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Research Article

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Cyclopedic Analysis of Medication-Related Osteonecrosis of the Jaws in Patients with Diabetes Mellitus.

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Abstract

Medication-Related Osteonecrosis of the Jaw (MRONJ) is a complex condition which involves localized bone necrosis of maxilla and mandible among patients undergoing treatment for chronic debilitating diseases including multiple myeloma, breast cancer, prostate cancer and osteoporosis. Common clinical symptoms include non-healing painful socket, tooth mobility, foul oral odor, sometimes accompanied with fever and lymphadenopathy. Higher incidence of osteonecrosis of the Jaw is associated with long term therapeutic use of bisphosphonates, Receptor Activator of Nuclear factor Kappa-β Ligand inhibitors, and antiangiogenic agents. Bisphosphonates and Receptor Activator of Nuclear factor Kappa- β Ligand inhibitors regulate osteoclast differentiation, bone remodeling and repair in osteoporosis. The antiangiogenic drug controls proliferation, growth and metastasis of carcinomas by suppression of angiogenic pathways. Though the exact pathology underlying MRONJ is still unknown but patients with long-term history of diabetes mellitus have shown to present deteriorating effects on bone physiology. Diabetes alters the immune response, promotes inflammation, suppress differentiation of osteoclast and bone turnover rate. In modern times, though establishing a diagnosis and ubiquitous treatment modalities are readily available for the patients with diabetes, determining the same for MRONJ has never been precise due to under-reporting of the cases. Other systemic diseases contributing as risk factors in MRONJ include rheumatoid arthritis, hypertension, auto immune disease and recently discovered Coronavirus Disease-19. The intractable course of the disease affects quality of life with proportionate impact on global medical healthcare system. Thus, diagnosis of ONJ is critical to reduce morbidity among these patients. The objective of this review is to focus on the molecular effect of drugs which escalates the risk of MRONJ among diabetic patients.

Keywords: Diabetes, MRONJ, BRONJ, Cancer, Antiresorptive, Antiangiogenic, Bone Remodeling, SARS-CoV-2.

Introduction

Osteonecrosis of the Jaw (ONJ) is described as a condition of subacute onset with localized necrosis of alveolar ridge often precedented with dental extraction, endodontic treatment or procedures related to dental implants [1,2]. Delayed healing of the surgical site [3] that may persist longer than 8 weeks without history of radiotherapy accompanied by localized pain, erythema, suppuration and formation of exposed necrotic bone are the suggestive features of ONJ [4]. Histopathology predominantly composed of reduced number of osteocytes surrounding necrotic areas with numerous empty lacunae in demineralized bone matrix [5]. Due to the increase incidence of ONJ observed with various medications including Bisphosphonates (BPs), Receptor Activator of Nuclear factor Kappa-β Ligand (RANKL) inhibitors and antiangiogenic drugs, American association of oral and maxillofacial surgeons in 2014 proposed the use of Medication-Related Osteonecrosis of the Jaw (MRONJ) [6]. The stages of MRONJ according to its severity has been mentioned in table 1. It frequently involves mandible in females with a ratio of 2:1 in an average age population of 65 years old [7] The presence of various communal micro-organism in the oral cavity increases the vulnerability of jaw bones. Literature suggests the presence of actinomyces and staphylococcus species maintains the inflammatory cytokines at the wound site that may delay the wound healing. The effects of anatomical irregularities are also suggested to impart to the clinical course of the disease. Protruding cortical bone with thin mucosal coverage like tori and exostoses, periodontal disease, any surgical intervention exposing bone, especially tooth extractions pose higher risk for alveolitis [8]. The level of risk is observed to be directly influenced by type of drug, length of exposure, cumulative dose and potential co-morbidities like history of endocrinal imbalance, osteoporosis, multiple myeloma, immunological conditions and fibrous dysplasia [9].

BPs and RANKL are used in the treatment of osteoporosis, Paget's disease and metastatic bone disorders. Though the incidence of ONJ is reported to be around 0.7–6.7% and 0.04–0.2% among patients being treated with BPs for cancer and osteoporosis respectively yet 75-86% patient develop MRONJ following dental procedures [10]. Antiangiogenic drugs are recommended in the treatment of cancer and ophthalmic disorders that acts by inhibiting formation of new blood vessels. Migliorati et al [11] reported a mean incidence of MRONJ in 6.1% patients exposed to anti-resorptive or anti-angiogenic drugs.

