



The Impact of High Dose Glucocorticoids on Bone Health and Fracture Risk in Systemic Vasculitides

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Systemic vasculitides are a range of conditions characterized by inflammation of blood vessels which may manifest as single organ or life-threatening multisystem disease. The treatment of systemic vasculitis varies depending on the specific disease but historically has involved initial treatment with high dose glucocorticoids alone or in conjunction with other immunosuppressive agents. Prolonged glucocorticoid treatment is frequently required as maintenance treatment. Patients with small and large vessel vasculitis are at increased risk of fracture. Osteoporosis may occur due to intrinsic factors such as chronic inflammation, impaired renal function and to a large extent due to pharmacological therapy with high dose glucocorticoid or combination treatments. This review will outline the known mechanism of bone loss in vasculitis and will summarize factors attributing to fracture risk in different types of vasculitis. Osteoporosis treatment with specific consideration for patients with vasculitis will be discussed. The use of glucocorticoid sparing immunosuppressive agents in the treatment of systemic vasculitis is a significant area of ongoing research. Adjunctive treatments are used to reduce cumulative doses of glucocorticoids and therefore may significantly decrease the associated fracture risk in patients with vasculitis. Lastly, we will highlight the many unknowns in the relation between systemic vasculitis, its treatment and bone health and will outline key research priorities for this field.

Keywords: vasculitis, osteoporosis, glucocorticoids, bone, fracture risk, fractures, large vessel vasculitis, AAV

INTRODUCTION

Systemic vasculitides frequently present as acute inflammation of various sized blood vessels which can lead to stenosis and aneurysm of the aorta and its branches in large vessel vasculitis (LVV) or necrosis of arterioles, capillaries and venules in small vessel vasculitis (SVV). Untreated large and small vessel vasculitis can lead to rapid organ damage and consequent threat to life. Hence many conditions require strong immunosuppression most commonly with a prolonged course of high dose Glucocorticoids (GC). Long-term sequelae are frequently a result of acute and chronic inflammation, failure to suppress

inflammatory activity or secondary to immunosuppression, in particular GC (1, 2). Osteoporosis and increased fracture risk are known comorbidities of prolonged and high cumulative GC doses (3, 4). It is unclear how much the disease process and the inflammation itself contribute to accelerated bone loss or if the increased fracture risk is mainly a result of the negative impact of GC on bone health and muscle strength. This narrative review will explore the mechanism for rapid bone loss and increased fracture risk in vasculitis, summarize current fracture data in various vasculitis subgroups and outline recent developments which can prevent or mitigate this issue.

MECHANISM OF BONE LOSS AND INCREASED FRACTURE RISK IN VASCULITIS

Bone undergoes continuous remodeling and restructuring to maintain its strength and function. In healthy individuals, a

precisely coordinated process of bone resorption through osteoclasts and bone formation by osteoblasts allows the repair of damaged bone and replacement of old bone with newly formed mineralized osteoid. Disruption of this remodeling cycle and an increase in bone resorption and/or suppression of bone forming activity leads to systemic bone loss and osteoporosis (5). The most important factors influencing bone turnover in systemic vasculitis are shown in **Figure 1** and discussed in detail below.

Chronic Inflammation in Vasculitis

In large and small vessel vasculitis the inflammation of vessels is frequently widespread with multisystem involvement and patients usually present with signs of pronounced systemic inflammation (1, 6). The impact of acute or chronic vasculitis on bone physiology is poorly studied. Most data about the interplay between inflammation and bone derives from more common chronic inflammatory conditions such as rheumatoid arthritis (7), spondyloarthritis (8), or connective tissue diseases such as systemic lupus erythematosus (SLE) (9, 10).

