REVIEW ARTICLE

Analysis of ADAMTS, MMPs, Versican and Related Proteoglycans in Origin and Progression of BRONJ

Ramandeep Kaur Sidhu

Dr. Ramandeep Kaur Sidhu, BDS, MSc, School of Health Sciences, 3333 University Way, Prince George, British Columbia V2N 4Z9, Canada, Email: kaurr@unbc.ca http://dx.doi.org/10.18049/jcmad/311

Abstract

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a complication basically associated with dento-alveolar surgical procedures in patients receiving intravenous and oral bisphosphonate therapy for various malignancies and bone-related conditions. So far, the pathogenesis of BRONJ is assumed to be related to oral surgical traumas to dento-alveolar structures, which have already limited bone-remodelling capacity due to the effects of bisphosphonate therapy. However, the etiology of the disease is still unclear, while the literature review of past studies is inconclusive. The aim of this paper is to review the literature and current evidences and to explore the possibility of association between changes in the expression level of ADAMTS (1, 4, 5, 9) "a disintegrin and metalloproteinase with thrombospondin motifs", matrix metalloproteinases (MMPs), Versican, and other related proteoglycans in oro-musculoskeletal tissue, and the onset and progression of BRONJ. This paper outlines a huge body of literature indicating the key role of versican, aggrecan, bioactive degradation products of versican and aggrecan, ADAMTs and MMPs in bone repair, angiogenesis, and BRONJ pathogenesis, and demonstrating a strong clinical correlation between jaw necrosis and bisphosphonate therapy. The paper concludes that in order to establish a definitive causal relationship, there is a critical need of research investigating the expression and localization of these factors during the onset and progression of BRONJ by utilizing advanced analyzing techniques.

Keywords: *ADAMTS, Bisphosphonate-related osteonecrosis of the jaw (BRONJ), MMPs, Versican*

Address for correspondence: Dr. Ramandeep Kaur Sidhu, BDS, MSc, School of Health Sciences, 3333 University Way, Prince George, British Columbia V2N 4Z9, Canada, Email: kaurr@unbc.ca

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as "exposed necrotic bone without evidence of healing for at least 8 weeks in the maxillofacial area in patients with a history of n-BIS use without a history of head and neck irradiation."[1] This BRONJ is a complication basically associated with dento-alveolar surgical procedures in patients receiving intravenous and oral bisphosphonate therapy for various malignancies and bone-related conditions, for example, osteoporosis. As per the National Osteoporosis Foundation's report (2008)[2], approximately one in two women will have an osteoporosis related fracture in their remaining lifetime, and bisphosphonates are the most prescribed drug for post-menopausal osteoporosis. Thus, for a sound prevention and management of additional complications related to bisphosphonate therapy in patients already suffering from bone wasting diseases and malignancies, it is crucial to understand the exact etiology of this complication by quantifying the cellular and molecular factors associated with BRONJ pathogenesis. So far, the pathogenesis of BRONJ is assumed to be related to oral surgical traumas to dento-alveolar structures which have already limited bone remodelling capacity due to the effects of bisphosphonate therapy.[3,4] However, the etiology of the disease is still unclear.

In addition, the literature review of past studies is inconclusive. Many questions remain unanswered, for example, although lesion appears at sites of previous dental extractions, in some cases there is no antecedent dental surgical

procedure and no history of pre-existing infection. Hence, it is still unclear as to what extent pre-existing infections (periodontal or dental diseases) may be contributing factors. Further, despite the presence of evidences relating the BRONJ pathogenesis to the profound inhibition of osteoclast function, bone remodelling, and anti-angiogenic action of bisphosphonates, no systematic attempt has been made to investigate the exact effects of bisphosphonates on the expression of growth factors, ADAMTS "a disintegrin and metalloproteinase with thrombospondin motifs", matrix metalloproteinases (MMPs), versicans, & other cellular/ molecular factors in oral tissues.

In light of the above mentioned facts, the aim of this paper is to review the literature and current evidences and to explore the possibility of association between changes in the expression level of ADAMTS (1, 4, 5, 9), MMPs, Versican, and other related proteoglycans in oro-musculoskeletal tissue, and the onset and progression of BRONJ. Thus, this paper attempts to investigate questions significant to the oral musculoskeletal health of aging populations world-wide, particularly postmenopausal women, and in turn offers inputs for designing better approaches for preventing and managing BRONJ.

