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Consideration of Ketogenic Metabolic Therapy as a Complementary or Alternative Approach for Managing Breast Cancer

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Breast cancer remains as a significant cause of morbidity and mortality in women. Ultrastructural and biochemical evidence from breast biopsy tissue and cancer cells shows mitochondrial abnormalities that are incompatible with energy production through oxidative phosphorylation (OxPhos). Consequently, breast cancer, like most cancers, will become more reliant on substrate level phosphorylation (fermentation) than on oxidative phosphorylation (OxPhos) for growth consistent with the mitochondrial metabolic theory of cancer. Glucose and glutamine are the prime fermentable fuels that underlie therapy resistance and drive breast cancer growth through substrate level phosphorylation (SLP) in both the cytoplasm (Warburg effect) and the mitochondria (Q-effect), respectively. Emerging evidence indicates that ketogenic metabolic therapy (KMT) can reduce glucose availability to tumor cells while simultaneously elevating ketone bodies, a non-fermentable metabolic fuel. It is suggested that KMT would be most effective when used together with glutamine targeting. Information is reviewed for suggesting how KMT could reduce systemic inflammation and target tumor cells without causing damage to normal cells. Implementation of KMT in the clinic could improve progression free and overall survival for patients with breast cancer.

Keywords: glycolysis, survival, glutaminolysis, non-toxic, fermentation, metastasis, inflammation

INTRODUCTION

Breast cancer persists as a significant cause of morbidity and mortality in woman. According to the American Cancer Society, the number of new cases and deaths from breast cancer in US woman is estimated to be 268,600 and 41,760, respectively, for 2019 (1). Indeed, breast cancer alone will account for 30% of all female cancers. Although the incidence of breast cancer is lower in black women than in white women, the death rate is 41% higher in blacks than in whites possibly due

in part to diet and lifestyle (2). The failure to effectively manage malignant breast cancer, and most malignant cancers for that matter, comes in large part from a misunderstanding on the origin of cancer. Although cancer has long been considered a genetic disease based on the somatic mutation theory (3–5), recent revelations have raised serious concerns that question the validity of this theory. Major concerns include:

1 The absence of gene and chromosomal mutations in some cancers (6–9). Indeed, Greenman et al. found no mutations following extensive sequencing in 73/210 cancers (3), while Parsons et al. found no mutations in the P53, the PI3K, and the RB1 pathways in the Br20P tissue sample of a glioblastoma patient (10). Such samples should not exist according to the somatic mutation theory.
2 The presence and clonal expansion of numerous so-called driver gene mutations in a broad range of normal human tissues including breast tissue (11–15). It is not clear how the somatic mutation theory can account for malignant tumors that have no mutations or for normal cells and tissues that express driver mutations.
3 The absence of breast cancer and most other cancers in chimpanzees despite having about 98.5% gene and protein sequence identity with humans even at the BRCA1 locus (16–19). Indeed, breast cancer has never been documented in a female chimpanzee suggesting that diet and lifestyle issues, rather than genetic mutations, are largely responsible for the disease (18, 20).
4 The nuclear/cytoplasm transfer experiments showing that normal cells and tissues can be produced from tumorigenic nuclei as long as the tumorigenic nuclei are localized in cytoplasm containing normal mitochondria (21). Furthermore, recent studies show that normal mitochondria can down-regulate multiple oncogenic pathways and growth behavior in metastatic breast cancer cells (22, 23). These findings show that normal mitochondrial function can suppress tumorigenesis regardless of the gene or chromosomal abnormalities that might be present in the tumor nucleus. Viewed collectively, these findings suggest that the somatic mutations found in breast cancer and in most other cancers are not the primary cause of the disease. It is therefore unlikely that therapeutic strategies based on the somatic mutation theory will have major impact on the management of most cancers including breast cancer.

THE MITOCHONDRIAL METABOLIC THEORY OF CANCER

Emerging evidence indicates that most if not all cancers display deranged energy metabolism (24–35). It is well-documented that the tumor cells found in most cancerous tissues including breast cancer tissue, have abnormalities in the number, structure, and function of their mitochondria (26, 27, 29, 33, 36–42). These abnormalities would compromise efficient energy production through oxidative phosphorylation (OxPhos). **Figure 1** documents ultrastructural abnormalities in breast cancer mitochondria that are linked to abnormalities in proteins of the electron transport chain (43). In addition to abnormalities in mitochondrial membranes, breast cancer cells also express abnormalities in mitochondrial-associated membranes (MAM), that would further reduce energy production through OxPhos (44, 45). Consequently, increased fermentation metabolism would be necessary to compensate for OxPhos deficiency in order to maintain sufficient energy for breast cancer viability and growth.

