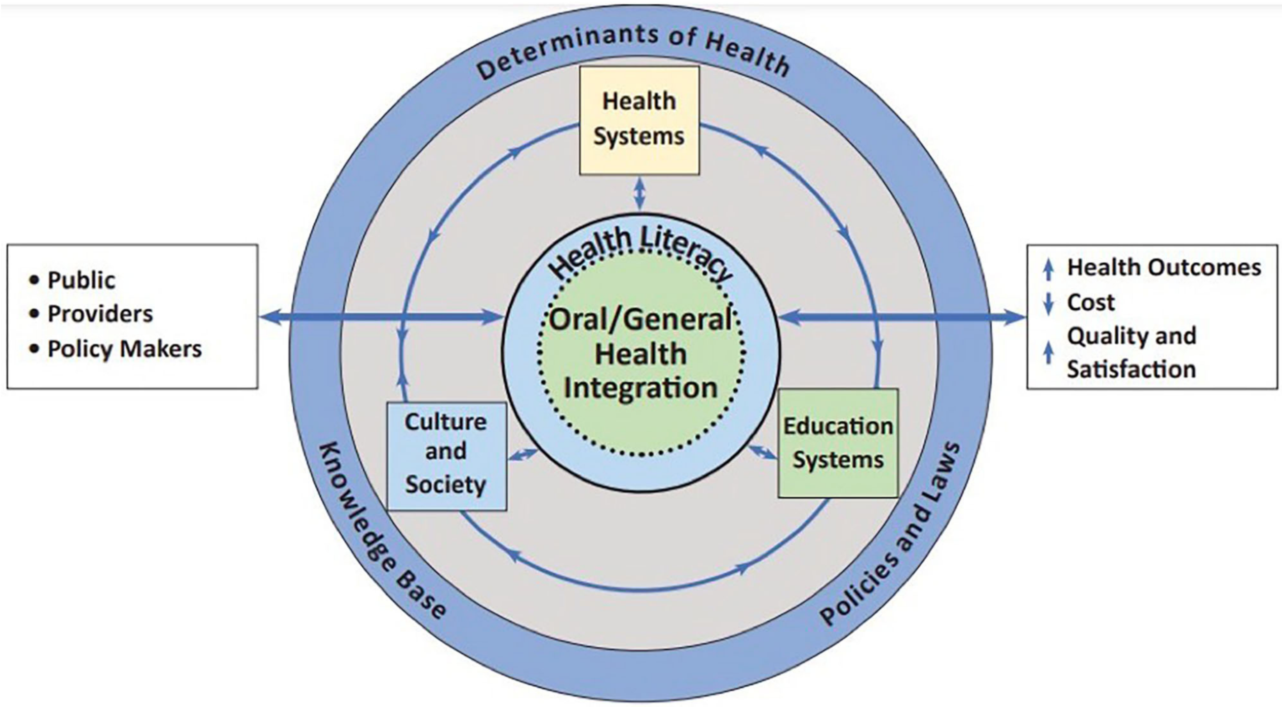

FIGURE 1 | Oral health literacy and health integration framework. Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, DC (24).

in this paper. The new health literacy definitions broaden the imperative for action.

Oral health-related highlights of the pre-pandemic years include activities of the NASEM Roundtable on Health Literacy (Roundtable), which reviewed oral health literacy (25). The 2013 workshop investigated the importance of community support for health literacy, particularly in relation to:

- the health problems of vulnerable populations,
- the role of dental providers in communicating with a diverse patient population, and
- the role of health delivery systems in advancing an understanding of the patient's needs in order to obtain necessary care.

The Roundtable commissioned an environmental scan to assess ways in which health literacy promotes integration of oral health in primary care (26). During a 2018 workshop (27), discussion addressed changes needed in the health system, pointing to:

- the lack of interprofessional collaboration,
- payment systems that minimize prevention, and
- the need for consumer involvement.

TOWARD A HEALTH LITERACY FRAMEWORK TO INFORM INTEGRATION

To discuss the catalytic role of health literacy and health integration, we have selected the health literacy framework presented in the 2004 IOM Report (1) as the foundation. The IOM developed the framework as the organizational principle of the report. It provides a useful visual of "the potential influence on health literacy as individuals interact with educational systems, health systems and cultural, and social factors" at home, work and in the community. It also illustrates that these factors may ultimately contribute to health outcomes and costs. Health literacy sits within a network of systems, culture, and society, each with its own attributes and related legal, social, and ethical issues, which the IOM report refers to as "intervention points." Importantly the IOM report recognized that health systems play a significant role, but that improvements in health literacy must be shared by all sectors.

Our Oral Health Literacy and Health Integration Framework, is designed to recognize the complex factors that contribute to both integration and health literacy and ultimately to health equity (**Figure 1**). The Framework is based on the premise that effective integration of oral and general health is critical, and is enhanced by health literacy. This situation requires a clear understanding of health conditions and needs, care services, community needs and the roles played by individuals, health care providers, and health policy makers.

Health literacy and oral/medical integration are partnered and centrally placed with a permeable membrane between them, emphasizing the interplay. Health literacy is a determinant of health. Limited health literacy by individuals and systems is associated with poor health outcomes, health disparities, reductions in health care quality and increased costs (1, 28, 29).

Equally important, limited health literacy and lack of integration are impediments to achieving health equity. As a determinant of health, health literacy plays a critical role in facilitating:

- the ability of individuals to care for themselves and their families,
- shared decision-making between individuals and their health care providers,
- the ability of providers to communicate in a manner that all patients understand,
- actions that contribute to overall health and well-being,
- health care quality at the community and health care system level, and
- the development and implementation of effective health policies.

Through these roles, health literacy provides an essential foundation for the integration of comprehensive health and health care services, including the integration of oral and medical health care. In contrast, the limited or lack of integration of oral and medical care may contribute to continued poor health literacy within individuals and groups, ultimately resulting in poor population health.