Physiological functions - Versican, Aggrecan, ADAMTS & MMPs

Versican

Versican is expressed in many developmental as well as adult tissues. Versican performs several mechanical and biochemical functions. Its glycosaminoglycan side chains are involved in creation of a hydrated space that allows the resistance to stretch and compression through the reversible redistribution of water, a property termed visco-elasticity.[5] Versican plays important roles in forming hyaluronan-rich matrix, which give anti adhesive environments to cells.[6] Due to the physical size of the molecule, versican can alter accessibility of the cell surface and thereby indirectly alter cell surface binding and signalling. [5,7]

Versican plays an important role in the ordered deposition of collagen during normal wound healing as well as disorganization of collagen fibrils during cervical dilation.[8] This indicates that the concentration and localization of the molecule is critical to determining its effect on collagen organization. Further, versican is also associated with cell migration and proliferation. It is proposed to be a haptotactic factor promoting cell movement through creation of a gradient of cell-extracellular matrix adhesions.[9]

Aggrecan

Aggrecan is a critical component for cartilage structure and the function of joints. As a structural proteoglycan, aggrecan appears to be important in mediating chondrocyte-chondrocyte and chondrocyte-matrix interactions. Co-expression of a mini-aggrecan and link protein stabilizes cell-substratum interaction. Aggrecan provides intervertebral disc and cartilage with the ability to resist compressive loads. The localized high concentrations of aggrecan provide the osmotic properties necessary for normal tissue functioning. The swelling pressure produced by GAGs counters compressive loads on the tissue. The proteolytic degradation of aggrecan plays a key role in cartilage deterioration during joint injury, disease, and aging. The linker domain between the N-terminal globular domains, called the interglobular domain, is highly sensitive to proteolysis. Such degradation has been associated with the development of arthritis. Also, aggrecan has been shown to interact with versican.

MMPS and ADAMTs

Tissue-degrading enzymes of the metalloproteinase family have implication in the pathogenesis of several conditions and pathologies involving the extracellular matrix. The family includes the matrix metalloproteinases (MMPs), "a disintegrin and metalloproteinase" (ADAM), and "a disintegrin and metalloproteinase with thrombospondin motifs" (ADAMTS). Proteolytic cleavage and processing of wide array of cellular, extracellular and extracellular matrix (ECM) substrates (collagens and procollagens, proteoglycans, cytokines and cytokine ligands, chemokines, elastin and von Willebrand factor) by enzymes from the MMP and ADAMTS families impact the structural and functional properties of various tissues during development, growth, homeostasis and pathology. MMPs appear to have prominent roles in several diseases with a component of

tissue destruction, such as osteoarthritis and rheumatoid arthritis.[10] Additionally, some studies have shown that MMPs can exert anti-inflammatory actions, possibly by processing of anti-inflammatory cytokines and chemokines.[11]
One other group of proteases that is closely related to MMPs is ADAMTS. ADAMTSs are secreted into the circulation and constitute a heterogenous family of proteases with both anabolic and catabolic functions. There are 19 known subtypes of ADAMTS which are divided into 4 groups. The aggrecanases (ADAMTS-1, -4, -5, -8, -9, -15, and -20) can be roughly described as having proteoglycanolytic action, although there are other reported functions such as regulation of angiogenesis and degradation of other proteins for some of the group members.

Possible association between changes in the expression level of ADAMTS (1, 4, 5, 9), MMPs, Versican, etc and the onset and progression of BRONJ

A brief review of existing literature has been done to predict the possible association. The key search words were "ADAMTS-1,-4,-5,-6", "versican", "aggrecan", "MMPs", "bone/cartilage", "connective tissues", "healing", "regeneration and growth" .The inclusion criterion of the review is as below:

- Studies which have analyzed ADAMTS-1,-4,-5,-6, versican, aggrecan, MMPs in bone and connective tissues, particularly in bonny/cartilaginous tissue.
- Studies which have analyzed ADAMTS, MMPs, versican, and related proteoglycans in any tissue undergoing healing or regeneration process.

