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Association of insulin resistance with periodontal disease – Cause or effect

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Abstract

Insulin resistance is a complex condition involving many etiological pathways which is a key component in the pathogenesis of multiple disorders. It acts as a common denominator in the interrelation between periodontal disease, diabetes, obesity and other metabolic disorders. There are plausible mechanisms showing the effects of these pathologies on one another, the common thread being inflammation. There is limited literature pertaining to the role of insulin resistance perse in periodontal disease. The present review focuses on the relation between insulin resistance and periodontal disease, addresses the possible mechanisms linking both the conditions and provides an overview of the existing literature exploring this connection. The essence of existing evidence is a prelude to the critical association between periodontitis and insulin resistance. This warrants further long term and multicentric trials to elucidate the true nexus of pathophysiology of this bidirectional relationship. Clearly much progress has to be made in terms of aligning the contributions of medical and dental professionals in controlling the pernicious effects of both these pathologic conditions

Keywords: Insulin resistance, Periodontal disease, Periodontitis, Diabetes Mellitus.

Introduction

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids and proteins, in which hyperglycemia is a main feature.[1] Periodontitis is a

chronic polymicrobial multifactorial disease, triggered by the microbes in dental plaque biofilm and perpetuated by the exuberant host immuno-inflammatory response to these microbes which is further influenced by various local, systemic and genetic factors. Periodontitis and diabetes mellitus are chronic diseases which have major impact on the health and wellbeing of millions of individuals world-wide. Both the diseases can be considered as silent pandemics owing to their insidious and ubiquitous nature.[2]

Type 2 diabetes mellitus is a non-auto immune condition influenced by multiple factors, mainly mediated by insulin resistance. Insulin resistance is a complex condition involving many etiological pathways. Although the exact mechanisms are not completely cognizant, IR plays a part in the pathogenesis of numerous systemic diseases. The association between diabetes mellitus and periodontal disease is well established and rightly explained as a two-way street because of the bidirectional relationship.[3] However, there is limited literature pertaining to the role of insulin resistance perse in periodontal disease. The aim of the present review is to focus on the relation between insulin resistance and periodontal disease and to address the possible mechanisms linking both the conditions.

Periodontitis and systemic link

The hallmark of periodontitis is a progressive and irreversible tissue destruction mediated by immune responses mounted against dysbiotic periodontal microbiome. The periodontium is an integral part of the body's systemic ecosystem. Therefore, it is obvious that the local effects will influence and also be influenced by the entire ecosystem.[4] The notion that a relationship exists between oral and systemic diseases dates back to a century when William Hunter proposed the focal infection theory.[5] Since then, a wealth of evidence established the fact that periodontal inflammation can impact an array of systemic diseases through distinct pathways.

The direct pathway explains the effect of noxious products produced by the pathogens instrumental in causing periodontal tissue destruction. The periodontopathic bacteria are essentially gram-negative bacteria, present in deep pockets, thriving under anerobic conditions. As the periodontal disease progresses, pocket epithelium becomes ulcerated providing a direct entry point. These circulating pathogens and their toxins could have direct systemic effects.[6]

Alternatively, the inflammatory response to the microbes and their by-products may have indirect systemic effects. There is a systemic dissemination of inflammatory mediators that begin to act on other organ systems. Acute phase proteins produced in response to these mediators also have detrimental effects on other organs.[6] Therefore, it can be enunciated that this huge collection of the host factors, along with amplifying the periodontal tissue destruction, also act as a source of low-grade inflammation which has the potential to alter the systemic health.

Similarly, systemic diseases can also modify local inflammatory responses in periodontal diseases. The perception of periodontal disease pathogenesis underwent a tremendous shift in recent times. According to the current concept, periodontitis is not just a consequence of microbial disparity, but an interplay of numerous other systemic, environmental and genetic factors. These factors, especially the systemic factors act by modifying the host responses.[7]

Therefore, the interactions between periodontitis and systemic factors are two sided. Understanding this bidirectional relationship is crucial in devising treatment strategies to optimize oral and overall health of the

patients. This knowledge arms us with tools for opportune diagnosis and appropriate treatment of the diseases.[4]

Etiopathogenesis of Insulin resistance

Insulin is a pleiotropic hormone which has diverse functions including stimulation of nutrient transport into cells, regulation of gene expression, modification of enzymatic activity, and regulation of energy homeostasis via actions in the arcuate nucleus. Insulin promotes glucose uptake by translocation of GLUT-4 glucose transporter to the plasma membrane. In the liver, insulin inhibits expression of gluconeogenic enzymes. Adipose tissue insulin activity results in decreased hormone sensitive lipase activity and the anti-lipolytic effect inhibits free fatty acid efflux out of adipocytes.[8]