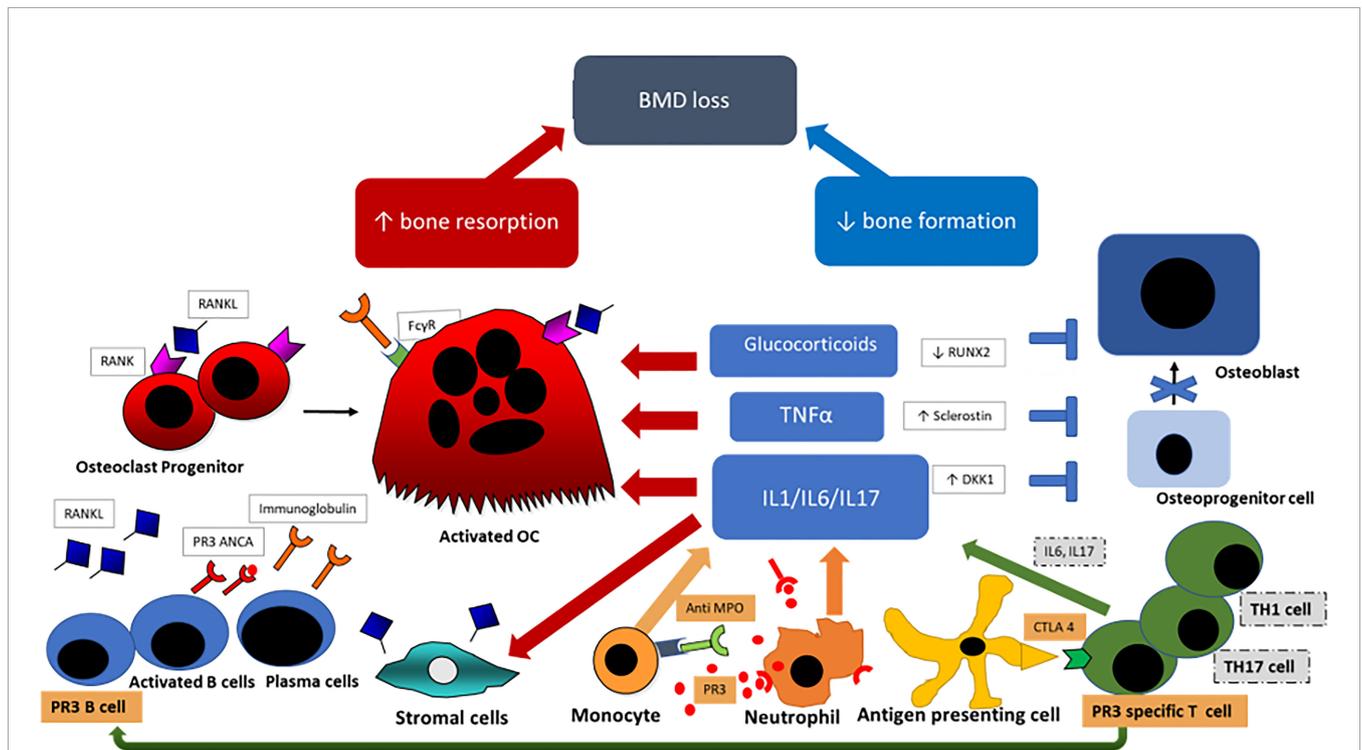


FIGURE 1 | Pathogenesis of bone loss in vasculitis; Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis specific cells and antibodies are highlighted in orange. Primed neutrophils express PR3 [proteinase 3] or MPO [myeloperoxidase] which bind ANCAs and trigger further neutrophil activation and through CD4+ T-lymphocytes stimulation further ANCA production by B-lymphocytes. Key cells and cytokines in the pathogenesis of large vessel vasculitis (LVV) are highlighted in gray. Dendritic cells in the adventitia trigger the inflammatory cascade by activation of T-lymphocytes, predominantly T helper 1 (Th1) and Th17 cells, and express interferon and IL17. Primed neutrophils and Th cells promote proinflammatory cytokine production (Interleukin-6 (IL6), IL1 and Tumour Necrosis Factor (TNF)-alpha) which stimulates osteoclastogenesis through increased RANKL production by stromal cells and through direct osteoclast stimulation. Inflammatory cytokines also inhibit the formation of osteoblasts by increased DKK1 and Sclerostin expression. Glucocorticoids suppress osteoblastogenesis by RUNX2 suppression and stimulates osteoclast proliferation and longevity. BMD, bond mineral density; RANK4, receptor activator of nuclear factor kappa-B (ligand); PR3, proteinase 3; ANCA, anti-neutrophil cytoplasmic antibody; FcγR, Fc gamma receptor; OC, osteoclast; TNFα, tumour necrosis factor alpha; IL, interleukin; MPO, myeloperoxidase; RUNX2, runt-related transcription factor 2; DKK1, Dickkopf WNT Signaling Pathway Inhibitor 1; CTLA 4, cytotoxic T-lymphocytes antigen 4; TH1/TH17, T-helper type 1/type 17 cell.

Inflammatory arthritides and vasculitides have a number of common pathways leading to chronic inflammation with key inflammatory cytokines and cells, supported by the fact that these conditions frequently share some immunosuppressive therapies (11–14). However vasculitides in particular anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) frequently present with an acute systemic inflammation which can affect multiple organs including kidney, lungs and peripheral nerves, and requires rapid potent immunosuppression including high dose GC in order to prevent severe organ damage and death (15). In contrast, inflammatory arthritides frequently present in an insidious way with polyarthritis as the main manifestation which can be treated initially with mild to moderate immunosuppression and if necessary with subsequent escalation of therapy (16).