The Framework is nested in a broader environment, including a rapidly evolving knowledge base, emerging health policies and multiple determinants of health. The knowledge base, nurtured by the research community, informs our understanding of health, well-being, and the diseases and conditions that affect the ability of individuals and populations to thrive. Integration is essential in our design and funding of research, from basic through implementation research (30). The knowledge base also informs the development of evidence-based interventions and programs and policies by health systems that support patient health and well-being and prevent harm to the public.

The determinants of health are conditions that affect an individual's or community's ability to thrive. As a determinant of health, health literacy contributes to how individuals manage the conditions of living: their housing, work and social environments, and their engagement in their communities and society at large. These are "non-health care system" determinants and play a major role in lowering or increasing the risk of disease, self-care, and access to health information and care services. Oral health literacy, including the promotion of oral health and access to oral health care contributes positively to the social determinants of health, enabling individuals to meet their basic food and hygiene needs, to be employed, and participate as social beings.

The Framework highlights the role of the public, health care providers, and policy-makers in improving population health and addressing health care inequities. These, and other critical players, such as researchers, educators, and administrators, contribute as individuals in their personal and professional roles and as members of organizations in each of the systems. Intermediate outcomes include improving overall health and well-being, reducing costs, enhancing quality of care, and consumer and provider satisfaction. These outcomes provide feedback into the various systems through the lens of health literacy and oral/general health integration.

Inherent to this Framework are basic questions as to whether the respective health systems, culture, community and society, or the education systems enable or limit integration, and how can health literacy skills and principles contribute to and support integration.

CONDITIONS OF INTEGRATION

Integration and care coordination of oral and general health are dependent upon a complex system of factors (26, 31). For health care, it requires having sufficient knowledge, enabling technologies, and supportive reimbursement mechanisms. The capacity and willingness to integrate and ensure quality of care reflect the level of commitment and agreement among individuals, clinical teams, organizations, and systems. While physical proximity has its benefits, the separation of dental and medical offices, geographically or within the same office building, need not be a deterrent if providers have established a communication system and means for making patient referrals. Even the co-location of providers, such as in a Federally Qualified Health Center housing both dental and medical offices, which allows for personal interactions, would better meet the needs of integrated care with technological enhancements such as interoperable electronic health records. Yet, the foundation for building and sustaining successful integration and care coordination requires a more extensive reach, one that can be enhanced with health literacy.

The interaction of health literacy and integration occurs within and among the larger contexts of culture and society, educational institutions, and health care systems—each of which may, or may not— support integration or promote health literacy.

CULTURE AND SOCIETY

Cultural and societal factors, including communities and neighborhoods, play a large role in determining how individuals identify themselves, the language they speak, the customs or behaviors they follow and their core moral beliefs on what constitutes proper attitudes and behaviors. But they are not static. They are subject to the changes wrought by historical events, developments in art, science and technology, environmental disasters and influences of the media and powerful leaders. The 2004 IOM report recognized the impact of culture and societal factors on individuals, highlighting the importance of ensuring health providers' language and cultural competency in communicating with patients (1). But even in 2004 the report recognized there were multiple challenges to health care information coming from competing sources. These have only grown in the intervening years and with the pandemic have worsened with the addition of misinformation and disinformation, further alarming the public, care providers and policy makers alike.

Achieving health literacy in society today will depend on gaining the trust of a disaffected public and establishing sources of information aligned with the best scientific evidence available. Venues for such resources include libraries, Extension programs, faith and social service groups, and city and county councils.

The perception of dentistry as an outsider contributes to how the public views health providers and services. This perception also affects health care professionals in their development and chosen role. Each specialty has its own traditional culture, norms, language, and how it sees itself (and as other health professionals see it) in relation to the health care system as a whole. This is reflected in where and how professionals practice, how they are reimbursed, and how they interact with other health professionals as well as with the public. For oral health/dental services, these characteristics place oral health care physically and in the minds of the public and policy makers, "outside" the medical care system. This is in addition to legal restrictions imposed by state practice acts that set formal limits on the scope of practice and in this way discourage integration of services among different health care providers. These cultural, societal, and legal factors and perceptions challenge the concept of integration of oral health into overall health and health literacy. On the positive side in support of oral/medical integration, are changes in practice acts and reimbursement for care that are paving the way for new workforce categories (advance practice dental hygienists, dental therapists, community dental health coordinators, and community health workers), and expanded access to oral and medical services. Examples include dental hygienists who practice in medical settings, physician and nurse practitioners who provide fluoride varnish, and dentists who provide vaccines for COVID-19 and triage other conditions. To benefit from these changes and accelerate their implementation, clear communication is needed to describe these changes, why they are important and their impact on health to the public. In turn this can inform the actions of policy makers and health care providers.

EDUCATIONAL SYSTEMS

Educational systems include primary, secondary, and higher education, including health professions education, and non-formal education that is incorporated into programs like Head Start, adult literacy programs and continuing education programs. The link between a student's health and academic outcomes, such as letter grades or test scores is well-established (32). Results from the 2015 national Youth Risk Behavior Survey showed that high school students who earned mostly A's, B's, or C's reported greater use of protective health-related behaviors and significantly lower use of risky behaviors than classmates with D's/F's. National Health Education Standards, currently provide eight comprehensive standards for PreK-12 grades (33). Yet despite national standards, the quality, quantity, and content of health education taught in schools is ultimately decided by state and local entities. The result is that the amount students learn about health in school varies dramatically, and frequently is given short shrift. Further, oral health is often omitted entirely because other health issues such as obesity or sexuality are deemed critical, ignoring the fact that oral health issues play a role in each of those areas (dental caries and sugary diet in obesity and HPV infection in sexuality).