Insulin exerts its functions in all cells by binding to specific receptor and thereby activating a cascade of intra-cellular signaling events. This signaling cascade branches into two main pathways. The first is the phosphatidylinositol 3 kinase (PI3K-AKT) pathway, which is largely responsible for insulin action. The second is Ras mitogen activated protein kinase pathway (MAPK), which also interacts with PI3K-AKT pathway. The common mediator to these pathways is insulin receptor substrate (IRS). Activation of the insulin receptor leads to tyrosine phosphorylation of IRS1, thereby initiating signal transduction. Alternative phosphorylation of serine by NFκβ and JNK/AP-1 pathways diminish downstream signaling ability.[8]

Insulin resistance is a complicated condition in which there is lack of bodily response to insulin despite its adequate secretion. It encompasses a wide spectrum of disorders such as defective insulin receptor signal transduction and mitochondrial function, microvascular dysfunction and inflammation.[9] Insulin resistance is the key primary defect underlying the development of Type 2 diabetes mellitus and is a central component defining the metabolic syndrome, a constellation of abnormalities including obesity, hypertension, glucose intolerance and dyslipidemia.[10]

Mechanisms interlinking insulin resistance and periodontal disease

Apart from the fact that insulin resistance is characterized by complex interactions between genetic determinants, nutritional factors, and lifestyle, it is increasingly recognized that mediators synthesized from the cells of immune system are critically involved in the regulation of insulin action. Serine phosphorylation of insulin receptor substrate by various inflammatory signals seems to be one of the key aspects that disrupt insulin receptor signaling.[10]

Owing to fact that inflammation is one of the key contributors to insulin resistance, it is prudent to affiliate insulin resistance to the inflammatory processes associated with periodontal disease. Pro-inflammatory cytokines expressed as a part of periodontal disease, aid in creating a low grade systemic inflammatory condition leading to aggravation of insulin resistance. This is predominantly mediated by Tumor necrosis factor α (TNF-α), a principal mediator of periodontal inflammation.[11] It induces serine phosphorylation of insulin receptor and IRS-1, resulting in inactivation of P13 kinase. This inhibition of messenger signaling results in insulin resistance.[12] It impedes insulin signaling in the liver, by activation of serine kinases such as JNK.[13] TNF-α also decreases the m-RNA stability of IRS -1, thus priming impaired insulin signaling, consequently leading to insulin resistance.[14] Moreover, TNF-α induces intracellular generation of H_2O_2 which further inhibits tyrosine phosphorylation of IRS-1 contributing to insulin resistance.[15] Therefore TNF-α is certainly “the” mediator between inflammation and insulin resistance. Other pro-inflammatory cytokines like IL-1β, MCP-1 and IL-6 may also contribute to insulin resistance

by reducing the expression of glucose transporter – 4 (GLUT-4) and IR-1.[10]

The role of obesity in insulin resistance is another facet that is pivotal in explaining the inter-relation between insulin resistance and periodontal disease. Obesity is a well-known contributing factor in both Type 2 diabetes mellitus and periodontal disease.[16] Metabolites of free fatty acids i.e. acyl CoAs, ceramides, and diacylglycerol inhibit insulin signaling by stimulating protein kinases.[17] Adipocyte released adipokines like leptin, adiponectin, visfatin, and resistin regulate the inflammation. Adiponectin plays a crucial role as a mediator of insulin sensitivity.[18] Moreover, TNF-α, which is the key inducer of insulin resistance also acts by reducing the adiponectin secretion by adipocytes.[19] Furthermore, the increase in reactive oxygen species, C reactive protein, and mitochondrial dysfunction instigated by the inflammatory mediators, results in β cell dysfunction and insulin resistance.[16]

Meanwhile periodontitis provokes hyperlipidemia, abnormal fat metabolism, and subsequent inflammatory changes in adipose tissue, which can increase cytokine and adipokine mediated insulin resistance and further worsening of periodontal inflammation. Therefore, it would be judicious to consider insulin resistance as a moderating factor between obesity, diabetes mellitus and periodontal disease.[16]

The other side of the coin is the effect of insulin resistance in modifying periodontal disease progression. This side of the coin is rather much explored. As insulin resistance contributes to the core metabolic abnormalities in diabetes, and diabetes increases the risk of periodontal disease, it can be deciphered that the impact of diabetes on periodontal disease is mediated by insulin resistance. The biologic plausibility of this association is explained through the effects of advanced glycation end products (AGEs) that bind to specific receptors (RAGE) on various cells. These interactions produce hyperinflammatory responses, vascular modifications, altered healing and increased predisposition to infections.[20]