A) ANCA Associated Vasculitis

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are ANCA associated vasculitides. AAV are characterized by small-to-medium size blood vessel inflammation and the presence of circulating ANCA antibodies which recognize proteinase 3 (PR3) or myeloperoxidase (MPO). Most GPA patients have ANCA with a cytoplasmic pattern (c-ANCA) that are specific for PR3 whereas in MPA patients ANCA with a perinuclear pattern (p-ANCA) with MPO specificity are frequently found. In AAV, an initial trigger such as infection causes T helper cells to stimulate macrophages, in turn activating neutrophils and leading to formation of neutrophil extracellular traps (NETs) (17–19). The complement system and altered T-lymphocyte homeostasis lead to priming of neutrophils (18, 20, 21). NET degradation is impaired, causing prolonged exposure to NET contents which disrupts tolerance to antigens including PR3 and MPO, leading to ANCA production (19). PR3 and MPO may be expressed on primed neutrophils which bind ANCAs and trigger further excessive neutrophil activation, and both neutrophils and CD4+ T-lymphocytes stimulate further ANCA production by B-lymphocytes, setting up a vicious cycle resulting in proinflammatory cytokine production [Interleukin-6 (IL6), IL8 and Tumour Necrosis Factor (TNF)-alpha (1, 22)] and endothelial damage *via* reactive oxygen species, lytic enzymes and NET components such as histones and matrix metalloproteinases (MMPs) (12, 19, 23–26). The pathogenicity of various immune complexes including PR3 ANCA can be modulated by posttranslational modifications such as glycosylation of immunoglobulins. Genetic associations support a predisposition to AAV or to disease relapse. Examples include patients more commonly expressing specific human leucocyte antigen (HLA) polymorphisms such as HLA-DPB4 or less commonly expressing functional immunoregulatory T-cell receptors such as the cytotoxic T lymphocyte antigen 4 (CTLA) and program death 1 (PD1) (27–29).

B) Large Vessel Vasculitis

LVV is characterized by inflammation of the artery wall with predominant CD4+ T-lymphocytes and macrophages which can undergo granulomatous organization in the form of giant cells. In LVV activated dendritic cells in the adventitia can trigger an

inflammatory cascade with activation of T-lymphocytes, predominantly T helper 1 (Th1) and Th17 cells, and express interferon and IL17 (30). Dendritic cells drive the inflammatory process and IL1, IL6 and IL21 are highly expressed in giant cell arteritis (GCA) (31, 32).

Chronic Inflammation and Bone Turnover

Proinflammatory cytokines and their interaction with T- and B-cells propagate chronic inflammation which in turn promotes the differentiation of myeloid cells into macrophages and osteoclasts. The differentiation from multinucleated precursor cells into mature bone resorbing osteoclasts requires the interaction of two crucial cytokines: Macrophage colony-stimulating factor (M-CSF) and Receptor activator of nuclear factor kappa-B ligand (RANKL) (33). Osteoprotegerin (OPG) is a decoy receptor to RANKL and an important regulator of osteoclastogenesis. Mechanisms such as binding of anti-MPO to monocytes or phagocytosis of PR3 expressing neutrophils stimulate the release of inflammatory cytokines including IL1 β , IL6, IL8 and TNF α (22, 34). Pro-inflammatory cytokines, particularly IL6 and TNF α , have also been shown to suppress bone formation. Overexpression of TNF α can inhibit osteoblast differentiation either directly through inhibition of Runt-related transcription factor 2 (Runx2) or *via* increased Dickkopf 1 expression which is an important regulator of the Wnt pathway (35–37).

A) Large Vessel Vasculitis- Inflammatory Cytokines

The crucial importance of IL6 in the pathogenesis of LVV was confirmed by the success of the introduction of IL6-inhibitors as corticosteroid sparing agents (7, 38). Inflammatory cytokines such as IL1, IL6, IL17 and TNF α can upregulate RANKL production by osteoblasts, T-cells and stromal cells and promote differentiation of osteoclast precursor cells (39) or stimulate osteoclast activity by RANKL independent mechanisms (40, 41). Murine and *in vitro* models have also demonstrated IL6 mediated suppression of osteoblast differentiation which can have a direct impact on skeletal development (42, 43).

B) ANCA Associated Vasculitis - the Role of B cells

The clinical success of B-cell depletion in AAV in suppressing disease activity and assuring long term remission provides strong evidence for the important role of B-cells in AAV pathophysiology (44–46).

B cell and bone cell development are closely interlinked.

Stromal cell derived cytokines including RANKL, Osteoprotegerin (OPG) and IL7 are important regulators of osteoclast maturation and differentiation and are also important factors for the development of B cells (47). In murine studies RANK knock out not only resulted in an increased bone mass phenotype (osteopetrosis) but also in impaired lymphocyte development (48).

B cells also produce cytokines which regulate bone cells, in particular RANKL which promotes osteoclastogenesis. Ovariectomy in mice not only causes bone loss through estrogen deficiency and osteoclastic bone resorption but also

due to proliferation of RANKL expressing B cells leading to further acceleration of bone resorption (49). In ovariectomized mice lacking B-cells bone loss is attenuated (50).

In particular, activated B cells in the context of chronic inflammation promote bone loss through increased RANKL production and other inflammatory cytokines that promote bone resorption. In addition B cells and in particular plasma cells may influence bone homeostasis through the production of immunoglobulins. In Rheumatoid Arthritis for example immunoglobulins have been shown to directly interact with bone cells, specifically with osteoclasts (51, 52), either *via* the Fc γ receptor on the osteoclast surface (51, 53) or indirectly through blocking OPG (52, 54).