In many ways providing appropriate oral health education for children through their school years is an optimal pathway for achieving oral health literacy. Teaching children about dental caries or teenagers about HPV infections may also increase their parent's oral health literacy. Adult literacy classes may also serve as sources for increasing oral health literacy, focusing on critical topics such as diet, drug use, and association with chronic diseases. Because many adult learners are either foreign born or from disadvantaged homes, they may have a great need for dental treatment and may lack understanding of the U.S. oral health care system, both of which could be covered in the class.

There are similar missed opportunities in health professions education, although progress is being made. In the past decade, more attention has been focused on oral/medical integration and related teaching, spurred by the general movement toward patient-centered care and interprofessional education and practice (34–36). These efforts have resulted in the creation of curricular modules, testing of new education strategies (37–39) and technical assistance toolkits (40, 41). Interprofessional communication is one of the four Interprofessional Education Collaborative (42) competencies, providing a place where health literacy principles and skills can easily be aligned and contribute to enhanced collaboration among health professionals. Health literacy includes communication, but also encompasses the health care delivery environment. This extends beyond the critical patient-provider interaction, and includes factors that guide access to care, care interactions and compliance with treatment, such as clinical information systems and decision support technologies (43). Health professions schools, as institutions, would be ideal sites to incorporate organizational health literacy. Adoption of the attributes of health literate health care organizations could create supportive environments and model how health literacy attributes enhance institutions that provide health care services (20). This exposure during health providers' formative training has the potential for lasting effects upon their graduation.

HEALTH SYSTEMS

Health systems include both public and private health care organizations and programs, third-party payers, health care administrators, employed, or independent private practitioners, plus all the licensing, certification, and accreditation entities as well as medical/dental trade associations. Health systems reflect the "culture of care" and are strongly and inextricably tied to our education systems. The health professions workforce continues to evolve, diversify, and extend into traditional health settings and the emerging knowledge base requires ongoing training and development.

Moving from formal educational settings into health care practice adds new challenges for graduates who may or may not be prepared and oriented to oral/medical integration. While medical and dental schools share similar course work in the first year or two of professional school, few medical schools cover oral tissues and diseases in their curricula or medical residencies. The IPEC competences added skills to non-dental providers to enable interprofessional practice, but there has been little adoption and follow up by physicians, outside of fluoride varnish (44). This means physicians are less likely to refer pregnant patients or diabetic patients for dental care and less likely to urge consumption of tap water to access publicly funded community fluoride programs. Similarly, dentists are less likely to refer their patients for medical care for high blood pressure, diabetes, and HPV vaccines. While all states now reimburse physicians and their staff for oral health counseling and the application of fluoride varnish, there is much more to learn about how the two professions can achieve seamless management of children under the age of 5 (45).

All health care providers contribute to both personal and organizational health literacy, and wherever they practice, their positions place them as front-line communicators and educators to the patients and publics they serve. Provider personal health literacy requires them to be fully capable of finding, understanding, and using information and services to inform health-related decisions, and to communicate the information to their patients, families, and collaborating health providers. Challenges include exponential growth of science findings, evolving changes in evidence-based protocols, the introduction of shared services among providers, and the emerging expansion of the scope of practice. These factors, together with policy changes that reinforce specific new knowledge and practices, such as re-licensure requirements and central monitoring systems, reinforce the importance of personal heath literacy for health providers.

Whether providers are in private practice or employed by health care organizations, they also play a critical role in addressing "organizational health literacy." For providers in hospital systems and health care settings, the relevant oversight accrediting and regulatory agencies provide incentives, such as alignment with The Joint Commission on Accreditation Standards for provider communication and health literacy (46). Dental school accreditation criteria include health literacy as one of the behavioral sciences curriculum elements. It states that "Graduates must be competent in managing a diverse patient population and have the interpersonal and communications skills to function successfully in a multicultural work environment" (47). Dental providers who work in academic institutions need to fulfill both the CODA requirements, and, if interfacing with the medical center, also that of the Joint Commission.

Professional organizations play an important role in providing clinical practice guidelines, techniques to simplify in-office communications, continuing education courses, ethical expectations, and new workforce models for their respective providers and the community. These organizations can also contribute by providing resources on Accreditation, and tools to support health care organizations in addressing provider-patient communication standards in health care settings (46, 48).

CHALLENGES TO MEDICAL AND DENTAL INTEGRATION

The many challenges to oral/medical integration include separate location of practice sites; lack of interoperable patient record systems, separate practice quality review systems, and a lack of common insurance coverage (49). These factors limit coordination and integration of care among health care providers and result in fragmented care for patients. As well, they pose health literacy challenges for patient self-management. In 1999, two-thirds of dentists worked in solo practice; the number in 2019 was 50.3% (50) compared with 15% of physicians (51). The separation of dental practice from the more corporate organization of medical care confuses patients who are accustomed to medical providers who collaborate with their colleagues to manage patients' care, often via referrals within the same health care system and even at the same site. Referrals between dentists and physicians are less common, placing a burden on the patient to manage the communication flow and exchange of patient records between providers (52). A common electronic patient record would facilitate bi-directional communication between practitioners, reducing the patient's burden. It would also facilitate the management of chronic conditions, such as obesity, diabetes, and others associated with common risk factors such as diet, smoking, alcohol use, the environment, and access to health care (53). Currently, several initiatives and health systems such as Marshfield Clinic Health System, HealthPartners, Kaiser Permanente, Apple Tree Dental and others, are addressing these challenges (26, 54–56).

Larger Links

Connecting a private dental practice to a larger health system such as an accountable care organization could introduce provider communication quality measures, such as measuring the extent to which the doctor listens carefully to patients, and explains things in a way patients can understand (57). Training physicians on The Joint Council of Accreditation's "What did the doctor say? Improving Health Literacy to Protect Patient Safety" (58) offers a roadmap for how dental education curricula could incorporate health literacy principles to improve safety and quality in next generation dental practitioners. These organizational standards help hospitals, ambulatory care facilities, and behavioral health facilities achieve a higher quality of care and patient safety. The provision of educational materials to medical practices on the Universal Precautions Health Literacy Toolkit, and the importance of adopting the National Standards for Culturally and Linguistically Appropriate Services (CLAS) can facilitate patient understanding of care instructions (59).

