Periodontal Healing and Osteoporosis in Postmenopausal Women

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Abstract

This article reviews how menopause and age related hormonal bone changes effect periodontal healing. After menopause, with the cessation of ovarian estrogen production and its bone protecting effects, women become more susceptible to periodontal disease and tooth loss. The inflammatory processes involved in osteoporosis and periodontal disease will be reviewed. Estrogen deficiency results in up regulation of the inflammatory mediators which are common to skeletal bone loss and periodontitis. Periodontitis is one of the two basic oral health problems; destruction to the structures which support teeth, alveolar bone, ligament, and gingiva, is cumulative over time. Progression of the condition rests on peaks and valleys in inflammatory immune response to pathogens contained in plaque biofilm. Chronic inflammation is common to many age-related conditions. Additionally, the article reviews how medications interfere with the inflammatory response. Treatment considerations, objectives and limitations for women living dynamic lives well into menopause will be discussed. Vigilant identification and referral for specialized care are needed to restore comfort, function and esthetics. As women are living longer and more vibrant lives than ever, the needs of this cohort require special attention. The balance between oral-health related quality of life and bioethics of minimalist management versus sometimes costly and time consuming options must be weighed. The clinicians caring for geriatric populations ought to keep in mind the intersections of periodontitis and aging such that each patient can be given appropriate referral and treatment.

ABBREVIATIONS

CVD: Cardiovascular Disease; RA: Rheumatoid Arthritis; TNF a: Tumor Necrosis Factor; OHIP-14: Alpha Oral Health Impact Profile

INTRODUCTION

Gingivitis is a reversible inflammatory response to plaque buildup. It is limited to the gingiva and does not involve underlying periodontal ligament or alveolar bone, which supports the tooth. If the causative agent, plaque biofilm, is not removed, gingivitis progresses beyond the gingiva. A Centers for Disease Control investigation reported that 70% of Americans over 65 suffer from periodontitis [1]. Inflammation spreads, down the path of least resistance, first to the periodontal ligament and then to alveolar bone. As periodontal disease progresses the biofilms change in character from aerobic coccus to anaerobic motile bacillus. Porphyromonal gingivalis, Treponema denticola, Tanarella forsythia are key periodontal pathogens known to have the virulent ability to modify the host inflammatory cascade [2]. Viruses such as cytomegalovirus, herpesviruses are also identified as disease initiators [3,4]. In the process, gums appear red and swollen; Interdental soft tissue appears to be blunted and rounded. Margins of the gingiva appear to pull away from the teeth and gather more bacteria as the condition waxes and wanes in chronicity. Although the condition is mostly painless, persistent bad breath, exudate, and loosening of the teeth or change in bite are often perceived by the patient and mentioned as chief complaint. Inflammation hydrolyzes the periodontal ligament and boney housing. This bone loss is the hallmark of periodontitis.

Without regenerative surgical intervention, the bone loss is irreversible. Spontaneous healing response to periodontal insult or wound healing after periodontal therapy rely on a variety of highly complex interactions at the molecular cellular and systemic levels. Studying wound healing elsewhere in the body where similar epithelial, fibroblastic and osseous tissues of similar embryologic origin are involved [5,6]. Clot formations in the immediate area of periodontal insult relies on a microenvironment rich in hormones, growth factors, and cytokines to initiate healing. Signaling processes borne out...
of the immune inflammatory response to the insult stimulate progenitor cell proliferation. Progenitor cells are drawn into the site and differentiate into specific tissue to which was lost to periodontal disease: bone, cementum and periodontal ligament. The recruitment, proliferation, migration, and accumulation of perioosteal progenitor and bone marrow stromal cells depend on cell to cell signaling. Fibroblasts, chondrocytes and osteoblasts secrete collagen matrices which mature and form into the structures lost to disease, but also these cells produce secondary signals that maintain the regenerative process and induce angiogenesis and remodeling. In younger patients studies have shown small numbers of progenitor cells derived from the systemic circulation; at best these cells have a limited, if any capacity to differentiate into the bone and cartilage cells necessary for regeneration. Regardless of whether the wound healing is a response to periodontal insult, surgical treatment or dental implant therapy, challenge is exacerbated in elderly patients, where cell to cell signaling mechanism is compromised in addition to the capacity of pluripotent cells [7,8].