B cell depletion therapy therefore may have a beneficial impact on bone and may prevent accelerated bone loss in chronic inflammatory conditions. To date only a small study of 45 patients with RA who received B cell inhibitor treatment (Rituximab) was performed. After one year of treatment no substantial improvement in BMD was found compared to baseline bone density (55). However this study was likely underpowered and the time frame was too short to detect a significant BMD change. Further studies and particular clinical trials are required to establish the impact of B cell depletion on bone.

Glucocorticoid Induced Osteoporosis (GIOP) Pathophysiology

GC remain a cornerstone of treatment for most vasculitides and the mainstay of treatment in LVV (56, 57).

The impact of corticosteroids on bone turnover is complex; the most profound effect seems to be on bone formation. Weinstein et al. (58) have shown that chronic GC treatment in mice decreases proliferation of osteoblast precursors and stimulates osteoblast and osteocyte apoptosis, which together leads to a reduction of bone formation. These findings were confirmed on biopsies of patients with GIOP (59). Long-term GC exposure increases expression of the transcription factor peroxisome proliferator-activated receptor (PPAR) γ 2 which promotes the differentiation of mesenchymal cells to adipocytes as opposed to osteoblasts. At the same time Runx2, a pivotal transcription factor for osteoblastogenesis, is repressed by GC. GC treatment also has a significant impact on bone resorption. Corticosteroids suppress OPG production (60) which leads to an increase in RANKL/OPG ratio and subsequent stimulation of osteoclast proliferation (59, 60). GC also prolong the lifespan of osteoclasts, further contributing to the imbalance of bone formation and resorption in favour of resorption and hence to net bone loss (58, 61). Therefore, long-term corticosteroid use leads to bone loss and fatty transformation of bone marrow (59, 62, 63).

Extra-skeletal actions of GC on organs such as muscles, kidney and the endocrine system contribute to accelerated bone loss and increased fracture risk. GC decrease calcium absorption in the gastrointestinal tract (64) and decrease the production of sex steroids such as Luteinising hormone (LH), Follicle stimulating hormone (FSH) or Testosterone and Growth hormone (GH) that puts a halt on bone turnover (65). Steroid

associated muscle loss (sarcopenia) leads to reduced skeletal loading and postural instability, which is an important risk factor for falls (66).

Other Medications

Parenteral or oral Cyclophosphamide is frequently used in organ- or life-threatening vasculitis (67, 68). The use of Cyclophosphamide is associated with a number of potential serious side effects including premature ovarian failure characterized by a sharp drop of oestrogens causing early menopause and accelerated bone loss (69). Recently Miyano et al. (70) showed that in an AAV group who sustained fractures, Proton Pump Inhibitor (PPI) users had a higher risk of fractures than histamine-3 receptor antagonist users. Of interest, Abtahi et al. (71) demonstrated in a cohort of patients with rheumatoid arthritis a synergistic effect of GC and PPI in increasing fracture risk. These findings may be of particular importance in patients with GCA and LVV who at disease onset are frequently treated with a combination of high dose GC and PPI.

Organ Involvement

Acute and chronic renal failure can occur as a consequence of an acute flare of small to medium sized vessel vasculitis (3). Patients with Chronic Kidney Disease (CKD) are at increased risk of osteoporotic fractures (72–74). The mortality associated to fractures increases with worsening renal function (6) and the risk of hip fracture in a population with End Stage Renal Disease (ESRD) is approximately two to four times higher than in the general population (72, 73). The reasons for disturbed bone metabolism in CKD are manifold. Beside accelerated bone loss causing osteoporosis, additional metabolic disorders such as secondary hyperparathyroidism, phosphate retention, elevated fibroblast growth factor -23 (FGF 23), sclerostin overproduction and chronic metabolic acidosis can have a detrimental impact on bone quality. Metabolic bone disorders can result in renal osteodystrophy, adynamic bone disease, osteitis fibrosa or osteomalacia. Additionally, secondary factors such as vitamin D deficiency may increase fracture risk even further (75, 76)

Peripheral neuropathy is one of the frequent long-term sequelae of AAV. A pooled analysis of multiple therapeutic trials showed that 14% of microscopic polyangiitis (MPA) and 22% of granulomatosis with polyangiitis (GPA) patients were found to have developed peripheral neuropathy in long-term outcomes analysis (3). Peripheral neuropathy can lead to gait disorders and increased falls risk (77) which strongly increases fracture risk (78), likely by bone mineral density (BMD) independent mechanism (79). Visual and hearing loss can occur both in LVV and SVV (3, 80) which again substantially increases falls (81) and subsequent fracture risk (82, 83).

Relative Immobilisation

Clinical manifestations of systemic vasculitis such as mononeuritis multiplex, stroke, blindness or severe arthritis can lead to relative immobility (84–86). A prolonged period of decreased physical activity and chronic inflammation leads to

bone loss in addition to an accumulation of visceral fat and sarcopenia (87–89). Recently sarcopenia, measured by reduced hand grip strength, and associated with the type of vasculitis, severity and high C-reactive protein (CRP), seemed to predict increased fracture risk (90). This is in line with previous studies which have shown that change of body composition in form of muscle loss and addition of visceral fat associated with glucocorticoid use increase the risk of osteoporosis and the risk of sustaining fragility fractures (91, 92).