AEROBIC FERMENTATION OF GLUCOSE AND GLUTAMINE IN CANCER CELLS

Glucose and glutamine are the major fermentable fuels used by cancer cells with impaired OxPhos (39, 46). Glucose is fermented to lactic acid through glycolysis in the cell cytoplasm, while glutamine is fermented to succinic acid through glutaminolysis in the tricarboxylic acid (TCA) cycle. Notably, both fermentation processes can generate energy in the presence or absence of oxygen through substrate level phosphorylation (SLP) at the pyruvate kinase reaction in glycolysis and at the succinate ligase reaction in glutaminolysis, respectively (46). Warburg first described the aerobic fermentation of glucose as a major phenotype of most cancers (47–51). This metabolic phenotype has become known as the Warburg effect (52). In contrast to the Pasteur effect, where fermentation is suppressed in the presence of oxygen, the Warburg effect involves robust glucose-derived lactic acid fermentation even in the presence of 100% oxygen (aerobic fermentation).

GLUTAMINOLYSIS

In addition to aerobic fermentation in the cytoplasm, glutaminolysis can also support high-energy phosphate synthesis in the mitochondria through the sequential conversion of glutamine-glutamate-*alpha*-ketoglutarate-succinyl CoA-succinate (**Figure 2**) (46). ATP synthesis through the succinate-CoA ligase reaction in the TCA cycle can compensate for reduced ATP synthesis through either glycolysis or OxPhos. We recently proposed that most of the ATP synthesized in tumor cells would come from mitochondrial substrate level phosphorylation (mSLP) at the succinate ligase reaction (46). Evidence showing that mSLP can compensate for OxPhos deficiency in cancer is emerging (57–60). mSLP could also compensate for minimal energy production through glycolysis due to the predominance of the glycolytic pyruvate kinase M2 (PKM2) isoform, which produces less ATP than the PKM1 isoform (61). The PKM2 isoform is predominant in many cancers including breast cancer (62, 63). As *Q* is the single-letter designation of glutamine, the aerobic fermentation of glutamine through mSLP was recently defined as the *Q effect*; which has been recognized as the missing link in the mitochondrial metabolic theory of cancer (32, 46, 64, 65).

Abbreviations: SLP, Substrate level phosphorylation; KMT, Ketogenic metabolic therapy; OxPhos, Oxidative phosphorylation; EMT, Epithelial mesenchymal transition; GKI, Glucose Ketone Index; SUCL, succinate-CoA ligase.

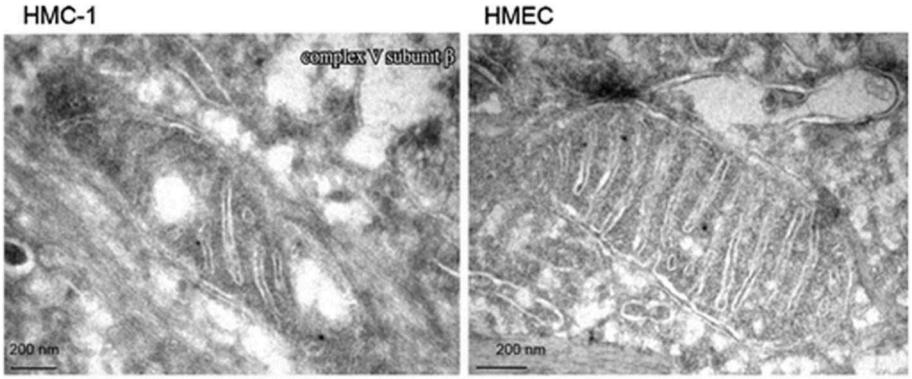

FIGURE 1 | Electron microscopy of primary breast cancer cells (human mammary carcinoma HMC-1) and human epithelial mammary cell control line (HEMC). Abnormal mitochondrial morphology in the HMC-1 cell showing loss of invaginations and vacuoles. These abnormalities in mitochondria ultrastructure were linked to abnormalities in the electron transport chain and are in general agreement with those from other studies of breast cancer mitochondria (37, 40, 42). Reprinted with permission from Putignani et al. (43).

Unfortunately, the glutaminolysis pathway and the role of glutamine and mSLP was unknown to Warburg (46). We find it remarkable that nearly all of the major reviews or previous studies on cancer energy metabolism have not addressed or possibly even recognized the role of SUCL activity and mSLP, as a compensatory energy mechanism for deficient OxPhos. We consider mSLP as the key mechanism that underlies energy production in tumor cells with defective respiration (46).