The altered immune response with underlying systemic disease has shown to have cascading effect on MRONJ. Studies suggest that diabetes is a crucial risk factor observed in 58% MRONJ cases [12] yet relationship of diabetes with MRONJ has never been thoroughly elucidated. DM suppresses osteoclastic differentiation by interfering with glycosylation of proteins that produce Advanced Glycation End-products (AGEs) in bone matrix leading to osteopenia. The lower bone density and reduced remodeling rate overall effect the calcium homeostasis. Microvascular ischemia due to increased oxidative stress in endothelial lining cell may cause apoptosis of osteoblast and osteocyte. Molecular and biochemical alterations affect Vascular Endothelial Growth Factor (VEGF), AGE, and Tumor Necrosis Factor- α (TNF-α) suggest a potential role in accentuating the pathogenesis of MRONJ in the presence of metabolic condition.

Contrarily, independent effect of diabetes has not shown any significant risk in the development of ONJ. It is therefore evident that the antiresorptive, antiangiogenic and immunosuppressive drugs along with diabetic micro- and macro-vascular alterations could result in elevating the risk of MRONJ. This article attempts to review and present the mechanism of various drugs affecting diabetic patients in MRONJ.

Table 1: Stages of MRONJ and imaging characteristics [6]

Stage	Clinical Conditions	Imaging Characteristics
	No necrotic bone present in patients	No specific radiographic changes

Patient at risk	who are administered with bone-modulating agents.	observed.
Stage 0	Absence of any clinical evidence of necrotic bone but non-specific clinical findings along with radiographic changes and symptoms.	• Loss or resorption of alveolar bone. • Sclerosis of alveolar bone and lamina dura with thickening of periodontal ligament and lamina dura.
Stage 1	Exposed and necrotic bone or fistula in asymptomatic patients with no evidence of infection.	• Features can be the same as stage 0. • Trabecular pattern can be disorganized with poor corticomedullary differentiation.
Stage 2	Exposed and necrotic bone or fistula which leads to bone on probing and associated with infection, pain, and erythema with or without purulent discharge.	• Mixed diffuse osteosclerosis. • Osteolysis from the alveolar to the jaw bone. • Maxillary sinusitis with sequestration. • Thickening of the mandibular canal. • Periosteal response.
Stage 3	Exposed and necrotic bone or fistula which leads to bone on probing and associated with pain, infection, and one or more of the following features: exposed and necrotic bone which extends beyond the alveolar bone resulting in pathologic fracture of the jaws, extra-oral fistula, oral antral or oral nasal communication or osteolysis extending to the inferior border of the mandible or sinus floor of the maxilla.	• Osteolysis or osteosclerosis of adjacent bone. • Pathologic fracture of the mandible. • Osteolysis extending to the floor of the maxillary sinus.

Role of Bisphosphonates

Bone remodeling is a biological phenomenon that aids to repair and reverse the osseous defects by regulating initiation and progression of bone deformities. In 1968, Fleisch identified the role of diphosphonates/BP in prevention of bone disease. Previous studies postulated that BPs suppress the precipitation of calcium phosphate and reduces the dissolution of crystals even at very low concentration. However, it was later unraveled that BPs have the tendency to deposit new bone dismissing the chief role of crystal removal from matrix as expressed in earlier studies.

BPs blocks the degradation of both bone and cartilage by arresting the remodeling of the bone that may appear dense than normal in the radiograph [13]. It can bind to the bone surface, allows cellular distribution and skeletal absorption. Therefore, it interacts with charged ions and matrix constituents including osteocalcin, osteonectin, bone sialoproteins, and proteoglycans [14]. Presence of sclerotic bone, obliteration of lamina dura and widening of periodontal ligament space surrounding affected teeth are specific radiological features of MRONJ [15]. BPs tend to decrease bone resorption by osteoclast apoptosis inadvertently affecting the bone remodeling rate. The long half-life of BPs in bone continues to show its harmful effect for considerable period after drug withdrawal. The effect of toxic levels of BPs are predominantly seen in the jaw bones due to greater sensitivity of osteoclast undergoing constant bone remodeling to accommodate various forces generated during mastication [16].