Numerous animal and clinical studies have analyzed the ADAMTS, MMPs, versican, and related proteoglycans in bone and the connective tissues in various health and pathological conditions. H. Enomoto et al.[12], identified the role of two evolutionarily related, secreted metalloproteases of the ADAMTS family, ADAMTS20 and ADAMTS9, in palatogenesis. They generated the evidence that two members of the ADAMTS (a disintegrin-like and metalloprotease domain with thrombospondin type 1 motif) protease family, ADAMTS9 and ADAMTS20, act locally in palate closure and cooperate in proteolysis of versican (VCAN).
The findings of the above study suggest that defective versican proteolysis is the definitive mechanism underlying the observed cleft palate phenotype. The research demonstrated that the proteolysis of versican by ADAMTS9 (acting in endothelium) and ADAMTS20 (made by mesenchymal cells) contributes to the overall level of cleaved versican. Thus, these proteases can be postulated to work cooperatively in the palatal shelf to enable mesenchymal proliferation. The results further suggested that ADAMTS9 and ADAMTS20 are not required solely for versicanclearance, but they might generate versicanproteolytic products that influence palate mesenchyme proliferation.
In addition, the study by Kern et al.[13] and Stankunas et al.[14] also identified a significant role for ADAMTS1 and ADAMTS9 in versican processing during myocardial compaction and valvulogenesis. They found that the decreased versican processing is associated with failed endocardial cushion remodeling in mice. In these mice, versican-haplo insufficiency led to substantial rescue of the valvular defect, suggesting that the versican clearance function of ADAMTS5 is highly significant in this developmental setting. Thus, depending on the context, ADAMTS proteases may primarily mediate versican clearance or contribute to both versican clearance and the generation of bioactive versican fragments.
Further, Pukkila M. et al. [15] investigated whether the versican expression level in the peritumoural stromal tissue of primary oral squamous cell carcinoma (OSCC) predicts relapse free or disease specific survival.They also studied the associations between versicanexpression and several other clinicopathological variables as well as tumour cell proliferation. The results from this study supported the hypothesis that strong stromal versican expression is an adverse prognostic sign in OSCC. This study proposed versican gene over expression to be a distinctive molecular marker of malignant transformation and impending invasive potential of the tumour cells.
In several other cancers, intense versican expression has been shown to be associated with both more aggressive tumour behaviour and unfavourable clinical course of the disease.[16,17,18] Versican was found to be

significantly overexpressed in malignant melanomas, compared with expression in melanocytomas.[19] Researchers found that in the presence of versican, angiogenesis, endothelial cell adhesion, proliferation, and migration are significantly enhanced, while removal of this molecule reverses these processes.

With regard to MMPs, there have been a few studies that have shown associations between MMP levels and outcome of tissue healing. Preoperative MMP-9 levels in nasal secretions and wound fluid were respectively found to show an inverse correlation with quality of healing after sinus surgery and inguinal hernia surgery.[20,21] MMP-1, -2, and -9 levels in peroperative intestinal biopsies were elevated in patients who developed anastomotic wound failure after colorectal resection.[22] While, MMP inhibitors have been shown to improve healing of intestinal and cutaneous wounds [23,24,25] MMP-3 levels appear to be related to the prognosis of osteoarthritis as well. MMP inhibitor therapy has already been tried.

Further, M. S. Kim [26], in his study on the effects of alendronate on the expression of ADAMTS in developing femoral epiphyseal cartilage found that the mRNA levels of ADAMTS-1, -2 and -9 in chondrocytes were unaffected with alendronate treatment. However, the levels of ADAMTS-5 and -4 were reduced significantly by the same treatment. In this study, primary cultured chondrocytes from this cartilage were treated with alendronate in vitro and postnatal day 1; rats were injected subcutaneously with alendronate (1 mg/kg) every second day in vivo.The researcher found that the hypertrophied chondrocyte layers became significantly thicker, and the size of the secondary ossification centre was reduced significantly by the same treatment ($P < 0.05$). Both ADAMTS-4 and -5 mRNA expressions were also reduced significantly in vivo. These results suggested that alendronate could inhibit the degradation of aggrecan in the articular cartilage by downregulating the expression of matrix enzymes such as ADAMTS-4 and -5.

Additionally, researchers investigated the expression of versican and ADAMTS1, 4, and 5 mRNA during bone development in rat mandibles and hind limbs.[27] Versican was analyzed by immunohistochemistry ad RT-PCR. The versican protein was found in abundance in the woven bone matrix but decreased in the lamellar bone matrix. The temporal and spatial mRNA expression pattern of ADAMTS1, 4, and 5 was comparable to that of versican. ADAMTS1, 4, and 5, all proteases capable of cleaving versican [28,29,30] also exhibited a temporal and spatial mRNA expression pattern similar to that of versican. These results suggest that woven bone rich in versican alters into lamellar bone containing little versican during bone development in both mandibles and hind limbs, where some osteoblasts may be involved in production as well as degradation of versican by secreting ADAMTS1, 4, and 5.