In summary fracture risk in patients with systemic vasculitides is a composite score of BMD-related and BMD-independent risk factors as shown in **Figure 2**. In order to modify fracture risk many factors, for instance suppression of inflammation, minimizing GC use and avoiding prolonged immobility, should be considered.

OSTEOPOROSIS AND FRACTURE RISK IN DIFFERENT VASCULITIS SUBGROUPS

Giant Cell Arteritis (GCA)/Polymyalgia Rheumatica (PMR)

GCA is the most common primary systemic vasculitis with incidence reported between 1.1 and 43.6 cases per 100,000 in populations aged over 50 years, with significant variation noted geographically (93). PMR is an inflammatory disorder characterized by bilateral upper limb and hip girdle pain and stiffness, with incidence rates of 41 to 112 cases per 100,000 (94–97) among patients over 50 years. GC remain the mainstay of treatment for GCA and PMR. In cohorts of GCA patients,

median starting Prednisolone dose was 20–50 mg/day and cumulative doses at 52 weeks were 4000–4800 mg (57). In PMR initial treatment of Prednisolone 15–25 mg is generally followed by a slow taper over 1–2 years (98, 99). Cumulative doses of 3.2 g to 5.4 g are reported (100–102). Treatment beyond 2 years is common, with up to 60% of patients remaining on GC at this point (103).

High rates of osteoporosis are seen in patients with GCA and PMR. Reported prevalence of osteoporosis in GCA varies from 6.25% to as high as 85% (104, 105). The risk of osteoporosis increases over time following diagnosis of GCA and PMR, with the rate of increase highest in the 6 months following diagnosis (105–107). **Table 1** summarises available studies (4, 57, 104, 105, 107–117) on bone health in LVV.

Higher rates of fractures are seen in both GCA and PMR compared to controls (4, 108) with hazard ratio for fracture 1.63 in PMR and 1.67 in GCA compared to controls. Prospective studies of GCA and PMR patients reveal fragility fracture incidence of 11–14% within 1 to 2 years of diagnosis (109, 110). Rates of fracture correlate with increased cumulative GC doses (4). Evidence from claims data suggests that higher cumulative doses of GC lead to higher complications and increased risk of osteoporosis and fracture, with hazard ratio (HR) for bone-related adverse events increasing 5% for every 1 g increase in cumulative dose of Prednisolone-equivalent GC (111). Similar findings have been established in cohort studies for cumulative doses over 10 g or duration over 2 years (112, 118).

There is some evidence that a lower dose of 5 mg Prednisolone daily can lead to reduced BMD (119), but rates

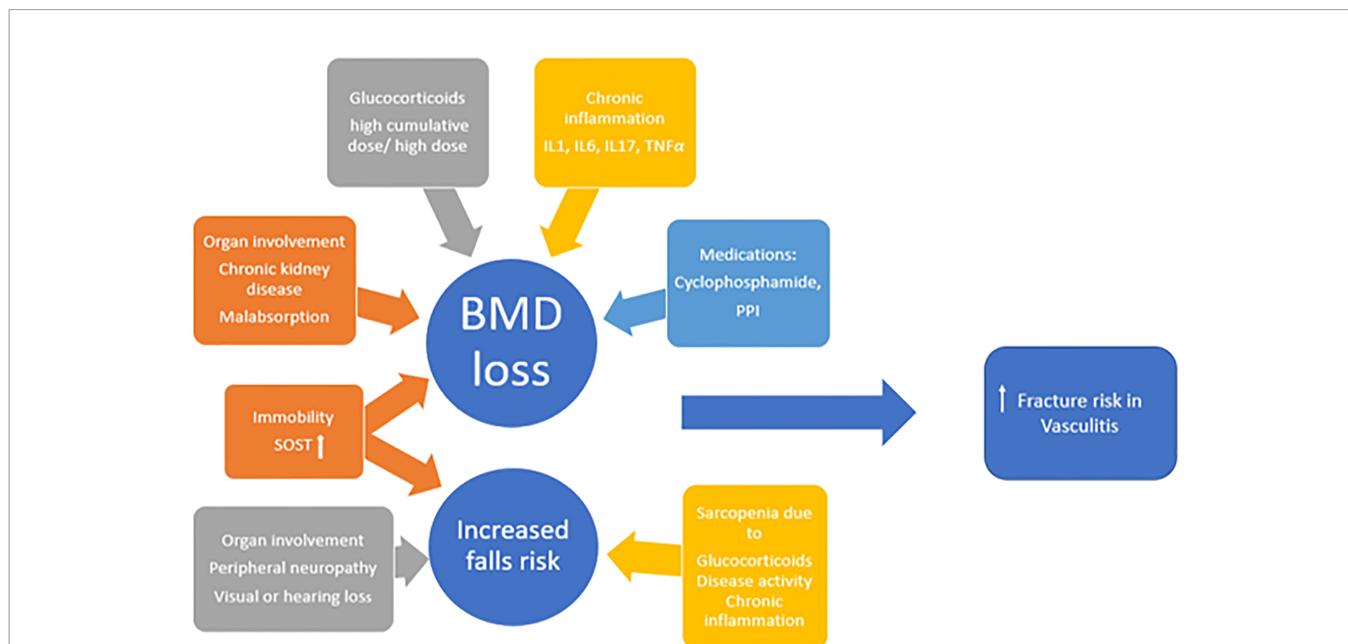


FIGURE 2 | The multifactorial aetiology of increased fracture risk in vasculitides; *IL* interleukin, *TNF* tumour necrosis factor, *PPI* proton pump inhibitor, *SOST* sclerostin, *BMD* bone mineral density.