BPs are broadly classified into the non-nitrogen containing bisphosphonates such as etidronate, tiludronate and clodronate. These compounds act on the phosphate chain of ATP-containing compounds that are resistant to breakdown by

enzymatic hydrolysis with long half-life. It accumulates in the bone and inhibits osteoclastic differentiation and apoptosis.

The next generation contains nitrogen substitute in an alkyl chain to the basic structure of BP making it 10–100 times more potent at inhibiting bone resorption. Risedronate and zoledronate are the latest drugs that are considered more efficacious than previous generation due to the presence of nitrogen atom within a heterocyclic ring.

Nitrogen-containing BPs inhibits farnesyl pyrophosphate synthase by blocking the mevalonate pathway. This inhibition leads to a decrease formation of isoprenoid lipids such as farnesyl pyrophosphate and geranyl pyrophosphate altering the GTP-binding proteins like Ras, Rho, Rac, and Rab.

These proteins are involved in various processes including inhibition of osteoclast recruitment and its differentiation. Any disturbance in this molecular pathway may alter the bone metabolic rate leading to decreased activity. The lack of geranyl pyrophosphate may shorten the life span of osteoclasts leading to decrease in bone turnover [17].

In addition, soft tissue toxicity has also been reported with the administration of zoledronic acid. The gingival fibroblasts in vitro have been found to show reduced expression of extracellular matrix (ECM) proteins, including collagens I, II and III. BMPs and TGF-β1 signaling enhance matrix production and osteoblast differentiation suggesting important role in both mucosal and osseous tissues of oral cavity. Lina et al noted that decreased TGF-β1 signaling is related to mucosal ulcerations due to impaired soft tissue repair marking as initial pathologic event in the pathogenesis of ONJ. Therefore, alterations in BMP-2 and TGF-β1 signaling might explain BP-associated changes in the oral tissues affecting MRONJ. [16]

The prevalence and severity of periodontitis are frequently observed in both type 1 and type 2 diabetes. Tooth loss/ mobility progresses due to inflammation mediated loss of connective tissue attachment and alveolar bone destruction. Teeuw et al [18] and Katagiri et al [19] stated bidirectional relationship of DM and periodontitis suggesting the severity of periodontal inflammation is directly influenced by glycemic control in diabetic patients. Similarly, effective periodontal treatment has also shown improvement in glycemic control in type 2 diabetes. Insulin receptors present on osteoblast has catabolic effect on bone in poor glycemic control affecting mineralization and bone strength [12]. Kalyan et al and Hoefert et al observed prolonged inflammatory mediators in the presence of decreased neutrophil, macrophage function and reduced chemotaxis as an aggravating factor in MRONJ [20,21]. The altered TGF-β signaling pathway in diabetes may also contribute to inflammatory response in alveolar bone underlying pathogenesis of ONJ.

Role of RANKL inhibitors

The role of osteoclast and osteoblast interaction is a well-known phenomenon in maintaining the bone integrity. Various therapeutic strategies target the osteoclast owing to their ability to regulate bone remodeling. Long term use of intravenous or oral BPs are often associated with renal toxicity, gastrointestinal problems and ONJ. Recently, human monoclonal antibody targeted towards RANKL, also known as RANKL inhibitors was introduced. In 2010, FDA approved the use of denosumab for treating osteoporosis and preventing metastasis from tumors like breast and prostate. Lack of covalent binding to bone and shorter half-life makes it more suitable than BPs [22].

RANKL is an important protein expressed in osteoblasts, stromal, dendritic, synovial, periodontal ligament, B cells, fibroblasts, odontoblasts, cementoblast, ameloblasts, and activated lymphocytes. RANKL binds to its receptor RANK, which is expressed on osteoclast precursor cells, to induce osteoclast differentiation through the activation of transcription factors, such as nuclear factor of activated T cell c1. Osteoprotegerin glycoprotein (OPG) is a decoy receptor for RANKL, critical in preventing RANK- RANKL interaction. Increase in molecular levels of OPG suppresses the expression of Osteoclast, inhibiting bone resorption. Therefore, precise balance of RANKL verses OPG is crucial in RANK signaling

regulating osteoclast differentiation and function [22,23].

RANKL inhibitors blocks RANK-RANKL interaction, decreasing bone resorption by altering osteoblast-osteoclast ratio by inhibiting physiological function of osteoclastogenesis, causing a decrease in the bone turnover rate. Aghaloo et al [22] observed RANK and OPG were equally effective in attenuating osteoclastic activity and producing radiographic and histologic ONJ-like changes in mice. The modifications might lead to over lasting of aged bone and its hyper-mineralization. The increase in overall bone density might lead to low influx of nutrient supply to the jaws leading to MRONJ. The incidence ranges from 0.9 to 5% with denosumab. which has a shorter half-life.