Separate Insurance

The lack of a common insurance system to handle medical and dental coverage is a point of serious confusion for even the most health literate consumers. Preventive messages from physicians rarely include the association with dental diseases, such as caries, which continues to be the condition representing the highest global burden of disease (60). This missed opportunity increases the challenge for people with lower health literacy to learn about the connection between the mouth and body, and to recognize the need for daily prevention and regular dental visits. Recent studies have demonstrated that medical organizations can reduce overall health care costs (predominantly hospital costs) for people with chronic medical conditions, such as diabetes by covering the cost of periodontal cleanings (61, 62). This approach provides an opportunity for enhanced education.

Workforce and Beyond

The report of the Primary Care Collaborative for 2021 provides a timely snapshot of the current state of innovations in oral health and primary care integration. A call to action recommends expanding oral health coverage and access, aligning oral health and primary care with new payment models, and enhancing the health workforce (31). Each of the integration challenges and their solutions have clear health literacy implications. Implementing the proposed "health literate care model" as described by Koh et al. could provide additional support and reinforce oral/medical integration practices (43). This approach could foster the anticipated health care transformation toward a greater prevention orientation, population health focus, and primary and social care-based systems (63).

CONCLUDING COMMENTS

The long-recognized need for oral and general health care integration has grown. Achieving such integration is complex and difficult, requiring a long-term commitment and coordinated efforts. Work to achieve integration has resulted in progress in some areas but remains challenging in others, necessitating a call for new and different approaches. A coordinated, sustained, multilevel approach that includes health literacy is needed. Along with investments in science assessments of policies and laws and their impact on the determinants of health are needed as well as implementation of quality improvement methods for clinical and public health services and systems.

The Oral Health Literacy and Health Integration Framework provides an interconnected structure to inspire discussion, drive policy and practice actions, and guide future research and intervention. We adapted the 2004 IOM health literacy framework (1), adding oral and general health integration, with an accompanying rationale for partnering health literacy and integration. The power of both personal and organizational health literacy efforts provides a strong foundation for an ever-changing and evolving society and environment. We propose that using the lens of the public we serve, health care providers we support, and policy-makers we inform adds an important dimension to foster systems thinking.

The Framework was developed to acknowledge the complexity of efforts needed to achieve an equitable health system that includes oral health, highlights the critical partnering role of health literacy, and stimulates systems thinking and systems-oriented approaches. Stroh's description of when the value of systems thinking is most effective suits the current stage and problems of integrating oral and general health. As Stroh [(64) p. 23–24] wrote, incorporating systems thinking into a broader systems approach is especially effective when:

- "A problem is chronic and has defied people's best intentions to solve it.
- Diverse stakeholders find it difficult to align their efforts despite shared intentions.
- They (diverse stakeholders) try to optimize their part of the system without understanding their impact on the whole.
- Stakeholders' short-term efforts might actually undermine the intent to solve the problem.
- People are working on a large number of disparate initiatives at the same time.
- Promoting particular solutions (such as best practices) comes at the expense of engaging in continuous learning."

An essential part of the systems thinking process involves taking the time to explore the direct and indirect contributing factors and to identify intended and unintended consequences. It also requires a continuous quality improvement and engagement approach.

Next steps involve testing the use of the Oral Health Literacy and Health Integration Framework as a tool to help with our collective work and impact. An initial phase may include mapping existing oral and general health integration efforts and noting the degree to which they include health literacy. The activity clusters could be used to identify advances, reveal knowledge gaps and inform collaborative efforts. Ultimately, we should strive for a common agenda with mutually reinforcing activities, shared measurement, and continuous communication.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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A Multi-Disciplinary Review on the Aerobiology of COVID-19 in Dental Settings

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The COVID-19 pandemic pushed dental health officials around the world to reassess and adjust their existing healthcare practices. As studies on controlled COVID-19 transmission remain challenging, this review focuses on particles that can carry the virus and relevant approaches to mitigate the risk of pathogen transmission in dental offices. This review gives an overview of particles generated in clinical settings and how size influences their distribution, concentration, and generation route. A wide array of pertinent particle characterization and counting methods are reviewed, along with their working range, reliability, and limitations. This is followed by a focus on the effectiveness of personal protective equipment (PPE) and face shields in protecting patients and dentists from aerosols. Direct studies on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are still limited, but the literature supports the use of masks as an important and effective non-pharmaceutical preventive measure that could reduce the risk of contracting a respiratory infection by up to 20%. In addition to discussing about PPE used by most dental care professionals, this review describes other ways by which dental offices can protect patients and dental office personnel, which includes modification of the existing room design, dental equipment, and heating, ventilation, and air conditioning (HVAC) system. More affordable modifications include positioning a high-efficiency particulate air (HEPA) unit within proximity of the patient's chair or using ultraviolet germicidal irradiation in conjunction with ventilation. Additionally, portable fans could be used to direct airflow in one direction, first through the staff working areas and then through the patient treatment areas, which could decrease the number of airborne particles in dental offices. This review concludes that there is a need for greater awareness amongst dental practitioners about the relationship between particle dynamics and clinical dentistry, and additional research is needed to fill the broad gaps of knowledge in this field.

Keywords: COVID-19, particle measurement, bioaerosol, dental procedures, particle topography

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the causative virus of coronavirus disease-2019 (COVID-19), presents challenges greater than that posed by seasonal influenza ($R_0 \sim 1.2$), Middle East respiratory syndrome (MERS) ($R_0 \sim 1.4$), or severe acute respiratory syndrome (SARS) ($R_0 \sim 3$) due to its high reproductive number ($R_0 = 1.4–3.9$) (1–3). The most recent global assessment of R_0 for COVID-19 is 4.08. This high reproductive number contributed to the unprecedented global spread of SARS-CoV-2 (4).