A recent review focused specifically on gingival wound healing and confirmed the similarity with other systems in the body. New tissue formation is affected through changes in stem cell populations. Regenerative stem cells decrease in number and capacity with age. After the initial lesion, regeneration potential is diminished as a result of telomere shortening and DNA damage responses. In humans, the gradual accumulation of products of cellular metabolism and extensive DNA damage contribute to the aging process. Angiogenesis is also compromised through lesser growth factor production, and slower signaling capacity. Tissue maturation is critical to successful periodontal treatment outcomes. This is most obvious in bone remodeling. In older patients, bone remodeling sways to a net loss of bone when osteoclast regulated hydrolysis of woven bone out paces osteoblastic action [9].

In postmenopausal women, estrogen deficiency leads to monocytes and macrophages producing greater pro-inflammatory cytokines. These cytokines up regulate osteoclasts and signal a more robust cytokine response. As a result, when challenged by bacterial plaque biofilm in the oral environment, the host immune response yields greater cytokine activation and increased osteoclast recruitment and activation. The host response is thus a supercharged inflammatory cascade and leads to a more constant activation of tissue proteinases and degradative enzymes. This up regulation has its endpoint in greater tissue destruction, alveolar bone resorption and tooth loss.

**Inflammatory diseases and aging**

Although nine hallmarks of aging have been noted, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication, the intersection between these factors appears to be through inflammation [10].

Like other common age-related diseases such as cardiovascular disease (CVD), some cancers, rheumatoid arthritis (RA) and chronic obstructive pulmonary disease, chronic inflammation is a key characteristic of periodontitis. These chronic inflammatory conditions occur in combination, particularly in elderly patients and implicate common underlying risk factors involving the nine noted aging hallmarks [11].

Cell signaling involves the secretion of inflammatory and immune-modulatory cytokines and chemokines. Aging is associated with increased release of inflammatory mediators. These mediators prolong inflammatory phase which may delay wound healing either around a periodontal lesion or peri-implant one, and similar roles in several inflammatory diseases [12].

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Increase in inflammation can play a role in modifying gene stability. Changes in gene expression which do not involve the DNA sequence can act through any instability around the DNA molecule. These epigenetic changes occur when host immune-inflammatory response to plaque biofilm kick starts a cascade of pro-inflammatory cytokines which enhance local response. Innate immune activation is responsible for host cellular response to pathogens but can also trigger chemical DNA modifications, their associated proteins and remodel the chromatin selectively activating or inactivating genes [20]. This host activation, meant to protect against pathogens, is the result of gene-activation pathways which are separate from the DNA sequence. Any number of epigenetic factors has been suggested: environment, stress, aging, and smoking [21]. Responding to environmental factors, some modifiable some not, multiple genes acting together seemingly play a role in these chronic diseases associated with aging.

Investigations centering on epigenetic modification supports the claim that chronic inflammation and infection can affect gene-specific epigenetic reprogramming in the periodontal environment [22]. If this is the case, inducing a change in cytokine
profile may subsequently change the pathogenic process and change the disease progression [23].

**Postmenopausal women as a susceptible host**

In women, menopause brings about a quick decline in hormone production and triggers a well investigated loss of skeletal bone mass [24]. Men are also said to lose skeletal bone, but since the hormonal drop off is not so extreme, the effects are more gradual [25]. A recent investigation into the differences between men and women underscores this finding specific to the buccal cortical plate thickness in the anterior maxilla, an esthetic area of concern for dental implant treatment plans. Although both sexes have very thin buccal cortex, that of women is thinner [26].

Although a recent study did not identify an association with current serum estrogen levels and alveolar crestal bone height, hormone therapy was found to be associated with less alveolar bone loss in postmenopausal women [27]. This supports an earlier 3-year randomized trial; postmenopausal women with moderate to advanced periodontal disease, estrogen therapy significantly increased alveolar bone mass compared to control, in addition to increasing bone density in the femur (but not lumbar spine) [28]. Additionally, women using hormonal therapy had significantly less gingival inflammation. For every 1% per-year decrease in whole-body mineral density, the risk of tooth loss quadruples. Furthermore, women with severe osteoporosis are reportedly more than three times more likely to be healthy, age-matched controls to be edentulous [29]. Although several studies find that alveolar bone density in the mandible correlates with skeletal bone density, and that generalized bone loss renders the jaw susceptible to accelerated alveolar bone resorption, there are findings to the contrary which call the relationship into question. One longitudinal investigation found no association between skeletal bone loss, periodontitis and edentulousness [30]. On the other hand, when five-year changes in periodontal measures were performed on females with a history of severe periodontitis or osteoporosis, accelerated bone loss was found despite stability in routine probing measures. A recent investigation reports that alterations in hormone levels do not directly favor the growth of periodontal pathogenic bacteria [32]. This finding implicates hormonal effects on bone itself and not the bacterial specificity.