Khan et al [24] and Hinson et al [25] suggested the role of local infection due to the presence of > 10^{11} bacteria/cm^3 could trigger the inflammatory pathways following invasive dental treatment. The presence of microbes is also observed with poor oral hygiene, diabetes mellitus or rheumatoid arthritis (RA) patients, who are often at high risk for infection. It is further understood in the mice models that presence of TNF-α produced by osteoclast progenitor cells accelerates the apoptosis of osteocytes with anti-resorptive drugs. Similarly, Morita et al [26] reported that Porphyromonas gingivalis also strongly induces TNF-α expression in bone previously treated with antiresorptive drugs causing osteomyelitis followed by osteonecrosis. However, contrasting outcome was observed in the presence of sterile environment. Hence, presence of inflammation may regard as the confounding factor in mice exposed to combination of staphylococcus aureus and antiresorptive agents.

Alteration to the immune system characterized by reduction in subtypes of T-cells, reduced activation of T-lymphocytes in the peripheral vasculature predisposes a lower response to infections, especially in oral cavity. Karina et al reported immunosuppression as a potential side effect of chlorpropamide, biguanides and sulfonylureas both in vitro and in vivo [27]. Oliveria et al suggested increased production of pro-inflammatory cytokines has often been associated with hyper-inflammatory state in diabetes [28]. Inflammatory markers such as TNF-α present in higher levels in such patients. In addition, localized inflammatory diseases such as gingivitis and periodontitis are among the most dominant forms of oral complications in patients with diabetes suggesting increased risk of MRONJ in hyperglycemic patients [29].

Role of Antiangiogenic drug

Several crosstalk occurs to strictly regulate the interaction between cancer cells, host immune cells and tumor microenvironment to downstream the proliferating tumor. Studies have shown that antiangiogenic drugs have impending role in suppressing tumor development by inhibiting Receptor Tyrosine Kinase (RTK). Downregulation of RTK impairs proliferation, migration, differentiation, neoangiogenesis, and invasion of cancer cells, thus providing an attractive target for cancer therapy. Contrarily, angiogenic pathways have biological significance in repair and regeneration of damaged tissue. Similarly, osteogenesis and angiogenesis work in tandem during physiological bone remodeling and repair [30]. Rabie demonstrated that during demineralized bone matrix induced osteogenesis, the angiogenic load enhances osteoinduction ability to promote localized healing [31]. VEGF mediates angiogenesis for osteogenic differentiation. Antiangiogenic drugs like bevacizumab suppress VEGF receptor (VEGF-R) that may compromise the microvascular integrity affecting the osteoblast. The ability to repair new bone is reduced in the event of any micro-trauma further deteriorating the strength of the jaw. Reduced number of leukocytes in hypoxic environment significantly increases the risk of infection leading to avascular necrosis in ONJ [30].

Sunitinab is widely known antiangiogenic drug with multi-targeted action. It inhibits pathways including VEGF-R, Platelet Derived Growth Factor Receptor (PDGF-R) and stem cell factor receptor (KIT), tyrosine kinase type 3 (FLT3), the Colony Stimulating Factor 1R (CSF-1R) and the neurotrophic factor receptor derived from the glial cell line (RET). In 2006, it was approved by the Food and Drug Administration to use in combination for renal cancer. Though sunitinab produces transient adverse effects such as

diarrhea, mucositis, altered taste, skin abnormalities, and hypertension, interruption therapy or dose adjustment has shown to be beneficial in reversing these symptoms. In Contrast, inhibition of pathways including VEGF and platelet derived growth factor (PDGF) may serve potential mechanism underlying the pathogenesis of ONJ by inhibiting fibroblasts and endothelial cells preventing repair [32]. Hoefert et al mentioned that sunitinab given as a maintenance therapy over a longer period could lead to potential effects on vasculature. [21]

Suppressive role of sunitinib on KIT described in keratinocytes may trigger tissue breakdown and bacterial invasion in the exposed bone. Suwattee et al observed healing of mucosal erosion in the oral cavity and perianal area following withdrawal of sunitinib [33]. Mignosa et al reported necrotizing ulcers in the hard palate and glossitis among patients without any previous drug history of BPs during treatment [34]. Sunitinib discontinuation and application of steroids with improved oral hygiene resulted in complete remission of the lesions.