According to a scientific brief published by the WHO on March 29, 2020, the primary transmission mode of SARS-CoV-2 is through respiratory droplets and contact routes (i.e., oral secretions) with a diameter >5 μm (5, 6). These droplets enter the air through speaking, coughing, and sneezing by individuals in close contact with each other (5–8). Short-range inhalation of aerosols can be a route of COVID-19 transmission as with many respiratory pathogens (9). Oral cavity is another important site for SARS-CoV-2 infection (10). The most reported mode of pathogen spread is through respiratory droplets. Individuals that are pre-symptomatic or asymptomatic do not significantly cough or sneeze, yet are responsible for more than 50% of COVID-19 transmission (11), and hence it is important to study the effect of particles expired through normal breathing and oral cavity secretions (10, 12).

Dental practices across the globe closed down for non-emergency dental care during peak COVID-19 periods because of the higher risk of virus transmission during dental appointment due to the close proximity of patient–provider and the use of modern dental tools, such as high-speed handpieces, ultrasonic scalers, air turbines, and air-water syringes, in the presence of contaminated salivary secretions (5, 10, 13–15). It is important to note that dental professionals demonstrated high compliance (72.8%) to CDC guidelines during the COVID-19 pandemic, which has led to very low cases of COVID-19 transmission in dental settings (16). In this review, the authors present studies focused on the transport of particles, the various methods of characterizing the particles, bioaerosols in dentistry, and finally recommendations for reducing the transmission of potentially virus-laden droplets generated during routine dental treatments.

PARTICLES

To better understand the modifications that could be adopted by dental offices to minimize transmission of SARS-CoV-2, the team elaborates on the definition of particle and droplet, transmission of particles *via* bioaerosols, and the natural production and dissemination of aerosols produced during cleaning or treatment at a dental office.

Definitions of Particle and Droplet

In dental settings, particles are generated from patient–provider interactions, dental equipment, and dental procedures. Our review defines droplets as water-based with a mean diameter >5 μm. Aerosols (or airborne nuclei) are defined as liquid or solid particles typically <5 μm in diameter. Particulate matters (PMs) are arguably interchangeable with aerosols and typically refer to solid (or liquid) particles in the size range of sub-micron to 10 μm. Particle concentration refers to the count (or particle mass) per unit volume, e.g., count/m^3 (or μg/L).

Size influences the behavior and trajectory of droplets and aerosols/particles. Within a 1 m radius, droplets larger than 50 μm display ballistic or jet-like movements. Intermediate size droplets can either fall on the surface or can stay in the air and travel approximately 2 m before settling down. Smaller droplets and aerosols are the least impacted by gravity and can stay airborne for long durations. For example, a dust particle with a diameter of 10 μm falls 1 m in air at rest in ∼5.5 min, whereas a 1 μm particle takes over 9 h to travel the same distance. Owing to air currents, such small particles may spread throughout the room, especially after the volatile liquid in the droplet dries out (17).

Bioaerosols Production and the Influencing Factors

Human lungs inspire approximately 0.5–0.75 L per breath during rest. Air expelled through nasal respiration produces an exit velocity of ∼0.5 m/s, whereas the exit velocity while speaking with a normal volume and pace exhibits ∼0.3 m/s. In contrast, during periodic coughing, the exit velocity dramatically increases to 4–5 m/s (18). Direct observations of human sneezing and coughing reveal that these airflows consist of initially hot and moist turbulence followed by cool and buoyant clouds containing droplets of varying sizes. A single cough may expel ∼700 particles as compared with a sneeze that may produce over 40,000 particles (19). In this regard, most of the particles and droplets produced from a sneeze are relatively large and may be easily blocked by the use of a simple mask. In addition to coughing and sneezing, speaking can generate droplets of size ranging from 20 to 500 μm (5). However, the estimated concentration of droplets per cough is 2.4–5.2 cm^{-3}, which is significantly more than that of speech, 0.004–0.223 cm^{-3} (20).

In addition to particle size, environmental factors such as temperature and relative humidity influence the potency and distribution of infectious respiratory droplets and particles. For example, a 100 μm droplet will evaporate in approximately 10 s after expulsion while a 1 μm droplet will evaporate within 0.001 s (19). Increased air temperature, however, leads to an immediate decrease in particles post expulsion. By contrast, however, in an environment of elevated humidity, these numbers increase. Regardless of humidity or temperature, particles or droplets with a diameter of <0.1 μm evaporate almost immediately or cannot contain enough viral material to be infectious (9).

Viruses can be transmitted *via* droplets produced by sneezing and coughing, with diameters varying in the range of 0.1 μm-0.9 mm (21). Once an individual begins coughing, the duration and position of the mouth influence the area covered by the expelled droplets, which can degrade into categories of smaller size (9). Viral, fungal, and bacterial particles react in different ways depending on changes in temperature or humidity of the environment. The maximum stability of influenza occurs at 20–40% humidity and has a minimum stability at 50% humidity (22). Studies have suggested that SARS-CoV-2 exhibits similar survival curves in response to increases in temperature and humidity (23). With respect to coronaviruses at room temperature, they remain viable on surfaces for up to 9 days (24). At temperatures $>30^{\circ}$C, the survival of these viruses decreases dramatically (24).

Bioaerosols in the Practice of Dentistry

Dissemination of Microorganisms

Dissemination of microorganisms in dental operatories can occur directly, by contact with bacteria on the surfaces of dental instruments and dental providers, or indirectly, *via* splatter of droplets larger than 100 μm in diameter or by particles $<100\ \mu$m in diameter suspended in air (25). Most dental bioaerosol studies have investigated bacterial colonies on the surfaces of dental instruments as the main pathogen. The potential for disease transmission of airborne bacteria (e.g., tuberculosis), viruses (e.g., measles and SARS), and bloodborne viruses, which can become aerosolized by blood splatter *via* high-speed handpieces used in dentistry and orthodontics, is not known (26–28). COVID-19 transmission is primarily through respiratory droplets and less likely through fomite transmission (29). The two most notable sources of droplet and aerosol generation in dental settings are procedures involving air turbine handpieces and ultrasonic instruments.