A study limited to Japanese women concluded that estrogen may promote tooth retention by strengthening the periodontal attachment around teeth, but no effects were seen in bone height or in bone porosity [33]. Finding supported earlier assertions that hormonal changes related to menopause are associated with increased interleukin 1, (IL-1, IL-6, IL-8, and IL-10), tumor necrosis factor alpha, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor. These cytokines stimulate mature osteoclasts, which modulate bone proliferation and induce bone resorption [34].

A similar mechanism explains how postmenopausal women are susceptible to periodontitis and tooth loss. Genco and Grossi suggest that since estrogen deficiency leads to increased cytokine production by monocytes, macrophages and osteoblasts, when responding to plaque biofilm and pathogenic factors such as lipopolysaccharides and toxins, the host immune system produces even more inflammatory cytokines than usual [35]. This makes the estrogen deficient patient more susceptible to periodontal disease due to a more pronounced inflammatory cascade, and increased activation of tissue proteinases and degradative enzymes, leading to increased destruction of periodontal structures. This proposed mechanism helps explain why the Framingham study of over two decades ago found that hormone therapy protects against tooth loss in this cohort [36].

This evidence taken together suggests that menopause related hormonal changes may play a role in making the host more susceptible to periodontal disease and tooth loss [37]. With evidence on both sides of the argument considered, the American Academy of Periodontology considers osteoporosis to be a risk factor for periodontal disease [38,39].

**Pharmacologic intersections with surgical treatment**

Medications which modulate the inflammatory cascade intersect with the periodontitis pathogenesis. Corticosteroids, cyclooxygenase inhibitors, immunosuppressants, statins and anticytokines have all been shown to interfere with the inflammatory response. On the positive side, the potential to apply some of these medications for the benefit of periodontitis and down regulate the host inflammatory response is being investigated. Anti-inflammatories and biologics may play a role [40]. Antibiotics in anticollagenolytic role rather than an antibiotic one have been identified as an early possibility. And a recent review supports the similar assertion that cytokine reducing agents can down regulate the immune response to periodontitis [41]. Similarly, selective cyclooxygenase-2 inhibitors, flurbiprofen, and doxycycline in sub anti-microbial dosages are shown to down regulate inflammation [42,43]. Statins show promise in stimulating osteoblast differentiation and osteoclast activity, and patients using statins have been shown to show lesser effects of clinical periodontitis [44].

Bone modulating agents given longer term for prevention and treatment of osteoporosis show promise in modulating host response to periodontal inflammation. In other words, these bone modulating agents work along a similar long term strategy as antibiotics given as anticollagenolytics, and statins as a means to reduce osteoclast activity. Sclerostin, for instance, has shown such promise in early studies [45]. However, on the negative side, medications have consequences can make the host more susceptible to periodontal disease. For instance, corticosteroid therapy is associated with secondary osteoporosis, which for reasons discussed, place the patient at risk for bone loss. An older patient on long term therapy would have long term cumulative therapy effects. On the other hand, corticosteroids have shown some promise in a randomized trial to modulating proinflammatory cytokines and bleeding on probing, a key clinical sign of periodontal inflammation. Furthermore, the question remains is an adjunctive treatment with a powerful biologic appropriately being applied. The case of bisphosphonate medications underscores this important question. Bisphosphonate medications have also been suggested as a host modulating medication, as a result of investigations which have identified beneficial long-term effects [46]. Analogues of pyrophosphates, this class of medications prevent bone resorption by selectively inhibiting osteoclast activity.
Used mostly in oral, smaller doses this helps prevent and treat bone loss resulting from age related hormonal changes, such as menopause in women. In addition these medications, in larger doses, are used for bone pain and hypercalcemia in malignancy and skeletal diseases such as Paget’s disease. Published case series and systematic reviews documented an association between bisphosphonates and osteonecrosis of the jaw [47-49]. Osteonecrosis, a general loss of bone tissue resulting from cell death, can occur anywhere in the skeleton, most typically in the long bones such as femur, tibia and humerus. In the maxillofacial complex, it manifests as an area of exposed bone in the region which does not heal within 8 weeks, in a patient who is currently or had previously been receiving bisphosphonate therapy but has not been exposed to radiation. Often pathogenesis is triggered by an oral surgical procedure involving mucoperiosteal flap elevation; compromising blood supply to the area has been hypothesized as the culprit. The condition can result in significant morbidity because it is resistant or refractory to conventional therapy. Although its incidence remains low, the severity of the condition focuses our attention on it [50]. On the other hand, bisphosphonates have shown promise on the periodontal condition of postmenopausal women. A growing body of research shows that the family of drugs, through its ability to decrease bone resorption at the osteoclastastic interface, may be a means to modulate the host response to inflammation triggered hydrolysis of alveolar bone [51]. Although the association between bisphosphonate and osteonecrosis of the jaws does not prove causation, and the condition has occurred in patients not using bisphosphonates the wisdom importance of preventing the condition is obviously effective form of management [52]. Early referral to a dentist or periodontist by the care giver first to prescribe a bisphosphonate can lead to treatment of underlying dental pathologies which may trigger the condition later on. Additionally, good communication between multi-disciplinary care givers helps ensure the best possible care [53]. Elucidating the full potential of bisphosphonates and other host modulating medications involves understanding the mechanisms of action of these drugs, limiting unwanted side effects and expanding indications. Developing medications to slow the immune inflammatory response is a direction for the future, but highlights the importance of interrelationships between oral and systemic care to clinicians today.