The mucosal breach is also observed with patients undergoing treatment with BPs, therefore the combined additive effect of mucositis might not be an unusual clinical oral feature in initiation of ONJ. Brunello et al described case report indicating that impaired angiogenesis by sunitinib delays mucosal healing and defective bone remodeling due to BPs entrapped within the osteonecrotic mineral matrix amplify the risk of ONJ [35].

Diabetes, known to be associated with decreases of VEGF and VEGF receptor 2 (VEGF-R2), causes dysfunction of endothelial cells and reduces arterial remodeling. Maahs et al reported greater incidence of ONJ in diabetic wistar rats [36]. Gingival tissue of patients with periodontitis has shown mitochondrial DNA damage due to increased oxidative stress. Insulin resistance is often associated with microvascular ischemia of the bone and endothelial cell dysfunction. The bone turnover and remodeling rate is reduced in chronic diabetes induced by apoptosis of osteoblasts and osteocytes. Peer A observed that microvascular complications are higher among MRONJ patients with underling diabetes than among those without systemic disease [12,37].

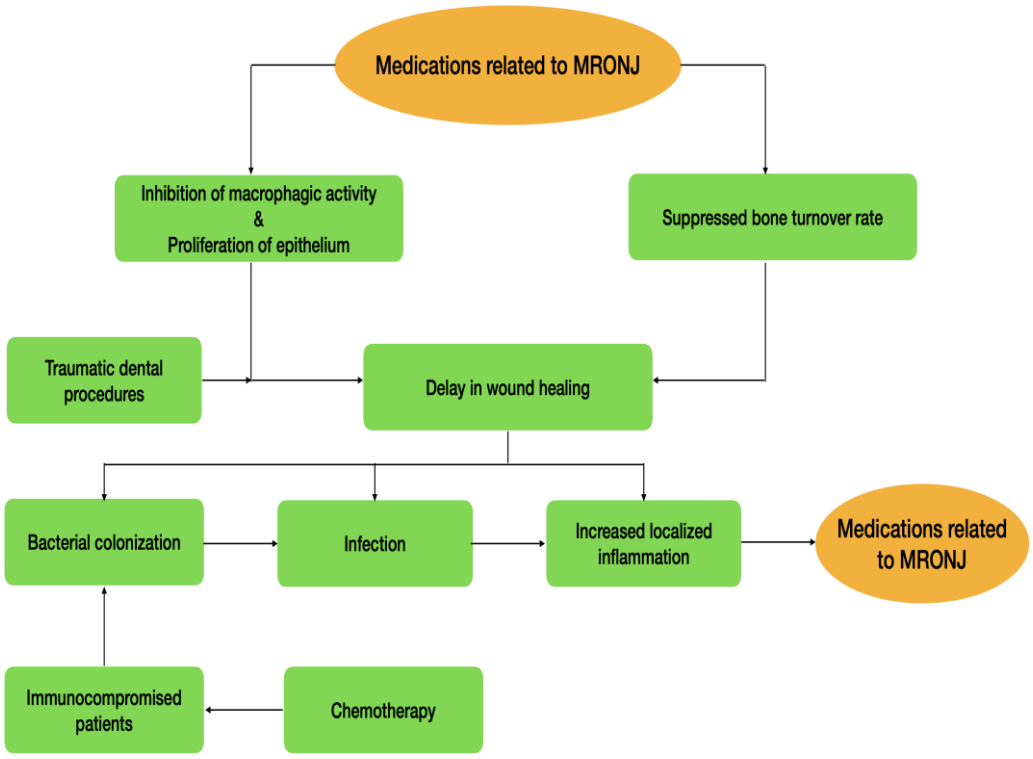

Figure 1: Pathogenesis of MRONJ

Other Drugs Related to MRONJ

Other pharmaceutical agents like immunosuppressants, radiopharmaceuticals, selective estrogen receptor modulators, and

mammalian target of rapamycin inhibitors has been cited for ONJ development. Apart from its use in oncology, they are administered for various autoimmune and inflammatory conditions including rheumatoid arthritis, Chrohn's disease, systemic lupus erythematosus, sjogren's syndrome, ankylosing spondylitis, and ulcerative colitis. Literature suggests that association of bone pathology can be either direct manifestation of the disease itself or might be related to the use of corticosteroids or immunosuppressant drugs [38].