Air Turbine Handpieces

Studies have demonstrated that air turbine handpieces atomize 20 times more bacteria when compared to air spray. This production of bioaerosols is equivalent to the concentration produced by biological motions such as sneezing (30). A prophylactic hygiene handpiece with a pumice cup and pumice is often used for cleaning teeth. This common dental procedure produces a volume of aerosolized bacteria comparable to that resulting from a cough (31). *Tubercle bacilli* were found in droplet scatterings generated by dental air turbine handpieces within a range of 6 inches to over 4 feet from the patient's mouth (26). This distance is larger than the distance between providers and patients, indicating a working dentist/assistant will undoubtedly be affected (30).

Ultrasonic Instruments

Ultrasonic instruments also produce significant amounts of aerosols and the vibration of the tip generates significant amounts of heat. Water is used to cool the instrument, which results in the generation of significant splatter. When mixed with saliva and plaque from the oral cavity, aerosolized splatter from ultrasonic instruments has the potential to become highly infectious and a major risk factor for disease transmission (31). Moreover, ultrasonic instrumentation can transmit 100,000 microbes/ft^3 with aerosolization of up to 6 ft (32). In the absence of a favorable air current, microbes can survive for a period ranging from 35 min to 17 h. Using microbiological analysis, significantly higher bacterial counts were detected after scaling treatments, with the presence of Staphylococcus and Streptococcus species being the most notable (26). Results also showed high numbers of colony forming units (CFUs) and identified strictly oral anaerobes on all microbial plates from both groups, which meant that a significant amount of contamination occurred during ultrasonic scaling (26).

METHODS OF CHARACTERIZING BIOAEROSOLS

Aerosolized particles can be classified into three categories: natural (e.g., fog, dust, and mist), anthropogenic (e.g., air pollution and smoke), and biological (e.g., bioaerosols) which are primarily released by humans and animals. These particles are carried through natural and anthropogenic means (33, 34). Bioaerosols contain both volatile and non-volatile material and their behavior and transmissibility depend on their size. Smaller bioaerosol particles penetrate more easily and go farther into the respiratory tract, which means they are more likely to transmit diseases compared to the larger particles (19).

Over the years, researchers have developed a variety of instruments to assist with particle sizing and classification. A broad list of instruments used in bioaerosol particle counting and sizing is presented in **Table 1**, and a summary of measured particle size distributions is shown in **Figure 1**. More recently, researchers have started using machine learning to analyze SARS-CoV-2 infected particles (44).

RECOMMENDATIONS TO MINIMIZE COVID-19 TRANSMISSION IN DENTAL SETTINGS

Patient/Staff as Source of Particle

Although there are differences in aerodynamic behavior and properties between droplets and particles, both provide mechanisms for transmitting pathogenic microorganisms between patient and dental personnel. Human interactions (speaking, sneezing, and coughing), even without any symptom, can be a source of respiratory pathogen transmission in an indoor setting (5, 20), such as in dental offices. Dental providers working with high-speed handpieces have routine exposure to bodily fluids including respiratory particles and oral secretions (10, 34). Ultrasonic scalers, air turbines, three-in-one syringes, and air-water syringes are also significant contributors to bioaerosol generation (31).

Personal Protective Equipment

Personal protective equipment (PPE) is an important mitigation strategy (45). Global sources for producing PPE continue to be insufficient due to a large number of COVID-19 cases, misinformation, panic buying, and stockpiling (6). It is imperative to revisit the current and developing PPE options with respect to their efficacy. The WHO has listed the following PPEs as necessary for healthcare workers: medical masks, N95 respirators, filtering facepiece respirators-2 (FFP2) standard or equivalent, gowns, gloves, aprons, and eye protection (goggles or face shields) (6). A recent study on COVID-19 prevalence among dentists, while adhering to

TABLE 1 | Experimental methods used for particle count and characterization.