Further, in a study titled "Expression of versican in relation to chondrogenesis related extracellular matrix components in canine mammary tumors" researchers investigated whether the high expression of versican relates to prechondrogenesis in these tissues.[31] Therefore, they aimed to identify cartilage markers, such as collagen type II and aggrecan both at mRNA and protein level in relation to versican. RT-PCR revealed upregulation of genes of versican, collagen type II and aggrecan in neoplastic tissues, especially in complex and mixed tumors. In another study, Boeuf et al.[32], analyzed the expression and function of ADAMTS with aggrecanase activity during chondrogenic differentiation of human mesenchymal stem cells (MSCs). The results showed that while the expression of ADAMTS4, 9, 16 and furin was up-regulated during chondrogenesis, ADAMTS1 and 5 were down-regulated. Submission of differentiated MSC pellets to IL1β treatment for 3 d resulted in strong upregulation of ADAMTS1, 4 and 5, rapid proteoglycan depletion, and stimulation of ADAMTS-induced, but not MMP-induced, cleavage of aggrecan.

Discussion

The results of the literature review support the key role of ADAMTS, MMPs, versican, and aggrecan in bone and connective tissues regeneration and healing. The results of various studies indicate that versican is synthesized by migrating and proliferating fibroblast cells and is involved in development and wound healing. Proteolytic cleavage and processing of versican and aggrecan by enzymes from the MMP and ADAMTS families impact the structural and

functional properties of various tissues during their development, growth and regenration.

As the review of literature indicated, the concentration and localization of the versican and aggrecan is critical to determining their effect on tissue regeneration and collagen organization. Not only these proteoglycan but also their proteolytic products influence the developmental and regeneration processes. The review of literature strongly suggests that defective proteolysis of these proteoglycans is a definitive mechanism underlying various developmental and regeneration anomalies/pathologies. The results further suggested that proteolytic enzymes, ADAMTS and MMPs are not required solely for versican/aggrecan clearance, but they might generate proteolytic products that influence tissue proliferation and healing. Thus, a balanced versican and aggrecan processing by ADAMTS' and other proteolytic enzymes is crucial in an ideal developmental and regeneration setting.

Therefore, it can be hypothesized that long-term bisphosphonate treatment (before and after dento-alveolar surgical procedures) of patients with bone wasting or malignant diseases causes suppression/ down regulation of the versican and aggrecan, and certain ADTAMS in the lower jaw. This in turn leads to delayed wound healing and tissue regeneration at the surgical/ trauma sites and might end up with BRONJ.These lesions can be asymptomatic or present with pain, purulent discharge, swelling, tooth mobility, and paresthesia.

Hypothetically, the etiopathogenesis of BRONJ can be attributed to suppression of bone turn over (caused by bisphosphonate induced osteoclast inhibition, suppression of versican and other related proteoglycans and degrading enzymes) and anti angiogenic properties of bisphosphonate that may contribute to poor wound healing properties. The higher rates of bone turn over in jawbone than in long bones may result in higher uptake and greater amount of local concentration of bisphosphonates with profound impact on osteoclast activity and on expression of proteoglycan and degrading enzymes. The hypo dynamic bone may not be able to respond to the repair process associated with physical trauma or infection and may result in bone necrosis. (The fact that tooth socket in patients who develop BRONJ may be evident years after extraction is further evidence that bone turn over in these areas is severely compromised). This slow healing & regeneration process can be endorsed to decreased level of versican and aggrecan at the healing site as well as suppression of ADMATs, which leads to decreased processing of these proteoglycans and in turn to delayed healing & growth.