Monoclonal Antibody

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor. Tocilizumab binds soluble and membrane-bound interleukin-6 receptors. Autoimmune diseases like rheumatoid arthritis shows abnormally high interleukin-6 levels that may promote development of immunological and inflammatory reactions. The neutralizing effect of tocilizumab on interleukin-6 reduces the pro-inflammatory effects and disease progression. Though tocilizumab was considered for its aggravating effects on ONJ but impact of other synergistic drugs was not excluded in previous studies. Sakkas et al observed osteonecrosis involving jaws under the tocilizumab drug regime. Therefore, the therapeutic use of tocilizumab without previous exposer to bisphosphonates confirms the potential role of interleukin-6 receptor inhibitor in the pathogenesis of MRONJ [39].

Elevated interleukin-6 levels are frequently observed in Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) associated with immune dysregulation and hyper-inflammatory response. The severity of SARS-CoV-2 persist with increased levels of Interleukin-6 causing cascades of events involving accumulation of lymphocytes and inflammatory monocytes, endothelitis, apoptosis, thrombosis, and angiogenesis in the pulmonary vasculature. The vascular inflammation and dysfunction contribute to the classical features of SARS-CoV-2 pneumonia. Better outcomes in patients with severe SARS-CoV-2 pneumonia were noticed with tocilizumab combined with dexamethasone. Retrospective observational cohort studies showed reduction in fever, reduced use of oxygen support and mechanical ventilation, and improved lung manifestations [40].

Davis N et al reported a significant difference in mortality rate between the group receiving tocilizumab (28%) compared to those receiving standard care (35.8%) in randomized controlled trial. The increase use of tocilizumab for SARS-CoV-2 pneumonia may show higher number of patients showing MRONJ like symptoms which may require detailed history of drugs prior to surgical dental procedures [41].

Immunosuppressants

Methotrexate (MTX), a classic immunosuppressant and anti-rheumatic drug previously used as the first line treatment for various cancers [42]. A decrease in the proliferation of the malignant cells has been noted when high doses of MTX are administered. This is due to the cellular starvation of purine and pyrimidine precursors which fails to maintain appropriate DNA and RNA synthesis. Due to excessive toxicity of the drug in high doses, it is used only in mild doses as an anti-inflammatory regimen. Extracellular adenosine accumulation has been found to mediate the anti-inflammatory effect of MTX in conditions like rheumatoid and psoriatic arthritis. MTX have been reported to inhibit osteoblastic proliferation and development of osteoclasts, hence altering the bone turnover rate. Such changes in the bone turnover rate along with immunosuppressive properties can lead to MRONJ [43].

MTX-stimulated adenosine release suppresses chronic inflammation that is known to indirectly improve glucose homeostasis. It promotes glucose uptake, fatty acid oxidation, and mitochondrial biogenesis, which helps to ameliorate different aspects of metabolic dysregulation, including hyperglycemia and insulin resistance. Though MTX-induced adenosine's exact role is ambiguous in metabolic diseases, both adenosine receptor activation and its blockage improve insulin sensitivity in diabetic patients [44].

However, a relatively high threshold for activation in peripheral skeletal muscle in conjunction has been a clinical limitation due to poor bioavailability. Clearly, the potential risk of ONJ may elevate following MTX exposure but its relation to metabolic disease in the pathogenesis of ONJ remains undefined.

Corticosteroids, along with being an immunosuppressant, also has anti-inflammatory effects. They directly affect angiogenesis by suppressing the production of VEGF [45]. It reduces the bone turnover rate by diminishing recruitment of osteoblast and osteoclast. Study by Nisi and Wong has described cases on long-term steroid therapy with non-healing mandibular lesions after dental extraction without any other MRONJ causing agents [46,47].

Radiopharmaceutical Agents

Radiopharmaceutical agents like radium 223, strontium 89, rhenium 186, and samarium 153 are used either orally or intravenously for investigating and imaging various benign and malignant carcinomas. Such agents are classified based on the radiations they emit, i.e., alpha, beta, gamma, or positron rays. The drug acts on the calcium hydroxyapatitite in bone matrix and localizes in areas of greater osteoclastic activity preventing metastases to distant organs.