Taken together, these findings suggest that there is a bidirectional relationship between insulin resistance and periodontal disease. The basic premise underlying this belief is that there are plausible mechanisms showing the effects of these pathologies on one another, the common thread being inflammation. These facts ultimately point to the importance of control of diabetes and/or periodontal disease, which has the potential to improve significantly the quality of life in diabetic subjects.[19]

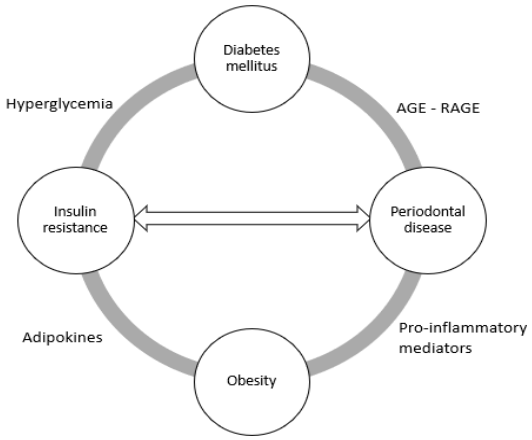

Fig 1: Multifaceted association of insulin resistance and Periodontitis

Methods to assess insulin resistance

It is of great importance to know about the tools for quantifying insulin sensitivity/resistance in humans that may be used to appropriately investigate the epidemiology, pathophysiological mechanisms, outcomes of therapeutic interventions, and clinical course of patients with insulin resistance. A variety of methods are currently available for estimating insulin sensitivity/resistance. These range from complex, time consuming, labor-intensive, invasive procedures to simple tests involving a single fasting blood sample. It is important to understand

Table 1: Methods to detect insulin resistance

Methods	Examples	
1. Direct methods	Hyper insulinemic euglycemic clamp method	
	Insulin suppression test	
2. Indirect methods	Minimal model analysis of frequency sampled intravenous glucose tolerance test (FSIVGTT)	
3. Surrogate indices	Derived from fasting steady state condition	Derived from dynamic tests
	Homeostasis model assessment-insulin resistance (HOMA-IR)	Mastuda index
	Quantitative insulin sensitivity check index (QUICKI)	Gutt index
		Avignon index
		Stumvoll index
4. Others	Metabolomics	

A myriad of techniques is now available to assess insulin resistance and Hyper insulinemic euglycemic clamp method is considered as the gold standard. However, HOMA-IR is commonly used in most epidemiological studies which can be explained due to its simplicity

1. Periodontitis and insulin resistance – Evidence – What we know

Although many studies evaluated relation between metabolic disorders and periodontal disease, in various populations across the world, there is still a sizeable vacuum in the evidence-based literature regarding insulin resistance and periodontal disease. Table 2 & 3 outlines the animal and human studies relating insulin resistance and periodontal disease.

Table 2: Animal studies on insulin resistance and periodontal disease

Author	Aim	Conclusion
Pontes Anderson et al (2007)[22]	To investigate whether periodontitis affects the prediabetic state of ZFRs.	Periodontitis is associated with higher IR and deterioration of glucose metabolism in ZDFRs,
Watanabe et al (2008)[23]	To determine the causal effect of periodontal disease and impact of diet on IR & DM using rat model	Periodontal disease accelerated the onset of severe IR and impaired glucose homeostasis in ZDFRs
Ekuni et al (2010)[24]	To investigate the effects of ligature-induced periodontitis in ZDFRs on initiation of atherosclerosis by evaluating aortic IR	Periodontitis in obesity, induced the initial stage of atherosclerosis and disturbed aortic insulin signaling.
Columbo NH et al (2012)[25]	To investigate whether periodontal disease, is able to increase TNF-α, and decrease insulin sensitivity and insulin signaling in non-diabetic rats.	Periodontitis is able to cause alterations to both insulin signaling and insulin sensitivity, probably because of the elevation of TNF-α

Blasco-Baque V et al (2015)[26]	To identify the causal mechanisms responsible for the increase of IR and hyperglycemia following periodontitis in mice fed a fat enriched diet	P gingivalis induced modulation of adaptive immune responses are causally responsible for periodontitis induced IR.
Huang Y et al (2016)[27]	To investigate the mechanism by which periodontitis affects the inflammatory response and systemic IR in an obese rat model	Periodontitis plays an important role in aggravating the development of adipose inflammation and systemic IR

IR- Insulin resistance; ZDFRs- Zucker diabetic fatty rats.