TABLE 1 | Summary of studies on osteoporosis and fracture risk in Giant Cell Arteritis (GCA) and Polymyalgia Rheumatica (PMR).

First author	Year	Study population	Age	Details	Level of evidence	Outcome measures	Results
Healey (109)	1996	25 GCA or PMR patients in treatment group 23 GCA or PMR patients in placebo group	71.6	RCT of GC-treated GCA or PMR patients receiving calcium, vitamin D and calcitonin, or receiving calcium, vitamin D and placebo	1b	- Change in BMD at lumbar spine after 2 years - New vertebral fractures at 2 years	- Mean change in lumbar BMD (intervention group), -0.2% (placebo) - Vertebral fracture incidence 11% and 14% - Higher cumulative GC dose associated with greater loss in BMD
Kermani (107)	2017	204 GCA patients	71.3	Prospective cohort of GCA patients	2b	- Damage items as per Vasculitis Damage Index and LW Index of Damage	- 22 (10.8%) developed osteoporosis
Petri (104)	2015	4671 GCA patients	N/A	Retrospective cohort of GCA patients (n=4671)	2b	- Incidence of GCA - Cumulative GC dose - Comorbidities associated with GCA	- RR 2.9 for developing osteoporosis after diagnosis of GCA
Mohammad (113)	2017	768 GCA patients 3072 controls	76.1	Retrospective cohort of GCA patients	2b	- Occurrence of osteoporosis or fragility fracture	- RR 2.81 for incident osteoporosis - RR 1.56 for incident fracture
Broder (111)	2016	2497 GCA patients	71	Retrospective cohort of GCA patients	2b	- GC-related adverse events including osteoporosis and fragility fracture	- For every 1g increase in cumulative GC dose, HR 1.05 for osteoporosis and 1.04 for fracture - Osteoporosis rate 0.099 events per person year - Fracture rate 0.066 events per person year
Gale (57)	2018	8777 GCA patients	73	Two retrospective cohorts of GCA patients	2b	- GC cumulative dose - GC-related adverse events - Association of adverse event risk with GC use greater than 52 weeks	- OR of osteoporosis for every 1g increase in cumulative GC dose 1.03-1.06 - OR for fracture for every 1g increase in cumulative GC dose 1.02-1.09 - Risk of osteoporosis for every 1g increase in cumulative GC dose 3-3.4% - Risk of fracture for every 1g increase in cumulative GC dose 1-1.9%
Hatz (105)	1992	47 GCA or PMR patients	N/A	Prospective cohort of GCA and PMR patients	2b	- Side effects attributed to GC at 6 months	- 7 (15.0%) developed osteoporosis within 6 months
Andersson (114)	1990	26 GCA patients	78	Retrospective cohort of GCA patients	2b	- BMD at heel - X-ray signs of osteoporosis	- 69% of female patients developed severe spinal osteoporosis after 5 years
Mazzantini (115)	2012	222 PMR patients	71	Retrospective cohort of PMR patients treated with low-dose GC	2b	- Fragility fractures - Osteoporosis	- 55 (24.8%) developed osteoporosis - 31 (14.0%) sustained fragility fractures - GC duration and cumulative dose were significantly associated with osteoporosis and fragility fractures
Sokhal (110)	2021	652 PMR patients	72.4	Prospective cohort of PMR patients	2b	- Fragility fractures at 12 and 24 months	- 72 (11.0%) sustained fragility fracture within 12 months of diagnosis - 60 (9.2%) sustained fragility fracture 12-24 months after diagnosis
Mateo (112)	1993	28 GCA patients 28 PMR patients 48 controls	N/A	Case-control study of patients with GCA, PMR and controls	3b	- BMD at lumbar spine and femoral neck	- Age and cumulative GC dose significant predictors of femoral BMD in men - Age and weight, but not cumulative GC dose, were significant predictors of femoral

(Continued)