Method	Description	Select bioaerosol studies and comments
Aerodynamic particle sizer (APS)	Uses the principle of inertia to size particles. Particles pass between two laser beams and the scattered light is collected on a photodetector. By measuring the time delay between pulses generated as particles pass through the laser beams, the velocity and diameter of particles are measured.	Morawska et al. (35): studied particle concentration and size distribution near the mouth for a range of breath exercises. Voiced activities produced higher particle concentrations than whispered ones which indicated particles were produced by the vibrating vocal cords. Whispered counting and breathing produced similar amount of particles.
Andersen cascade impactors (ACI)	Also known as cascade sampler impactors. Used to measure the size distribution of non-volatile aerosolized particles (36). A suction pump is used to draw air through a series of 6-8 stages which are used to separate different particle sizes.	Two types can be found; one for viable particles (meaning viruses and bacteria which can be grown on a series of Petri dishes) and the other for non-viable particles.
Droplet deposition analysis (DDA)	Uses optical or electron microscopes to measure the size of deposited droplets on a surface by using a substrate which preserves traces of the deposited droplets.	Duguid (37): measured the droplet size of sneezing, coughing, and speaking. Found similar size distribution for all activities, but smaller droplets much more frequent in sneezing. 95% of droplets were between 2 and 100 μm. Most common are in the range of 4-8 μm (38).
Interferometric Mie imaging (IMI) and particle image velocimetry (PIV)	An out-of-focus imaging technique of particles illuminated by a laser light sheet (39). It may be used simultaneously with particle image/tracking velocimetry (PIV/PTV) to measure instantaneous velocity fields.	VanSciver et al. (40): measured cough velocity of 29 healthy subjects within the range of 1.5 and 28.8 m/s. Chao et al. (20): studied 11 human subjects and measured the size distribution and velocity of droplets during speaking and coughing using IMI APS and PIV. Found the mean diameter of particles was 13.5 and 16 μm and velocity was 11.7 and 3.1 m/s for coughing and speaking respectively. Zhu et al. (41): studied transport properties of the saliva droplets of coughing in an indoor environment by using both PIV and numerical methods. The initial coughing velocity was estimated between 6 and 22 m/s with an average velocity of 11.2 m/s and the impacted area was 2 m or larger.
Laser diffraction (LD)	Utilizes the light scattering principle to measure the distribution of particle size by determining the unique variations in the intensity of light scattered as a laser beam travels through a scattered particulate sample. Large particles scatter light at small angles and vice versa. The angular light intensity data is then evaluated to assess the size of the particles responsible for producing such scattering patterns.	Zayas et al. (21): used laser diffraction to measure voluntary cough aerosols of 45 healthy non-smokers and found a size range of 0.1-900 μm of which 97% of droplets were found to be less than 1 μm.
Optical particle counters (OPC)	Works on the concept of light scattering from illuminated particles. Two types are generally found: LED and laser-based counters; the first is better for counting larger particles, while the latter is better for smaller particles.	Papineni and Rosenthal (42): measured exhaled droplets from mouth breathing, nose breathing, coughing, and talking. They also used an analytical transmission electron microscope (analytical TEM) and found particle sizes with the OPC in the range of 0.3-2.5 μm and with the analytical TEM in the range of 0.4-7.6 μm. Edwards et al. (43): measured expired air particle count and size and reported the size range of droplets between 0.085 μm and >0.5 μm with a mode between 0.15 and 0.2 μm.
Spray droplet size analyzer (SDSA)	A laser diffraction-based droplet sizer that can detect aerosols and particles between 0.1-2,000 μm.	Lindsley et al. (22): measured the concentration of aerosols from a cough aerosol simulator. A major peak in aerosol concentrations was measured in the size range of 3-10 μm.

the listed PPEs, indicated a very low percentage of only 0.9% (16). While combinations of PPE are recommended, the effectiveness of specific PPE at preventing SARS-CoV-2 infection has not been quantified. Determining the effectiveness of PPE is complicated due to the limited controlled human infection studies. "Silent spreaders" may expose healthcare workers at work and elsewhere if basic non-pharmaceutical interventions are not universally adopted and enforced (46, 47). In the absence of PPE measures, historical data from similarly transmitted respiratory diseases, such as tuberculosis in dental settings showed a transmission of 10%, which was more than double the reported data from the National Health and Nutrition Examination Survey (NHANES) in the year 2000 (48).

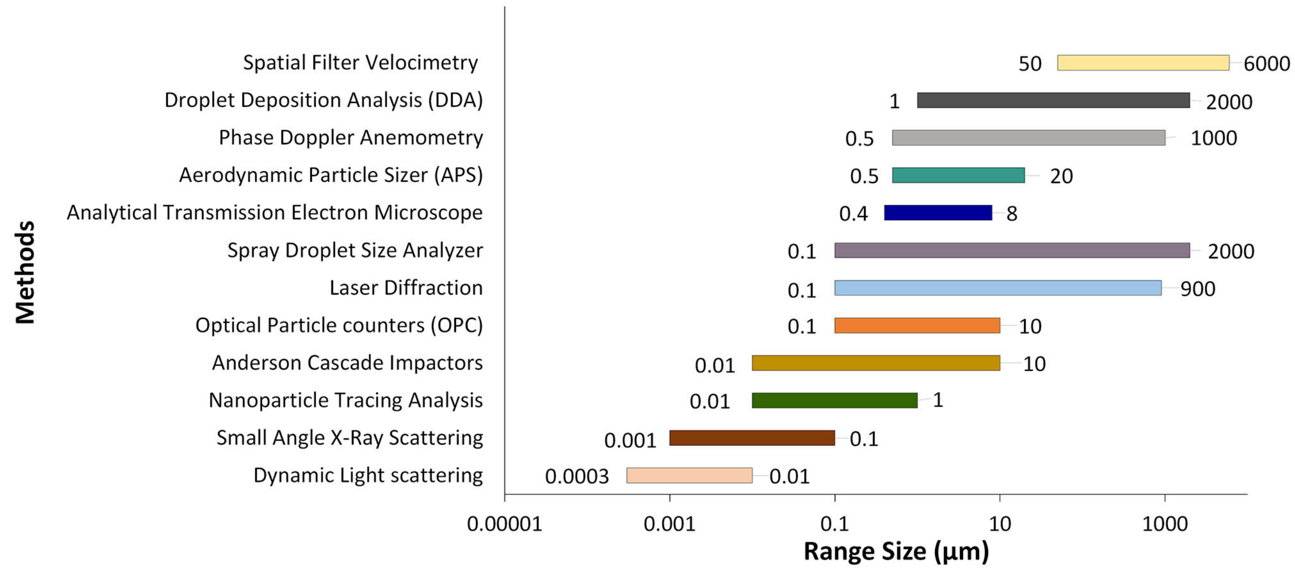

FIGURE 1 | A summary of identified bioaerosol particle size distributions measured using select methods.

Face Shields

Most harmful particles are generated during the initial part of a cough (49). Healthcare providers working at a distance of 46 cm from an infected patient may inhale 0.9% of these harmful particles. Wearing a face shield can reduce the inhalation of aerosols by 96% and surface contamination by 97% for droplets with a volume median diameter (VMD) of 8.5 μm. However, for smaller droplets with a VMD of 3.4 μm, the reduction rates are lower with 68 and 76% for aerosols and surface contamination, respectively (45). Face shields may reduce the inhalation of large harmful aerosol particles for a short time. However, smaller particles remain in the air for longer periods and could bypass the face shield. These particles pose inhalation risks for healthcare providers and patients (50).

