Sclerostin-A Potential Biomarker And A Possible Link Between Diabetes Mellitus And Periodontitis –A Review

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ABSTRACT:

Peridontitis is a multifactorial disease which is found to cause destructions to the supporting structures of the tooth which inturn is found to cause tooth mobility.It has been found that periodontitis is also interlinked with many metabolic disorders incuding diabetes mellitus.Diabetes mellitus is found to cause deletorial effects in many organs including the bone.In recent years a protein called sclerostin has been identified which is found to inhibit the Wnt signalling pathway which is one of the major pathways for bone formation.Hence this reiew aims atexplaining the importance of sclerostin and its link with priodontitis and diabetes mellitus thereby finding the sclerostin protein as a potential biomarker for periodontitis and whose therapeutic use may help in future.

INTRODUCTION:

Periodontitis is a destructive disease which is found to target the tooth- supporting structures through complex and multifactorial pathogenic processes. It is a complex biological process which is related to the interaction between group of microbes and the immune/inflammatory response of the host.The interaction between the bacterial components of the biofilms and response of the host mechanisms initiate them[1] .Although gingivitis actually represents the reversible inflammatory reaction to biofilms, periodontitis is the nonreversible and the destructive stage of a persistent bacterial infections[2].when left untreated, periodontitis can result in destruction of the soft tissues and the progressive bone destruction, which inturn will be leading to tooth mobility and subsequent tooth loss. Microbes and their byproducts are the primary etiologic factors for periodontal disease. However, the majority of periodontal destruction is found to be caused by the endogenous proteases such as the matrix metalloproteinases and the inflammatory mediators, such as prostaglandin E2 and tumor necrosis factor (TNF) α, resulting in activation of bone resorption mechanism.

The defects in insulin secretion, insulin action or both will result in a metabolic disorder which is characterized by hyperglycemia that results in disturbances in carbohydrates,fats and protein metabolism is called the Diabetes Mellitus. The prevalence of type 2 diabetes worldwide, which is being increasing rapidly, represents a burden to the human health because of its numerous and more severe complications. As per estimation by WHO, the number of incidence of adults with diabetes will rise from 171 million in the year 2000 to 366 million in the year 2030 over the whole world. The capital of diabetes is declared as India because there are about 41 million people who are diabetic till date in India and every 1 in 5 person who are diabetic are Indians[3].

Epidemiological data has confirmed diabetes as a major risk factor for periodontitis; susceptibility to periodontitis is also being increased by approximately threefold in people with diabetes. There is a clear interrelationship between the degree of hyperglycaemia and the severity of periodontitis. The mechanisms that links between these two conditions are not completely understood, but involve aspects of immune functioning, neutrophil activity, and cytokine biology. There are so many evidences which are found to support the existing interrelationship between diabetes and periodontitis, with diabetes increasing the risk for the periodontal disease, and inflammation of periodontal tissues also negatively affecting glycaemic control[4].

What Are Sclerostins:

The common pathways which regulate the cell activity of the bone are the receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system (Liu & Zhang, 2015) and the Wnt/β-catenin pathway (Duan & Bonewald, 2016).Wnts are a large family of secreted glycoproteins that are able to activate nuclear β-catenin. β-catenin, which is a cytoplasmic and nuclear protein, acts as a activator of the transcription process and regulates transcription of the target genes which are responsible for the process of proliferation of the cell and differentiation. The Wnt/βcatenin pathway, is also called the canonical pathway, is, an important regulator which regulates the proliferation of the osteoblasts and hence resuting the process of bone formation ,further the wnt signaling is also found to play a role int the osteoclast cells.In the osteoclast lineage cells the Wnt pathway components, including receptors, inhibitors and activators, are expressed. Furthermore, by increasing the OPG/RANKL ratio the β-catenin is found to indirectly regulate the process of osteoclastogenesis and thereby reducing resorption of bone.Sclerostin (SOST) and Dickkopf (DKK) are the most important inhibitors of the Wnt/β-catenin pathway, which plays a major role in preventing nuclear translocation of ß-catenin by interfering in the interactions between the Wnt receptors and proteins. SOST is a negative regulator of bone formation which are derived from the osteocytes . Sclerostin is a glycoprotein molecule which is encoded by the SOST gene. Sclerostin is being secreted by the mature osteocytes during process of completion of osteon formation. It therby inhibits bone formation. These proteins act as inhibitors to the Wnt signaling pathway and thus inhibit in the bone formation. Immobilization in humans increases the levels of sclerostin , leading to bone loss . Sclerostin is thought to be the link between mechanosensing process by the osteocytes and bone formation by the osteoblasts and can be measured in the serum by ELISA. A deficiency of sclerostin protein can lead to sclerosteosis and van Buchem disease, which are characterized by high bone masses. Sclerostin is produced by the osteocytes, as OPG and RANKL. In a broader context, osteocytes are naturally occurring modulators of bone metabolism which are found to regulate the balance between osteoclastic and osteoblastic activity. Sclerostin is a marker of the mature osteocytes and affects bone metabolism by inhibiting differentiation of osteoblasts. It is believed to act by promoting the osteoclast formation through RANKL-dependent pathway as well as by interacting with osteoblasts. At the molecular level, osteocytes are found to regulate bone homeostasis through at least three key molecules: sclerostin, OPG, and RANKL[6].

The Possible Relationship Between Sclerostin And Diabetes:

It has been found that sclerostin is present at increased levels in diabetes mellitus (DM). The duration of T2DM, HbA1c, and BMD in T2DM patients are found to be positively related to sclerostin levels which is negatively realted to the turn over rate of bone. Also, it has been found that the lower concentrations of sclerostin are found in T2DM who have osteoporosis than in T2DM without osteoporosis. These findings suggest that type 2 DM is found to impair the pathway of wnt signaling whose dysfunction will lead to a effect in the quality of the bone. It has been found that hyperglycemia affects the bone cells both directly snd indirectly through thr Advanced Glycation End Products which inturn reduced the strength of the bone Also the increase in sclerostin levels in T2DM can be owed to the glycosylation of the sclerostin proteins[7].

The Relationship Between Sclerostin And Periodontitis:

We know that the role of sclerostin in bone osteocytes is reduction of bone formation.Many studies have been conducted so far to reveal the relationship between sclerostin and periodontitis. Evidence suggests that the ligature-induced alveolar bone loss is found to be associated with the increased expression of the RANKL (enhanced osteoclast formation) and the sclerostin (suppressed osteoid formation)[8]. In periimplantitis sclerostin levels are found to be elevated when compared with patientswho have perimucositis and healthy peri-implant tissues[9]. The levels of sclerostin in GCF were also higher in patients with chronic periodontitis than in healthy individuals. The involvement of sclerostin in periodontitis being studied in only one clinical study so far. In which,the sclerostin levels was up-regulated in the tissue samples of gingival in chronic periodontitis patients. It was also reported that sclerostin levels were positively correlated with PPD and CAL.The deletion of the SOST gene or the blockage of SOST function is found to have restored the bone defects in periodontitis models .

Sclerostin –A Possible Link Between Peridontitis And Diabetes:

Furthermore, it has been found that the number of osteocytes with positive presence of SOST gene was higher in diabetic rats with presence of periodontitis than in non-diabetic controls. In humans beings, SOST and DKK1 genes are found to be upregulated in the periodontal tissues with chronic periodontitis (CP). In patients with diabetes and smoking it is found that these two gene levels are found to be upregulated[5].Hence studies suggests that the expression of sclerostin has been increased in type 2 diabetes mellitus as well as periodontitis suggesting a possible co-relation between the two. It has also been found in a study conducted rat models that the presence of the Advanced Glycation End Products and the lipopolysaccharides of the *Porphyromonas gingivalis* are also potentially increasing the expression of sclerostin in the bone osteocytes hereby increasing the osteoclastic activity thereby resulting in the bone loss[10].