Aerobic fermentation (Warburg effect) is a common metabolic phenotype in breast cancer regardless of histopathological type, grade, or gene expression profile (24, 66–74). In addition to glucose, glutamine is the other major fuel necessary for breast cancer cells (73, 75–78). The elevated utilization of glucose and glutamine becomes necessary to sustain the viability of OxPhos-impaired cancer cells through SLP in the cytoplasm and mitochondria, respectively. The Q-effect provides a rational explanation for the high glutamine use in cells with compromised OxPhos (46). The aerobic fermentation of glucose and glutamine in cancer cells would be the expected consequence of impaired OxPhos, as fermentation can compensate for insufficient respiration. Some have suggested that the function of the Warburg-effect is to provide a growth advantage for tumor cells. This is a teleological explanation, i.e., design with a purpose or intelligent design, which should not be part of modern biological thought (79–81). Cells do not make choices or have preferences, but simply respond to conditions in their internal and external environments according to evolutionarily designed metabolic programs. As proliferation, rather than quiescence, is the default state of metazoan cells (8, 82), unbridled proliferation becomes the consequence when fermentation gradually replaces respiration in cancer cells (21, 83, 84). Indeed, unbridled proliferation was the dominant growth phenotype of all organisms that existed on the planet before oxygen entered the atmosphere some 2.5 billion years ago (83). Hence, glucose and glutamine become the drivers of cancer cell fermentation and growth.

FIGURE 2 | The glutaminolysis pathway. The succinyl-CoA ligase reaction, metabolizing succinyl-CoA to succinate, produces high-energy phosphates (ATP) in the absence of oxidative phosphorylation through the process of substrate-level phosphorylation in the mitochondrial matrix. Provision of succinyl-CoA by the α-ketoglutarate dehydrogenase complex is crucial for maintaining the function of succinyl-CoA ligase thus preventing the adenine nucleotide translocase from reversing. Succinate contributes to inflammation and stabilizes Hif-1a, a key transcription factor that contributes to the aerobic fermentation (53–56).

ROLE OF REACTIVE OXYGEN SPECIES (ROS) AND ONCOGENES IN THE ORIGIN AND PROGRESSION OF CANCER

Impaired OxPhos together with compensatory fermentation leads to the accumulation of reactive oxygen species (ROS) (85–87). ROS are carcinogenic and mutagenic, and are largely responsible for the genomic instability and mutations seen in tumor cells (85, 87–93). In other words, the mutations seen in tumor cells arise as a consequence of impaired energy metabolism (32, 64). Oncogenes such as *Hif-1alpha*, *Myc, Ras, BRAF*, etc., facilitate the dependence of tumor cells on glucose and glutamine while defects in the tumor suppressor genes *p53* and *pRb* will compromise OxPhos function thus causing further dependency on fermentation for growth (28, 46, 84, 94–99). These genes mutations are linked to breast cancer and other cancers through mitochondrial dysfunction. Compromised OxPhos would require compensatory glucose and glutamine fermentation to maintain membrane pump activity and tumor cell viability (64, 100). A mutation in the *p53* gene was found to increase glucose consumption and the

Warburg effect, whereas the retinoblastoma Rb protein was found to increase glutamine metabolism through an effect on the E2F-3 transcription factor (101, 102). Mutations in these and in other oncogenes, and tumor suppressor genes, have been detected in breast cancer cells (103, 104). It is interesting that Her2 signaling in breast tumor promotes glycolysis and glucose utilization with lactate accumulation (105). Moreover, the ErbB2 targeting antibody, trastuzumab (Herceptin), inhibits glycolysis via downregulation of HSF1 and LDH-A in ErbB2-positive cancer cells. The results of Ding suggest that ErbB2 not only promotes glycolysis, but also inhibits mitochondrial oxidative phosphorylation by decreasing ETC activities (106). Mutations in the *BRCA1* gene, which is known to play an important role in maintaining metabolic homeostasis, have also been linked to elevated glycolysis and other metabolic disturbances (107, 108). As no known inherited breast cancer gene is 100% penetrant, germline mutations are considered secondary risk factors and cannot therefore be considered primary causes of cancer. A penetrance of 100% is necessary for any tumor gene to be considered a primary cause of cancer. OxPhos impairment with compensatory glucose and glutamine fermentation is the common underlying phenotype of most if not all cancers.

ORIGIN OF METASTASIS

Metastasis involves the dissemination of cancer cells from the primary tumor to surrounding tissues and to distant organs and is the primary cause of cancer morbidity and mortality (109). Most tumors that fail to show local invasion or metastasis are considered benign and do not pose serious risk despite expressing a majority of the so called "Hallmarks of Cancer" (110). Tumor cell metastasis involves a stereotypic cascade of biological phenomenon including local invasion, intravasation into the blood, survival in the circulation, immune suppression, extravasation from the blood, and growth in a distant organ or tissue (111). Identification of the unique features of the metastatic cell can expand understanding of metastasis and facilitate rational therapeutic strategies based on knowledge of cell biology and biochemistry.