Literature suggests that radium 223 may express synergistic effect in development of MRONJ when combined with other bone modulating agents. A retrospective analysis by Cao et al showed that the patients treated with radium 223 along with BPs or denusumab or monoclonal antibodies had a rate of ONJ development of 9.7% [48].

Selective Estrogen Receptor Modulators (SERM)

Raloxifene is a non-steroidal benzothiophene used as an alternative treatment for osteoporosis. They are partial estrogen agonist that maintains the density of bone in post-menopausal women. It reduces osteoclastogenesis and bone resorption reducing the risk of skeletal fractures. Due to its action on estrogen sensitive breast cancers these modulators are also included in the preventive therapy for breast cancer. Though, relation between SERM and MRONJ are not yet fully established, concerns have emerged due to its detrimental effects on osteo-homeostasis. Luvizuto et al observed delayed wound healing of alveolar bone in rats under the inhibitory effects of raloxifene on osteoclast. Similar findings along with mandibular fracture were observed by Baur et al. in 67-year-old female following multiple extractions. with pre-existing condition of type 2 diabetes mellitus, osteoporosis, rheumatoid arthritis, cirrhosis, hypertension, hyperlipidemia, and hypothyroidism [49]. Though the case developed ONJ yet it is challenging to isolate the effects caused by raloxifene alone. Hence, therapeutic history with bone modulating agents and comorbidities like diabetes and rheumatoid arthritis may have additive effect in the etiology of MRONJ. Long term studies with a greater number of subjects would further allow pathologist to elucidate the risk associated with its usage.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin is a protein which is a vital target for the treatment of anomalies caused by abnormal cellular proliferation. These agents downgrade VEGF expression, hence reducing the endothelial proliferation, angiogenesis, and migration [50]. Due to such modulations, they are effective immunosuppressive agents in the cases of organ transplant, treatment of breast cancer, pancreatic neuroendocrine tumors and renal cell carcinomas [51]. Kneissel et al has shown that the mammalian target of rapamycin inhibitors affects the bone turnover rate by inhibiting osteoclastic cells [52]. A study by FDA's adverse event reporting system in 2016 has emphasized on the risk of ONJ with the use of the agent, though a relatively clear theory has to be ascertained [53]. However, mammalian target of rapamycin inhibitors along with antiangiogenic drugs were the agents with lowest risk of potentiating ONJ.

First generation mammalian target of rapamycin inhibitors like everolimus and temsirolimus has been shown for causing ONJ. Yamamoto et al and Lee et al has reported incidences of mandibular necrosis in patients administered everolimus with no other bone or vascular modulating agents.

Multiple reports are available with temsirolimus causing ONJ with only one case where this agent was solely used without any adjunctive medication [51].

Conclusion

Though the cases of MRONJ are relatively uncommon, this multifactorial condition is debilitating enough to alter the patient's quality of life. The majority of MRONJ cases were observed in patients under antiresorptive, antiangiogenic or RANKL inhibitor medications although few non-bone modulating agents have been found as causative factor. Overall, the prevalence was found to be higher in patients with preexisting diabetes.

Accumulation of bisphosphonates in the craniofacial area exacerbates MRONJ, hence increasing the risk and prevalence of the condition. Dosage and route of administration play a pivotal role in establishing severity of the condition. Trauma and injury to the craniofacial apparatus has also been cited as an etiological factor for MRONJ.

The number of reports available are relatively scarce, hence more human clinical trials are required to understand the depth of the relation between MRONJ, its pathogenesis and its relation with diabetes. New advent of drugs administered for the treatment of multiple debilitating illnesses will increase the risk of MRONJ. Future prospective studies with quantitative analysis would shed a significant light on the condition which will eventually aid clinicians in understanding the pathogenesis and treatment modalities of MRONJ, especially in patients with diabetes. More clinical data should be gathered on preferred antiglycemic agents which could lower risk of MRONJ for patients with diabetes. Presently, detailed patient medical history and proper clinical examination of patients with diabetes can lower the risk of MRONJ increasing the impact of clinical outcomes. Monoclonal antibody like tocilizumab when administered with dexamethasone has observed with favorable response in SARS-CoV-2 infections.

Many of these agents may not be used for osteoporosis but can be a potential cause for MRONJ due to variety of action mechanism. It is the responsibility of the medical and dental practitioners to report such cases which will help to develop a therapeutic blueprint.

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