Face Masks

A study conducted on 47 human subjects with influenza showed that the average cough profiles had a volume of 4.16 L with a peak flow rate of 11.1 L/s (22). A mask designed to suppress droplets at this volume and flow rate could be an effective inhibitor for smaller cough volumes and lesser peak flow rates (18). A different study reported that each patient suffering from influenza released ∼38 pL of particles in the size range of <10 μm. After being diagnosed and receiving treatment, the study participants released ∼26 pL of particles per cough. Droplets become infectious when they encounter the mucous membranes, e.g., oral and nasal cavities of the body (51). Studies on influenza-related diseases support the use of surgical masks for effective reduction of infection (47). Using masks in crowded places could reduce the risk of contracting influenza-like respiratory infections by 20% (52). Masks made of foam, cloth, or paper are less effective at filtering bacterial aerosols (50).

Masks vs. Respirators

According to the CDC, the N95 FFP can block at least 95% of 0.3 μm particles. Most research pertaining to the efficacy of face masks has been done by quantifying the number of respiratory viruses in exhaled breaths of participants with acute respiratory virus illness (17). Surgical masks can effectively reduce the emission of influenza-laden respiratory droplets but not particles (53). When subjects cough while wearing a surgical mask or N95, the dispersion of forward moving viral aerosol particles decreases but the lateral dispersion patterns of particles increases (54). N95s and surgical masks offer similar levels of protection against viral infection of respiratory diseases in non-aerosol producing environments (55).

Equipment as Source of Particles (Room Design/Equipment Modification)

Dental buildings can contain high levels of circulating bioaerosols. Air-conditioning and ventilation systems in these settings should be maintained on a regular basis to minimize recirculation of contaminants (56). Cooling towers, air-conditioning, and mechanical ventilation systems are known sources of *Legionella pneumophila* (57). The risks to dentists, patients, and others who are routinely exposed to bioaerosols remain unclear, prompting the need for further research (14).

Office or Clinic Design

Multiple actions can be taken to decrease the transmission of infectious particles in healthcare settings. Electronic-based patient triages and check-ins, automatic doors, motion-sensing lights, and hand-sanitizer dispensers reduce the physical interface among patients, physicians, and interior surfaces. The use of thermal imaging to screen for elevated body temperatures ensures a safe distance between ingress patients and office staff while shortening the initial screening process. Since dental procedures generate mists and aerosols, local exhaust ventilation should be positioned with consideration of the aerosol flow direction as well as the location of the physician and the patient (9, 58–61).

Heating, Ventilation, and Air Conditioning System Design

Dental offices are advised to use a systems-based approach with engineering controls to minimize cross contamination. For example, fans could be used to direct the airflow first through the staff working areas and then through the patient treatment areas, thereby reducing workplace risks involving airborne particles or droplets (62). Positioning of patients in front of each other should be avoided whenever possible (9). Operatories should be oriented parallel to the direction of airflow, which will assist in directing the flow of airborne contaminants (62).

The CDC also recommends positioning the heads of patients away from pedestrian corridors and closer to the back wall and return air vents (9, 63). Several studies have evaluated the characteristics of plumes generated by exhaled droplets and noted that a top exhaust system is more efficient than the traditional air conditioning systems (64). Ultraviolet (UV) germicidal irradiation, including UV-C at 254 nm, in conjunction with ventilation is emerging as a cost-effective tool for reducing viral aerosols (52, 65, 66). In the design of future dental offices, the designation of negative-pressure isolation rooms, antechambers, and 24/7 HVAC systems could improve aerobiological controls (63).

Interior Design

It is important to consider an interior design that prompts safe conduct of ordinary activities. Visual signage is a good option to communicate instructions clearly to the general public. For example, clear marking of risk zones with visual aids or creating visual cues for specific activities raises awareness and allows policies to be followed easily (58). Additionally, creating signage that indicates "clean" areas around donning rooms and PPE carts can establish easy-to-follow protocols. Efficient and regimented routines create less interaction and reduce cross-contamination. The efficacy of visual signage is increased if supplemented with an office culture based on safety and education. Additionally, anti-bacterial surface coatings reduce healthcare-associated infections (HAIs) by 36% while also decreasing CFUs and clinically relevant pathogens by ∼59–75% (67). Other design initiatives worth considering are sanitizing stations, maintaining social distancing whenever possible in the reception and treatment rooms, and dedicated PPE recycling bins in each room (58).

CONCLUSIONS

Respiratory droplets are the primary mode of SARS-CoV-2 transmission. Human and simulated studies have demonstrated that sneezing and high-volume coughs in patients pose a significant risk for viral transmission. Environmental conditions effect the potency of viruses shed from human coughing and sneezing as well as dental procedures. SARS-CoV-2 reacts inversely to temperature and humidity, which are factors that can be controlled in a closed dental setting. One of the biggest concerns for dental providers is the working proximity to potentially active SARS-CoV-2 sources, as intermediate size (10–50 μm) droplets can travel as far as 2 m away from the source. Furthermore, these droplets are easily disseminated by air currents. Surgical masks and respirators appear to provide significant protection against viral particle transmission from infected individuals, although the risk is not completely eliminated. While we highlighted various methods used to study the size and distribution of airborne droplets and particles, these methods for the most part do not measure the viral load and more specialized tools need to be developed. Implementing some of the recommendations we proposed and a greater awareness amongst dental practitioners about the relationship between particle dynamics and clinical dentistry, can help improve safety in dental practice. Finally, while this review provides a broad overview of past and current studies related to pathogen and particle transmission in dental settings, there is a clear gap in our understanding of how dental practices specifically affect the transmission of SARS-CoV-2; therefore, much more research is needed in this area. This knowledge is imperative to addressing the current crisis, and those that might be faced in the future.

AUTHOR CONTRIBUTIONS

All authors gave their final approval and agreed to be accountable for all aspects of the work.

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