Two major theories have been advanced to explain metastasis that include the epithelial-mesenchymal transition (EMT), and the macrophage fusion hybrid hypothesis. The EMT is the dominant explanation and is based on the somatic mutation theory of cancer. The EMT proposes that an initial series of random mutations disturb cell-cell interaction causing a normal epithelial cell to transform into an invasive mesenchymal cell. Further additional random mutations cause the mesenchymal cell to intravasate, and subsequently extravasate into the parenchyma at some distant organ site (4, 112). Once established at the distant site, the metastatic tumor cells transform back to an epithelial phenotype via the so called mesenchymal epithelial transition (MET) (4, 112). No explanation has been presented, however, as to how the multiple random gene mutations responsible for the initial events of the metastatic cascade could be reversed or suppressed during the MET (4). Despite its linkage to phenomenology, the EMT is considered the dominant explanation for breast cancer metastasis (113).

In contrast to the EMT, the macrophage fusion hybrid hypothesis posits that metastasis arises from macrophages either directly or indirectly from the fusion of macrophages with neoplastic cells (109, 114–117). The metastatic breast cancer cell, like many metastatic cancer cells, expresses characteristics of myeloid cells and macrophages (109, 114, 118–125). These characteristics include phagocytosis, fusogenicity, and expression of multiple myeloid/macrophage biomarkers. Fusion hybridization could also better account for the large degree of cellular and genetic heterogeneity seen in metastatic breast cancer than can the EMT (126, 127). A macrophage origin of metastasis is also more consistent with Paget's "seed soil" hypothesis than is an origin based on EMT (109, 128, 129). Macrophages (seeds) are known to infiltrate organs (soil) non-randomly (109). As glutamine is a major fuel for macrophages (130, 131), targeting the availability of glutamine together with glucose becomes a rational, yet largely overlooked, therapeutic strategy for managing metastatic cancer (60).

CURRENT STANDARD OF CARE (SOC) FOR BREAST CANCER

Current standard management of breast cancer requires histological diagnosis obtained by core needle biopsy prior to surgical procedure (132). Therapies for breast cancer depend largely on the stage, grade, and the biology of the disease. Surgery and radiotherapy (breast and axilla) are used for local disease control, staging, and tumor extirpation. It is important to mention, however, that the extent of surgery and radiotherapy are not linked to a survival advantage (133). Chemotherapy, hormone therapy (tamoxifen, aromatase inhibitor, or one followed by the other), targeted therapies, trastuzumab (Herceptin) and pertuzumab (Perjeta), or combinations of these are designed to destroy local residual cancer cells and latent metastasis, while also reducing the risk of recurrence. Mechanical interventions (core needle biopsies and surgery) can cause wound-induced inflammatory oncotaxis, which influences the natural history of breast cancer (129). Data from several studies show that biopsies and surgery can cause inflammatory oncotaxis thus increasing tissue angiogenesis and spread of tumor cells (134–140). Invasive and metastatic behavior would be expected for breast cancer cells with myeloid properties (123). Some have hypothesized that growth factor stimulation in response to intraoperative tissue damage, can increase HER2 receptor activation in incompletely resected pre-invasive breast cancer thus increasing risk for tumor cell proliferation and spread (141). Procedures that might elevate blood glucose or insulin levels should be avoided, as glucose is known to accelerate breast cancer development (142–147). Products used in anesthesia might also increase blood glucose and insulin levels (148). The type of anesthesia and analgesia used during and after surgery should be carefully monitored for possible influence on glucose and insulin metabolism (149). Glucocorticoids, which are given to some breast cancer

patients, can also elevate blood glucose levels thus supporting glucose-dependent aerobic fermentation. In addition to elevating blood glucose, glucocorticoids can also block estrogen-induced apoptosis to further stimulate breast cancer growth (150). Hence, risk for tumor spread can be associated with accepted procedures used in breast cancer management.