**Dental treatment considerations for women with osteoporosis**

According to the American Geriatric Society, there is no question that dental comfort, function, and esthetics impact the quality of life. What is in question is which factors are associated with quality of life [54]. This study and others like it use Oral Health Impact Profile (OHIP-14) as a measurement device.

However In 2011, research refocused to consider how oral health affects quality of life beyond the traditional dental centered endpoints, such as those measured in OHIP-14, to more patient centered ones such as psychosocial interaction, self-esteem, intimacy and overall health and adjustment [55]. This is especially important for women, who are enjoying socially, occupationally and emotionally robust lives long into menopause. Although interrelationships exist between these and traditional variables like dental diagnosis, quality of occlusion etc., the importance of patient centered variables is now more important than ever [56].

Considering this paradigm shift, there are two seemingly conflicting notions working. In an otherwise healthy patient with osteoporosis under the care and supervision of a physician the major biological consideration is the possibility that the cascade of events involved in healing around a more involved treatment, such as a dental implant, do not occur. The dot formation and the initial serum infiltrate at the bone implant interface involve an immune response which triggers undifferentiated mesenchymal cells to the interface. These undifferentiated cells proliferate and differentiate forming first woven bone then turnover in to more mature bone. The concern lies in the whether or not the complex series of cell to cell signaling involved in inflammation, angiogenesis and bone mineralization may not occur such that the already low quantities of undifferentiated mesenchymal cells will form as expected [57].

The other hand, there is the growing evidence that oral-health related quality of life is improved with the highest quality restoration. Research squarely focuses on dental implant retained treatments. Several studies in older women conclude that specifically in this cohort implant supported restorations significantly improve quality of life. This is true even for women otherwise affected by osteoporosis. A report from 2015 compares implant supported fixed restorations, with traditional tooth supported fixed and removable restorations and found that implant supported restorations had a statistically significant quality of life impact over traditional fixed and removable restorations [58]. Another investigation reports that this pattern holds true even when relatively more traumatic bone augmentation during implant therapy is undertaken [59]. Similarly, a retrospective review of patients aged over 70 concluded that when such patients with well controlled systemic conditions, should not be considered as a high risk for dental implant failure [60].

To explain these findings, it becomes clear that many of the same principles which improve masticatory performance, bite force, nutritional state and patient satisfaction with implants in younger patients, persist in osteoporotic elderly ones as long as the patient has the physical capacity to sit for the procedure and maintain the restoration [61, 62].

**CONCLUSION**

Reflecting on the management of elderly patients, Mersel and colleagues concluded that bio-ethics, on a case by case basis, drives the balance between restoring ideal comfort esthetics and function [63]. The importance of such thoughtful treatment planning is even more pronounced in postmenopausal women at having osteoporosis considering women are living longer more vibrant lives than ever. To resolve the older notion of limiting treatment in older, osteoporotic cohorts with the newer one of considering more involved treatment more research focused to women with osteoporosis needs to question anecdotal dogma which drove the previous treatment planning.

**REFERENCES**

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