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Association Of Obesity And Resistin Levels In Periodontal Disease- A Systematic Review

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Abstract

Obesity is considered as one of the risk indicators of periodontal disease. Resistin could be one such marker that could provide a link in the periodontitis obesity connection. The aim of this systematic review was to correlate the serum and saliva resistin levels and its association in obese individuals with chronic periodontitis. Relevant articles of the last 10 years were searched using relevant key indexing terms. The inter-relation between obesity and resistin levels in periodontal disease are included in this systematic review.

Keywords: Adipokine; BMI; Insulin; Interleukin; Periodontitis; Pro- inflammatory cytokines

Introduction

Obesity is defined as an excessive body fat accumulation, due to the imbalance between the food eaten and the calories spent [1]. It is evaluated through waist circumference (WC) [2] and body mass index (BMI= kg/m^2) [3] assessment and represents a risk to the general health. An adult is considered to be overweight if his BMI, is ≥ 25 and obese if BMI is ≥30. A high BMI has been found to be a significant risk factor for a variety of diseases including diabetes, cardiovascular disease, cancer and periodontitis. Obesity is thought to produce insulin resistance through adipokines such as resistin, tumor necrosis factor (TNF), interleukin (IL)-6, visfatin and adiponectin [4].

Resistin is an adipocytokine and is secreted from adipose tissue and monocytes/macrophages [5], involved in the inflammatory process, affecting the secretion of IL-6, TNF-α and adiponectin [6- 8], which have been studied for its role in insulin resistance and recently in inflammation [9]. Resistin was first described in 2001 during a search for genes that induced adipocyte differentiation and it was down-regulated in mature adipocytes during exposure to thiazolidinediones **(**TZD). This led to the discovery of a protein that the investigators named as resistin (for resistance to insulin) [10]. Resistin is a member of a secretory protein family, known as resistin-like molecules (RELMs). The family is characterized by a highly conserved, cysteine-rich C terminus in which the spacing of the cysteines is invariant. There are four members in the mouse RELMs family: Resistin, RELMα, RELMβ and RELMg. Only two counterparts were found in human: Resistin and RELMβ. Resistin could be one of the molecular links connecting obesity, periodontitis and diabetes and may serve as a marker that links periodontal disease with other systemic diseases[11].

Periodontitis is a chronic inflammatory disease caused by periodontal pathogens, leading to soft tissue destruction and loss of alveolar bone characterized by stimulation of host inflammatory system which causes the production of pro-inflammatory mediators such as IL-6 and TNF-α [12-16]. Periodontitis has been linked to systemic

conditions, including heart disease, diabetes, obesity and metabolic syndrome.

As all the three – obesity, resistin and periodontitis seem to share much in common (Fig. 1), this paper was designed to find if at all any relation existed in between them.

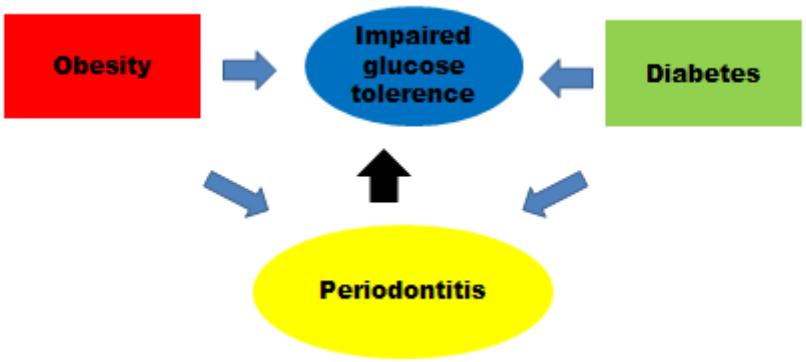

Fig. 1- A three way relationship between obesity, diabetes and periodontitis

Methodology

A literature search was conducted for relevant articles that had been published in Pubmed base using relevant MesH terms such as "adipokines", "adipocytokines", "biomarkers", "body mass index", "chronic periodontitis", "gingival crevicular fluid", "obese", "obesity", "overweight", "resistin", "saliva", "serum", "periodontal diseases", "waist circumference" and "waist-hip ratio". The inclusion criteria included cross-sectional, retrospective and observational studies that appeared in the last 10 years in Pubmed base and compared resistin levels in GCF, saliva or serum in individuals (aged between 20-65 years) with and without obesity (BMI: > 25kg/m^2- < 40kg/m^2) and it's relation with chronic periodontitis. The exclusion criteria included studies without control group and those that were just reviews.

Though 32 articles were shortlisted, their count came down to ten, when the inclusion and exclusion criterias were applied. They are summarized in Table 1.