KETOGENIC METABOLIC THERAPY

Ketogenic metabolic therapy (KMT) is emerging as an effective complementary or alternative therapeutic strategy for managing a broad range of malignant cancers including breast cancer (151–160). Calorie restriction and low-carbohydrate high-fat ketogenic diets (KD) reduce the glucose needed to propell the Warburg effect while also elevating ketone bodies (34). Cancer cells cannot effectively use ketone bodies or fatty acids for ATP synthesis through OxPhos due to defects in the number, structure, and function of their mitochondria (34, 46). Moreover, ketone bodies and fatty acids cannot be fermented, and thus cannot effectively replace glucose and glutamine as an alternative energy source for cancer (46). Bartmann et al. showed that the major ketone body, beta-hydroxybutyrate, could not stimulate breast tumor growth *in vitro* (161). Hence, KMT becomes a putative therapeutic strategy for managing most cancers including breast cancer (34).

There have been reports, however, suggesting that some cancers, including breast cancer, can oxidize ketone bodies and fatty acids for growth (162–165). The uptake of ketone bodies or fatty acids together with oxygen consumption in tumor cells is not proof that the ketone bodies or fatty acids can be used to generate energy through OxPhos (34, 46, 166). Indeed, Kuok et al. recently showed that palmitate could increase oxygen consumption rate (OCR) by stimulating ATP usage and insulin secretion rather than by increasing beta-oxidation (167). Fatty acids are potent swelling and uncoupling agents that can stimulate insulin secretion and glucose/glutamine consumption thus making it appear as if tumor cells can metabolize fatty acids for energy (166, 168–170). In other words, fatty acids can stimulate utilization of glucose and glutamine. Many tumor cells including breast cancer cells will store fatty acids as lipid droplets (166, 171, 172). Lipid droplet storage is considered a protection mechanism from the lethal effects of saturated fatty acids in cells that cannot metabolize fats for energy (171–174). If tumor cells could use fatty acids for growth, then water-only fasting and calorie restricted ketogenic diets should accelerate tumor growth, as these dietary changes elevate free fatty acids in the blood (175, 176). This is clearly not the case. Also, palmitic acid cannot support *in vitro* tumor cell growth in the absence of glucose and glutamine. Any disruption of the mitochondrial proton motive gradient will provide ATP for the F1-F0 ATP synthase thus hydrolyzing ATP rather than synthesizing ATP (46). mSLP will provide ATP for F1-F0-ATP synthase in an effort to maintain a moderate mitochondrial membrane potential and prevent reversal. Based on the foundational biological principle that structure determines function (43, 168, 177, 178), ketone bodies and fatty acids cannot serve as major respiratory fuels for tumor cells containing defects in mitochondrial structure and function (46, 84). Hence, it would be helpful to include evidence of normal mitochondria ultrastructure and electron transport chain activities in reports indicating that ketone bodies and fatty acids are fuels for OxPhos-generated ATP synthesis in cancer cells.

Depletion of fermentable fuels from KMT will facilitate catastrophic tumor cell death. Ketogenic diet appears to work better when used with glutamine targeting and is consumed in restricted amounts (60). The simultaneous targeting of glycolysis and glutaminolysis is now emerging as a potential therapeutic strategy for managing a broad range of cancers including breast cancer (60, 179, 180). KMT reduces circulating levels of glucose and insulin that are needed for rapid tumor growth (176). Excessive consumption of ketogenic diets, however, can provoke tumor growth by causing insulin insensitivity and glucose elevation (176, 181). Hence, KMT becomes a logical therapeutic strategy for managing breast cancer when used correctly.

The microenvironment of many tumors is hypoxic, acidotic, and enriched with glucose and glutamine. Under KMT, this pro-tumorigenic microenvironment becomes less inflamed (84, 182, 183). Restricted KDs and calorie restriction are antiinvasive, antiangiogenic, anti-inflammatory, and capable of killing tumor cells through a pro-apoptotic mechanism (181–188). Metabolism of the major circulating ketone body, D-beta-hydroxybutyrate, reduces reactive oxygen species production through the mitochondrial Co-enzyme Q couple in *normal cells*, while simultaneously elevating oxidative stress in *tumor cells* (34, 189–191). Implementation of KMT prior to any surgical procedure could also benefit patients (152). KMT should decrease the need for dexamethasone pretreatment, a problematic therapy that can inadvertently increase availability of glucose to the tumor cells while also inhibiting chemotherapy-induced apoptosis (192–194). It is well-known that glucose and hyperglycemia contribute to rapid breast cancer growth (146, 195, 196). Consequently, KMT could reduce inflammation and glucose systemically, thus enhancing the anti-tumorigenic properties of the microenvironment.