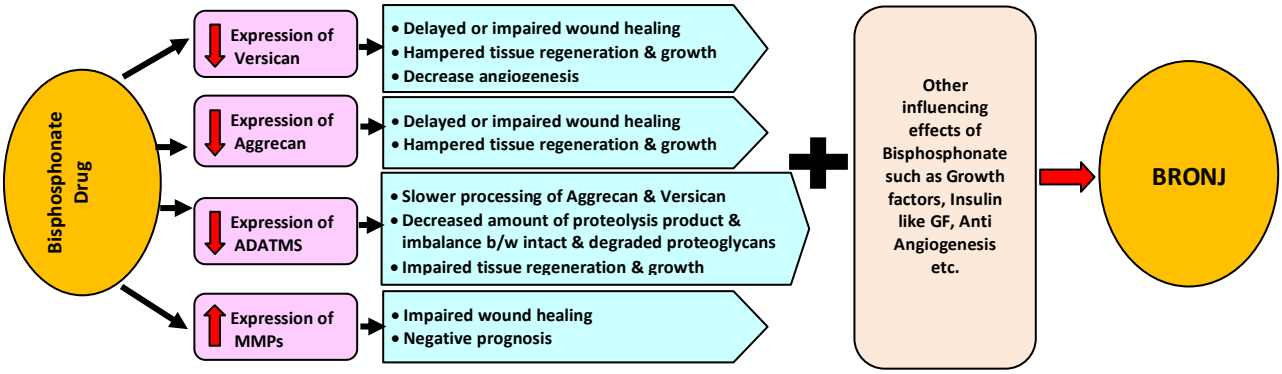
In addition to their osteoclast-inhibiting action, one of the key physiological effects of bisphosphonates is their ability to inhibit angiogenesis, which was earlier proposed as an important mechanism for the clinical utility of potent nitrogen-containing bisphosphonates in preventing the growth of skeletal malignancies and other cancers.[33,34,35] As discussed earlier in this paper, in various cancers and malignant conditions, intense versican expression has been shown to be associated with a higher rate of angiogenesis, more aggressive tumour behaviour and unfavourable clinical course of the disease. Studies using cultured human breast cancer cells have demonstrated that nitrogen-containing bisphosphonates inhibit angiogenesis pathways.[35] Therefore, I suspect that bisphosphonates have potential inhibitory action on versican expression and this anti-angiogenesis role for bisphosphonates is central to one of the our key hypotheses for the avascular nature of BRONJ.[36,37]

Based on the knowledge gained by review of literature, pathogenesis of BRONJ in subset of patients receiving bisphosphonates can be explained by the diseases, bisphosphonates are prescribed for, including osteoporosis and bone metastases/malignancies, which can be the underlying reason behind suppressed activity of osteoblasts/osteoclasts, down regulation of versican, agrrecan and ADAMTS. Alternatively, bisphosphonates themselves play a key role in suppressing the activity of the osteoclasts and down regulating the level of above mentioned elements in musculoskeletal tissues of oral cavity.[36]

Collectively, these factors contribute to the hypothesis that following extractions, dental surgical procedures, and trauma, the mandibular expression of ADAMTS-4 and -5 as well as of versican and aggrecan is decreased, and bone remodelling is compromised by

bisphosphonates which contributes to impaired healing and tissue regeneration.[36,38]

Figure- 1: Hypothesized influence of bisphosphonates on ADAMTs, Versican, Aggrecan & MMPs



Conclusion

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) adversely affects the quality of life, producing significant morbidity in afflicted patients. Although the current level of evidence does not fully support a cause and effect relationship between bisphosphonate exposure and necrosis of the jaw (causality), this paper outlined existing literature indicating the key role of versican, aggrecan, bio-active degradation products of versicanand aggrecan, ADAMTs and MMPs in bone repair, angiogenesis, and BRONJ pathogenesis, and demonstrating strong clinical correlation between jaw necrosis and bisphosphonate therapy. Thus, in order to establish a definitive causal relationship, there is a critical need of research investigating the expression and localization of these factors during the onset and progression of BRONJ by utilizing advanced analyzing techniques.

In addition to studies elucidating the etiopathogenesis of BRONJ and causality of association between BRONJ and bisphosphonate treatment, there is an urgent need of prospective studies including clinical trials to address issues such as alternative dosing schedules to reduce the incidence of BRONJ while maintaining the enormous benefits of bisphosphonate drugs. Prospective studies are also needed to more precisely determine the additional risk factors such as age, sex, pre-existing medical conditions, and individual genetic variations, which may predispose the patient in the development of osteonecrosis of the jaws.

The efficacy of bisphosphonates in treating and managing various bone wasting and metastatic complications has had a major positive impact for patients. A more accurate understanding of bisphonsphonate related jaw necrosis would allow clinicians/dentists to make more accurate judgments about risk, prognosis, and treatment selections as well as prediction of treatment outcomes.

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