TABLE 1 | Continued

First author	Year	Study population	Age	Details	Level of evidence	Outcome measures	Results
Wilson (108)	2017	5011 GCA patients 5011 controls	72.9	Retrospective case-control study of GCA patients versus control	3b	- Incidence of osteoporosis or fracture	BMD in women - GCA patients had lower BMD - IRR for osteoporosis 2.4 in GCA patients - IRR for fracture 1.4 in GCA patients
Paskins (4)	2018	2673 GCA patients 12,136 PMR patients 59,236 controls	71.9	Retrospective case-control study of GCA patients PMR patients	3b	- Time to fracture	- Fracture incidence rate per 10,000 person years 148 for PMR and 147 for GCA - HR for fracture 1.63 for PMR and 1.67 for GCA
Wilson (116)	2017	5011 GCA patients	72.9	Nested case-control studies of GC doses in GCA	3b	- Risk of osteoporosis or fracture associated with increasing GC dose	- 511 (10.2%) developed osteoporosis, mean time to developing osteoporosis 3 years - 408 (8.1%) developed fracture, mean time to fracture 3.2 years - Increased risk of osteoporosis with increasing cumulative GC dose
Haugeberg (117)	2000	GCA or PMR patients - 26 currently treated - 28 previously treated - 30 newly diagnosed	71	Cross-sectional study of BMD in currently treated, previously treated and newly diagnosed GCA or PMR patients	3b	- BMD at radius, spine, hip	- No significant difference in BMD between groups

GC, glucocorticoid; BMD, bone mineral density; RCT, randomized controlled trial; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk; LVV, large vessel vasculitis; HR, hazard ratio.

of BMD loss and fracture risk are generally shown to correlate with doses over 10 mg daily of Prednisolone (4, 112).

Few studies have established the risk of osteoporosis attributable to the disease process itself in LVV. Much of the work describing higher rates of osteoporosis in LVV is unable to definitively establish a causative link with GC therapy (120, 121). Rates of osteopenia and osteoporosis are higher in relapsing than newly diagnosed patients with GCA (122), which may relate to higher cumulative doses of GC use but cannot be distinguished from the effect of prolonged inflammation in relapsing cases.

The available data on bone health in LVV typically predate the introduction of the IL6-inhibitor Tocilizumab as a steroid-sparing agent. Adjunctive use of Tocilizumab alongside GC in trials facilitated faster reduction in GC treatment and lower cumulative GC doses in the treatment of GCA (38). Widespread use of Tocilizumab is expected to lead to fewer GC-related adverse events in GCA, including osteoporosis and fractures. However GC alone remains the primary treatment for GCA. BSR and EULAR guidelines recommend Tocilizumab for relapsing patients and those who have already developed, or are at high risk of developing, a complication related to GC (123, 124). The EULAR guideline emphasises that the addition of Tocilizumab must be balanced against the risk of treatment-related adverse effects in comorbid elderly patients. Recent ACR guidance however recommends Tocilizumab plus GC over GC alone for all new patients with GCA (125). As more patients at risk of osteoporosis and fracture are treated with Tocilizumab, the incidence of these outcomes is anticipated to reduce.

ANCA Associated Vasculitis

AAV is a necrotizing vasculitis that predominantly affects small vessels and is associated with ANCA specific for MPO and/or PR3. AAV mostly present as systemic disease affecting multiple organs. The main clinicopathologic subgroups of AAV are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Although these AAV variants are distinct entities, the clinical manifestations can be overlapping and available data on bone health and fracture risk mostly refers to a pooled AAV group (2, 126). A cross-sectional study (127) showed that amongst 99 AAV patients with an average age of 55 years, 57% had osteopenia and 21% had osteoporosis. Over two thirds (69%) of patients were treated with prolonged high dose GC with an average cumulative dose of 10.7 g. The cumulative GC dose was inversely related to Z-score of lumbar spine and proximal femur confirming the link between high cumulative GC dose and systemic bone loss. In addition to the negative impact of GC on BMD other factors were identified as potential contributors such as low dietary calcium intake and previous cyclophosphamide treatment. This study however was performed almost 20 years ago when the availability, knowledge and use of GC sparing therapies and osteoporosis treatments such as bisphosphonates was scarce.

A population based cohort study from Southern Sweden (128) found that osteoporosis was 4 times more commonly diagnosed in patients with AAV when compared to an age and sex matched general population control cohort (rate ratio 4.6,

95% CI 3.0-7.0). Two long-term follow up studies in SVV including AAV demonstrated that osteoporosis was one of the most commonly reported comorbidities affecting 14-16% of patients when followed up over 7 to 8 years (129). A recent study compared the bone mineral density of 35 treatment naïve AAV patients with 35 healthy, age and sex matched controls. The diagnosis with AAV was associated with osteopenia however when adjusting for other variables such as BMI the association was lost (130). The bone health in newly diagnosed treatment naïve AAV patients is however an interesting question and larger scale studies could provide valuable information on baseline bone status and fracture risk.

Fractures are more common in AAV patients than the general population, with one case control study of 543 AAV patients having twice the risk of hip fracture compared to age and sex matched controls (131). In a retrospective cohort of 22,821 AAV patients, Miyano et al. reported 0.6% developed fractures following diagnosis, with a median time to fracture of 52 days (70). In two further retrospective cohorts of 246 AAV patients 11/246 (4.5%) and 24/278 (8.6%) developed fractures following diagnosis (132, 133), whilst in a cohort of 83 AAV patients aged 65 and over, 8 (9.6%) developed fractures (134).