Therapeutic ketosis is linked to reduced blood glucose levels and to elevated ketone body levels within normal physiological ranges (**Figure 3**). Reduction of carbohydrate intake after breast cancer diagnosis in women reduces risk of recurrence (198). Evidence shows that therapeutic ketosis can act synergistically with several drugs and procedures to enhance cancer management while improving both progression-free and overall survival (34, 154, 199, 200). For example, hyperbaric oxygen therapy (HBOT) increases oxidative stress on tumor cells especially when used alongside therapies that reduce blood glucose and elevate blood ketones (201). By reducing blood glucose, KMT would also reduce the immunosuppressive effects of lactic acid in the tumor microenvironment (202). Recent studies show that therapeutic ketosis can facilitate drug delivery through the blood-brain barrier (60, 203). This would be important in helping to target breast cancer cells that metastasize to the brain. Also, it has been reported that caloric restriction reduces leaky tumor blood vessels by increasing neovascular smooth muscle (183). This could account, in part,

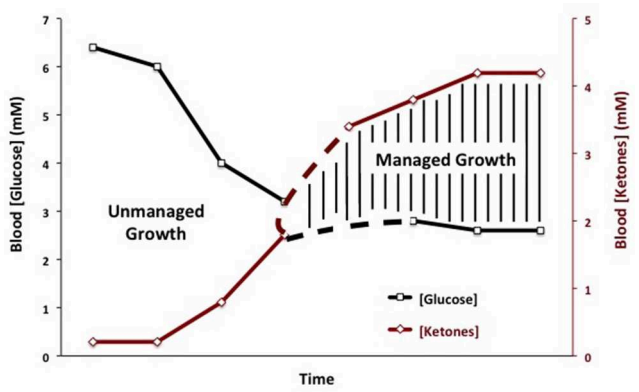

FIGURE 3 | Linkage of plasma glucose and ketone body levels to cancer management. The glucose and ketone (beta-hydroxybutyrate) values are within normal physiological ranges for humans that are under water-only fasting. This state is considered the zone of metabolic management for most cancers. The zone of metabolic management is obtained gradually, as circulating levels of glucose fall and ketones rise. the Glucose Ketone Index (GKI) tracks the transition to therapeutic ketosis. The dashed lines highlight individual variability that could exist in reaching a therapeutic GKI. GKI values approaching 1.0 and below are considered potentially therapeutic. [Reprinted from Meidenbauer et al. (197), and distributed under a Creative Commons license].

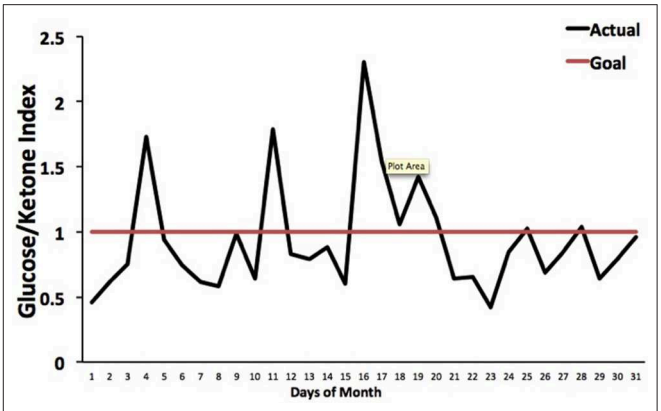

FIGURE 4 | Tracking an individual's GKI using the Glucose Ketone Index Calculator. Index values of 1.0 or below are considered best for managing cancer growth. Individual glucose and ketone values are shown, along with the corresponding GKI values. The GKI values are plotted over the course of a month, whereas the target GKI value (1.0) is plotted as a single line. Tumor management is predicted to be better (slower growth) within the metabolic target zone than outside of the zone. [Reprinted from Meidenbauer et al. (197), and distributed under a Creative Commons license].

for a better drug delivery to solid tumors under KMT. The anti-malarial drug, chloroquine neutralizes lysosomal pH reducing phagocytosis and autophagy, and thus depriving invasive and metastatic tumor cells from obtaining glucose and glutamine (34, 204, 205). Chloroquine can also inhibit mitochondrial diaphorases that oxidize NADPH to NAD+, which in turn would reduce mSLP (46, 206). The glutamine dehydrogenase inhibitor, epigallocatechin gallate (EGCG) is also proposed to target glutamine metabolism through an effect on glutamate dehydrogenase (207). The glutaminase inhibitor, 6-diazo-5-oxo-L-norleucine (DON), is a powerful glutamine-targeting drug that can work synergistically with a restricted KD for managing brain cancer and metastasis (60, 208, 209). Hence, KMT can, (a), target the multiple drivers of rapid tumor growth, (b), facilitate drug delivery to the tumor tissue, (c), work synergistically with glutamine-targeting drugs, and, (d), enhance the metabolic efficiency in normal healthy cells. To our knowledge, there are currently no cancer therapies that can target these multiple drivers of tumor growth while simultaneously protecting normal cells.