Study	Type	Result
Zimmermann GS et al, 2013 [17]	Cross-sectional	Periodontitis increases serum resistin levels in both the groups, suggesting that periodontal inflammation might have an effect on systemic levels of this pro-inflammatory marker irrespective of obesity.
Patel SP et al, 2014 [18]	Case- Control	Resistin levels were found in all of the samples in each group. Group 3 had the greatest mean resistin concentrations in GCF and serum, while Group 1 had the lowest mean resistin

		concentrations
Goncalves TE et al, 2015 [19]	Case- Control	Obese patients had elevated adipokine, resistin and TNF-α levels periodontally than non-obese patients.
Varghese T et al, 2016 [20]	Case- Control	Significant reduction in plasma oxygen reactive metabolite and GCF resistin levels were seen in obese subjects following non-surgical periodontal therapy (NSPT).
Suresh S et al, 2016 [21]	Case- Control	When compared to non-obese participants with healthy periodontium, obese subjects with periodontitis have higher GCF resistin levels.
Al-Hamoudi N et al, 2018 [22]	Prospective clinical trial	Patients with chronic periodontitis and who were obese showed significantly greater periodontal inflammatory markers, salivary IL-6 and resistin levels than those who were non-obese.
Suresh S et al, 2018 [8]	Case- Control	Obese patients with chronic periodontitis had higher levels of plasma ROM, serum and GCF resistin than non-obese patients with chronic periodontitis.
Li Z et al, 2018 [23]	Cross-sectional	Both the test groups showed considerably greater serum levels of visfatin, leptin and resistin than the control group and significantly lower serum levels of APN than the control group.
Mahmood TJ et al, 2020 [24]	Case- Control	Significant correlations were not found among the clinical periodontal parameters, BMI and the resistin levels in the four groups studied.
Tahir KM et al, 2020 [25]	Prospective study	No significant difference in serum resistin level and mean counts of *P. gingivalis, P.*

		intermedia and *T. forsythia* were noted between obese and non-obese groups following NSPT.

Table 1- Studies shortlisted after applying the inclusion and exclusion criterias.

Discussion

One of the global epidemic problems in the present scenario, which is growing at a very rapid rate, is obesity. Obesity as defined by the World Health Organization as a disease in which fat accumulates in the body to such an extent that it has a negative impact on health. Periodontal disease, on the other hand, is one of the most frequent chronic disorders initiated by periodontal bacteria colonization and an excessive inflammatory response, which results in loss of tooth-supporting tissues. The onset and progression of periodontal disease has shown to be affected by obesity. Adipose tissue in obesity is capable of secreting a variety of bioactive chemicals, including resistin, visfatin, leptin and adiponectin. Resistin enhances the synthesis of adhesion molecules and other pro-inflammatory biomarkers in peripheral blood mononuclear cells and macrophages and it also inhibits adiponectin's anti-inflammatory actions on endothelial cells. Thus a relationship could exist in between the trio- obesity, resistin and periodontal disease.

A positive correlation among various hormones, growth factors and bioactive compounds, such as adipokines and energy homeostasis, with the pathophysiology of obesity, has been reported in the past literature [26]. Obesity is an abnormal accumulation of body fat and is associated with increased risk of illness, disability and death and is considered a risk for cardiovascular diseases, some cancers and type 2 diabetes [27, 28]. Obesity creates an increased oxidative stress status and sub-clinical low-grade systemic inflammation associated with harmful effects such as atherogenesis and endothelial dysfunction [29]. Recent studies confirmed the pro-inflammatory and hyperoxidative state during obesity, by measuring several cytokines and oxidative stress markers in GCF [7, 30] and serum [31]. At baseline, the plasma reactive oxygen metabolites (ROM) level in both the groups were high as the individuals were in the state of oxidative stress. ROM level at baseline was found to be higher in obese or overweight individuals with chronic periodontitis compared to normal weight individuals with chronic periodontitis. Obesity-associated TNF-α is primarily secreted from macrophages accumulated in abdominal (as opposed to peripheral) adipose tissue. It provides an evident link between obesity and inflammation [32] and seems to play an important role in the progression of periodontitis [33]. Chronic periodontitis is a low grade infection which is characterized by infiltration of the inflammatory cells within the periodontal tissues that will act as a source of production for resistin [34, 35]. Lipopolysaccharides (LPSs) produced by periodontal pathogens are shown to induce the resistin gene in macrophages by a cascade involving the production of pro-inflammatory mediators thus causing the destruction of periodontal tissues [34]. Resistin acts as a pro-inflammatory molecule and stimulates the synthesis and secretion of pro-inflammatory cytokines: TNF-α, IL-6, IL-12 and monocyte chemoattractant protein (MCP)-1. In addition, several single-nucleotide polymorphisms (SNPs) have been identified in the human resistin gene (RETN), one of these (a C to G substitution at position −420 in the 5' flanking region of the gene) alters the transcriptional activity and is associated with increased resistin messenger ribonucleic acid levels in abdominal fat [35] and elevated serum resistin levels [36, 37]. Recently, resistin which is also produced by inflammatory immune cells (in high levels) and was originally identified in adipose tissue (in low levels) is also related to the activation of inflammatory cells to secrete TNF-α and IL-6 [38] and impairs the anti-inflammatory effects of adiponectin [39]. Increased levels of serum resistin have also been implicated in periodontitis [40].

Conclusion : Obesity and periodontal inflammation were associated with high resistin levels. Resistin can be considered as an inflammatory mediator, since it has been associated with obesity and periodontal disease. In summary, periodontal inflammation was associated with high resistin levels and GG genotype of resistin SNP at −420. This highlights the inflammatory role of resistin in periodontal disease. However it is not clear which other factors other than obesity parameters affect the levels of resistin in

chronic periodontitis subjects. The inflammatory role of resistin and its association with other adipocytokines in chronic and aggressive periodontitis also needs further probing.

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