Antisclerostin Antibodies:

Hence after knowing the important role of sclerostin in osteogenesis, the pharmacological inhibition of sclerostin by a antibody is being tested across various clinical trials and preclinical models with bone loss. In a study conducted in women with postmenopausal osteoporosis (PMO)it is shown that treatment with a humanized anti-sclerostin antibody (Scl-Ab), is found to reduce the risk of osteoporotic fractures when compared with the bisphosphonate alendronate. Sclerostin antibodies have also been investigated preclinically for other bone loss and bone injury settings, and Scl-Ab administration also increased the volume, mineral density, and alveolar bone height after peridontitis conducted experimentally. Moreover, in a rat model of chronic edentulism sclerostin antibody is found to be useful and Scl-Ab has also improved the mechanical fixation of oral implants by enhancing regeneration of the supporting bone structures. Hence Scl-Ab can act as a bone anabolic agent for treating larger alveolar bone defects where the help in increasing the bone volume and improving the quality of bone[11] .

CONCLUSION:

Owing to the physiological role of sclerostin and its potential link between diabetes and peiodontitis and the underlying pathos being caused this sclerostin expression in the GCF can be used as a potential biomarker for identifying periodontitis as well as periodontitis associated with Diabetes mellitus and also the therapeutic usage of sclerostin antibodies will tend to play a major role in controlling periodontal bone destruction thereby reducing the bone loss and eventually reducting the destruction of soft tissues also. Hence furthermore studies are required to know the therapeutic usage of these Anti Sclerostin Antibodies.

REFERENCE:

1. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. The lancet. 2005 Nov 19;366(9499):1809-20.

2. Giannobile WV. Host-response therapeutics for periodontal diseases. Journal of periodontology. 2008 Aug;79:1592-600.

3. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, Taylor R. Periodontitis and diabetes: a two-way relationship. Diabetologia. 2012 Jan 1;55(1):21-31.

4. Deshpande K, Jain A, Sharma R, Prashar S, Jain R. Diabetes and periodontitis. Journal of Indian Society of Periodontology. 2010 Oct;14(4):207.

5. Miranda TS, Napimoga MH, Feres M, Marins LM, da Cruz DF, da Silva HD, Duarte PM. Antagonists of Wnt/β-catenin signalling in the periodontitis associated with type 2 diabetes and smoking. Journal of clinical periodontology. 2018 Mar;45(3):293-302.

6. Balli U, Aydogdu A, Dede FO, Turer CC, Guven B. Gingival crevicular fluid levels of sclerostin, osteoprotegerin, and receptor activator of nuclear factor-κB ligand in periodontitis. Journal of periodontology. 2015 Dec;86(12):1396-404.

7. García-Martín A, Rozas-Moreno P, Reyes-García R, Morales-Santana S, García-Fontana B, García-Salcedo JA, Muñoz-Torres M. Circulating levels of sclerostin are increased in patients with type 2 diabetes mellitus. The journal of clinical endocrinology & metabolism. 2012 Jan 1;97(1):234-41.

8. Kim JH, Lee DE, Cha JH, Bak EJ, Yoo YJ. Receptor activator of nuclear factor-κB ligand and sclerostin expression in osteocytes of alveolar bone in rats with ligature-induced periodontitis. Journal of periodontology. 2014 Nov;85(11):e370-8.

9. Rakic M, Struillou X, Petkovic-Curcin A, Matic S, Canullo L, Sanz M, Vojvodic D. Estimation of bone loss biomarkers as a diagnostic tool for peri-implantitis. Journal of periodontology. 2014 Nov;85(11):1566-74.

10. Sakamoto E, Kido JI, Takagi R, Inagaki Y, Naruishi K, Nagata T, Yumoto H. Advanced glycation end-product 2 and Porphyromonas gingivalis lipopolysaccharide increase sclerostin expression in mouse osteocyte-like cells. Bone. 2019 May 1;122:22-30.

11. Yao Y, Kauffmann F, Maekawa S, Sarment LV, Sugai JV, Schmiedeler CA, Doherty EJ, Holdsworth G, Kostenuik PJ, Giannobile WV. Sclerostin antibody stimulates periodontal regeneration in large alveolar bone defects. Scientific Reports. 2020 Oct 1;10(1):1-0.