THE GLUCOSE KETONE INDEX

The Glucose Ketone Index (GKI) is single number representing the glucose-to-ketone ratio (expressed in mmol/L), and was developed as a guide for evaluating therapeutic efficacy of KMT. The GKI serves as a proxy for the degree of metabolic stress placed on tumor cells through the reduction of circulating glucose and elevation of ketone bodies (beta-hydroxybutyrate, acetoacetate) (34, 197). A GKI value of 1.0 or below has been suggested as the therapeutic goal for cancer management (**Figure 4**). However, therapeutic GKI values can be difficult to achieve for many cancer patients. For example, tumor burden, toxic treatment protocols, and emotional and physical stress can combine to elevate blood glucose and insulin levels thus preventing the patient from achieving therapeutic GKI values (34, 84, 210). Further refinement of existing KMT therapies along with introduction of new therapies may serve to mitigate this obstacle.

KMT AS A COMPLEMENTARY OR ALTERNATIVE TO SOC

KMT has been used together with low dose chemotherapy and other treatments to manage tumor progression in a woman with stage IV triple negative breast cancer (154). The woman responded well to the combined treatment, and initially reported as a complete therapeutic response. Although overall survival exceeded the median expected for her stage and grade, she eventually succumbed to her cancer. A failure to continue with the KMT protocol was considered responsible in part for her tumor recurrence (154). Nevertheless, a subsequent clinical study showed that a ketogenic diet combined with carboplatin/paclitaxel, hyperthermia, and hyperbaric oxygen therapy significantly improved progression-free and overall survival in patients with advanced non-small cell lung cancer (211). Currently, neoadjuvant therapies are commonly prescribed for a subset of invasive or late-stage cancers, including breast cancers. KMT initiated soon after diagnosis and prior to surgery may prove to be a non-toxic adjunct treatment capable of downgrading the aggressive and invasive nature of the cancer, thereby increasing the efficacy of subsequent treatments (212). It is our view that improvements in selection, dosage, timing, and scheduling of drugs, diet,

and procedures will offer benefits in survival and quality of life to patients with advanced metastatic breast cancer when used as a complementary or alternative therapeutic strategy alongside the SOC (**Figure 5**). The Press-Pulse therapeutic strategy for cancer management was based on the concept of Arens and West, who described how the simultaneous occurrence of "press-pulse" disturbances was responsible for the extinction of organic populations during prior evolutionary epochs (213). A similar concept can be used to show how tumors can be slowly degraded. Optimization of dosing, timing, and scheduling of KMT used together with synergistic drugs and procedures will facilitate the eradication of breast tumor cells with minimal patient toxicity. This therapeutic strategy can serve as a framework for the design of clinical trials for the non-toxic management of most cancers (34). Further details are described in **Figure 5**.

CONCLUSIONS

Breast cancer, like many cancers, are dependent on fermentation metabolism for growth. Substrate level phosphorylation drives the fermentation metabolism of tumor cells using glucose and glutamine as major fuels in the cytoplasm and