Bone Health in Miscellaneous Vasculitic Disorders

Several other forms of small and medium vessel vasculitis can affect children and/or adults [e.g., Behcet's Disease (BD), Polyarteritis Nodosa (PAN), IgA-associated vasculitis (IgAV)]. These miscellaneous vasculitides are relatively rare, occurring in approximately 1:500,000 people across Europe (135). High doses of GC, often administered to induce remission in the early phases of these rare vasculitides, are highly probable to be detrimental to BMD and fracture risk in affected patients. This is particularly true in these rarer disorders as they often occur in childhood or early adulthood when peak bone mass attainment may not have been achieved.

BD, a multi-system disorder characterized by the presence of recurrent oro-genital inflammation, most commonly occurs between the ages of 20 and 40 years. Typically, it follows a relapsing-remitting course and can affect multiple organ systems. Inflammatory ocular, vascular, neurological or gastro-intestinal disease is associated with a poorer prognosis and usually requires high dose corticosteroid treatment to promptly prevent irreversible end-organ damage. The current literature examining bone health in BD and the impact of corticosteroids is limited. However, two studies have compared BMD between patients with BD and age- and gender-matched healthy controls. Tekin and colleagues investigated differences in BMD and bone turnover markers between 30 patients with BD (mean age 37 years) and 30 healthy controls (mean age 35 years) (136). Lumbar spine and total hip BMD was no different between the two groups and there were no significant differences in markers of bone turnover. Another case-control study by Bicer and colleagues in Turkey compared BMD between patients with BD (n=35) and healthy controls (n=33) (137). This study excluded patients receiving oral corticosteroid therapy and post-menopausal women. Mean age in the BD group was 38

years and in the control group was 40 years. Mean disease duration in the BD group was 6.7 years. Similar to the study by Tekin, BMD was not significantly different between patients with BD and healthy control subjects. The European League Against Rheumatism (EULAR) guidelines for the management of BD advises that if required, high-dose corticosteroids should always be used in combination with concurrent immunosuppressives such as azathioprine, interferon α , or anti-TNF α therapy (138). This ensures that the requirement for long-term high dose corticosteroids in BD is minimized and attenuates the impact of corticosteroids on BMD and fracture risk.

For the management of systemic PAN, the French vasculitis group advise corticosteroid therapy starting at a dose of 1 mg/kg/day of prednisone to a maximum of 60 mg daily (139). There is no agreed or widely accepted reduction strategy and several different regimens are currently being employed worldwide, often for up to 6 or 12 months (140). A prospective study of patients with SVV assessing the long-term outcomes in patients with PAN or MPA identified osteoporosis as one of the three most common sequelae (129). Over a mean follow-up of 98 months, 18% of patients with PAN developed an osteoporotic vertebral fracture compared with 15% of those with MPA highlighting the importance of consideration of bone health in systemic vasculitis.

BONE PRESERVING TREATMENTS IN VASCULITIS: THE ROLE OF STEROID-SPARING THERAPIES

Prevention and management of GIOP is addressed in several guidelines and has been extensively reviewed in other articles and is beyond the scope of this review (141-144). It is worth highlighting that a dual-energy X-ray absorptiometry (DXA) scan for BMD measurement is required in the majority of cases for a fracture risk assessment. As glucocorticoids are particularly associated with osteoporosis of trabecular bone, vertebral fracture assessment (VFA) should be included routinely when DXA scans are performed (145).

Across the spectrum of systemic vasculitis, new, more targeted immunosuppressive and immunomodulatory treatments have been developed to assist with the treatment of systemic vasculitis.

ANCA Associated Vasculitis Treatment

In AAV, steroid-light and steroid-free regimens are beginning to be used with some success (134, 146). Use of the targeted complement 5a inhibitor Avacopan offers promise as a GC substitute in AAV but more work is required (147). Likewise, Mepolizumab, a monoclonal antibody against IL5 has also demonstrated promise as a treatment adjunct to facilitate greater chances of remission and a faster reduction in GC in EGPA (148, 149).

Publication of the GiACTA study heralded a new era for the treatment of GCA (38). The use of an IL6 inhibitor

(Tocilizumab) in GCA has facilitated a significantly more rapid reduction in corticosteroid treatment compared with corticosteroid therapy alone. Significantly the GiACTA trial showed reduced cumulative GC doses by 43.5% and 51.2% in the two arms where Tocilizumab was used alongside GC taper as compared to placebo plus GC taper. Evidence for the glucocorticoid sparing effects of older, more conventional disease modifying immunosuppressants such as methotrexate, azathioprine or mycophenolate mofetil in systemic vasculitis is extremely limited and merits further attention.

CONCLUSION

Osteoporosis and fragility fractures are significant long-term complications in vasculitis and most data is available for GCA. High dose GC are undoubtedly one of the main contributing factors. Other factors may increase fracture risk however further research is required to define the role of

inflammation, medications and organ involvement on fracture risk in vasculitides. Expansion of non-corticosteroid options for the treatment of systemic vasculitis offers a great hope that in the future, higher fracture rates and impaired bone health will not be a significant problem for our patients suffering from vasculitis.

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