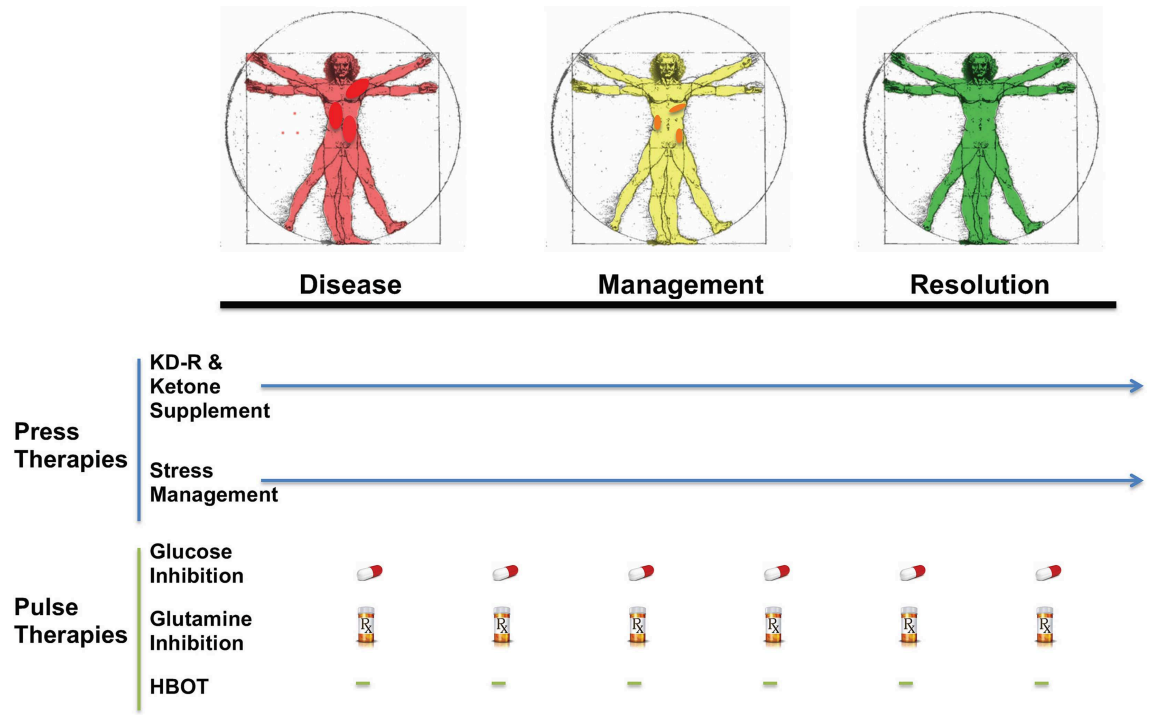

FIGURE 5 | Breast Cancer Management with Press-Pulse Therapeutic Strategy. Arens and West considered the simultaneous occurrence of "Press-Pulse" disturbances as the mechanism responsible for the mass extinction of organic populations during prior evolutionary epochs (213). We described how this concept could be adopted as a therapeutic strategy for the management and possible eradication of cancer (34). This therapeutic strategy considers all cancer, including breast cancer, as a single disease that can be managed by transitioning the energy metabolism of normal cells from glucose to non-fermentable ketone bodies, while simultaneously restricting the availability of fermentable fuels (glucose and glutamine) to tumor cells (34). The reduction in blood glucose levels will also reduce insulin and insulin-like growth factor 1, which are known to drive rapid tumor growth (184, 214, 215). This metabolic therapeutic strategy exploits the dependency of tumor cells on glucose and glutamine fermentation and their inability to metabolize ketone bodies for energy due to defects in the number, structure and function of the tumor mitochondria. In essence, the press-pulse therapy pits the metabolic demands of the mutated tumor cells against those of the normal cells, which evolved to adapt and survive under the extremes of nutrient stress (216). Collections of random mutations will prevent tumor cells from adapting to nutrient stress, thus leading to their extinction according to evolutionary theory (81). As a cancer diagnosis can increase emotional stress and blood glucose, stress management techniques together with exercise could improve general health while reducing glucose availability to the tumor. The press therapies would work synergistically with acute pulse therapies to further restrict glucose and glutamine metabolism. HBOT would work synergistically with the press therapies to increase oxidative stress selectively in tumor cells. The timing (spacing) between the various pulse therapies is designed to stress tumor cell metabolism while minimizing toxicity to normal body cells (34). This therapeutic strategy will target the fermentation metabolism common to most breast tumor cells, thus degrading tumor burden gradually with little or no toxicity. The color change from red (diseased with darker red spots indicative of metastatic lesions), to yellow (with reduced metastasis), to green (resolution) in the Vitruvian man indicates the gradual metabolic management and possible resolution of the breast cancer. The pill and Rx symbols are suggestive of drugs taken orally and/or intravenously (prescription) that would be effective in targeting simultaneously glycolysis and glutaminolysis. Pulse therapies would be eliminated with evidence of tumor management or resolution, while press therapies could continue under modifications or adjustments (arrow). Optimization of timing, dosing, and scheduling of the press-pulse treatments will facilitate eradication of tumor cells with minimal patient toxicity. This therapeutic strategy is a framework for future clinical trials. HBOT, hyperbaric oxygen therapy; KD-R, calorie restricted ketogenic diet. The figure is reprinted with modifications, as described previously (34) and distributed under a Creative Commons license.

mitochondria, respectively. The protracted replacement of respiration with fermentation in cancer cells leads to unbridled cell proliferation. Fusion hybridization of epithelial-derived cancer stem cells with glutamine-dependent tissue macrophages is an alternative explanation to the epithelial-mesenchymal-transition for the origin of metastatic breast cancer cells. The aim of our review is to illustrate that the restriction of glucose and glutamine together with elevation of non-fermentable ketone bodies offers a complementary or alternative therapeutic strategy to the SOC for the non-toxic management of breast cancer. It is our view that KMT could improve progression-free and overall survival for most breast cancer patients.

AUTHOR CONTRIBUTIONS

TS conceived and wrote the review. MI, AS, MK, and J-PS contributed clinical information and edited the review. PM and CC contributed scientific information to the review.

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Conflict of Interest: MK was employed by Dietary Therapies LLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.