Table 3: Human studies on insulin resistance and periodontal disease

Author	Study design	Aim	Parameters	Conclusion
Genco et al (2005)[28]	Cross sectional study	To evaluate the relationship between obesity, periodontal disease, and IR, as well as the plasma levels of tumor necrosis factor alpha (TNF-α) in NHANES population.	PPD, CAL, BOP, CRP, lipid profile, BMI, insulin, TNF-α	Obesity is a significant predictor of periodontal disease and insulin resistance appears to mediate this relationship.
Benguigui C et al (2010)[29]	Cross sectional study	To examine the relationships between metabolic syndrome, its various components, IR, and periodontitis.	PPD, CAL, HOMA-IR	Data supported the relationships between metabolic disturbances and periodontitis, with a central role of insulin resistance. (OR=3-97)
Timomen P et al (2011)[30]	Cross sectional study	To examine whether there is an association of insulin sensitivity with periodontal infection in a non-diabetic, non-smoking adult population.	PPD, HOMA-IR, BMI	Insulin sensitivity was associated with periodontal infection Controlling for body weight made the association between insulin sensitivity and periodontal infection disappear.
Sun WL et al (2011)[31]	Longitudinal study	To evaluate the effects of periodontal intervention on inflammatory cytokines, adiponectin, insulin resistance (IR), and metabolic control	PPD, CAL, BOP, adiponectin, CRP, TNF-α, IL-6, lipid profile, glucose, HOMA-IR, HOMA-β	Periodontal intervention can improve glycemic control, lipid profile and IR, reduce serum inflammatory cytokine levels and increase serum adiponectin levels.
Demmer et	Cross	To evaluate whether	PPD, Glucose	The data supported the role of

al (2012)[32]	sectional study	periodontal infection is associated with IR in NHANES sample of diabetes free adults	levels, WBC count, CRP, HOMA-IR	inflammation as both mediator and effect modifier of the association between IR and periodontal disease.
Timonen P et al (2013)[33]	Longitudinal study	To explore whether IR is related to periodontal pocket formation, in non-smoking adults without manifest diabetes.	PPD, HOMA-IR, HOMA-B	Both HOMA-IR and HOMA-B indices were associated with periodontal pocket formation during the 4-year follow-up.
Lim SG et al (2014)[34]	Cross sectional study	To investigate the association between insulin resistance and periodontitis among Korean adults.	CPI, lipid profile, BMI, HOMA-IR, HOMA-B	IR may be associated with periodontitis, especially when combined with obesity, among post-menopausal women
Islam SK et al (2015)[35]	Cross sectional study	To understand whether periodontitis is associated with IR in general Korean population	CPI, FG, BMI, WC, lipid profile, HOMA-IR	Demonstrated independent association between periodontitis and fasting glucose levels, but did not show such significant association with HOMA-IR
Song I et al (2016)[16]	Cross sectional study	Hypothesized that IR could aggravate periodontitis even with normal body weight	CPI, BMI, FG, CRP, lipid profile, HOMA-IR	IR can be considered as an independent risk factor of periodontitis in normal weight metabolically obese individuals
Seraphim AP et al (2016)[36]	Cross sectional study	To assess the association among periodontal disease, IR, perceived stress and cortisol levels in pregnant women.	CPI, BP, salivary cortisol, glucose, HOMA-IR., PSS.	There is a relation between higher levels of perceived stress, IR and occurrence of periodontal disease during pregnancy.
Pulido Moran et al (2017)[37]	Cross sectional study	To examine IR measured by surrogate indices in subjects with and without periodontitis and to find out any correlation between dietary intake with IR	PPD, CAL, BOP, recession, HOMA-IR, uric acid, lipid profile, FG, creatinine	A putative systemic relation exists between IR and periodontal disease without any effect of diet.
Oyarzo N et al (2018)[38]	Cross sectional	To quantify the clinical parameters of periodontal tissue	BW, WC, BMI, FG, CRP, TG,	In patients with recent diagnosis of type 2 diabetes,

	study	destruction in association with IR	LDL, HDL, insulin, HOMA-IR	BOP is associated with HOMA-IR & CRP suggesting that periodontal inflammation promotes IR possibly by increasing systemic inflammation.
Ashok vardhan et al (2018)[39]	Cross sectional study	To evaluate the relation between periodontitis and IR	FBS, insulin, HOMA-IR	Impaired glucose levels and IR is associated with periodontal disease.
Adriankaja OM et al (2018)[40]	Longitudinal study	Evaluated whether IR predicts risk of oral inflammation assessed as number of sites with BOP and PPD>4mm	PPD. BOP, HOMA-IR, TNF-α, adiponectin.	Participants with higher HOMA-IR at baseline had significantly higher number of sites with BOP (RR=1.19) & PPD>4mm (RR=1.39)

BOP- Bleeding on probing; FG- Fasting glucose; HOMA-IR- Homeostatic model assessment of insulin resistance; HOMA-B - Homeostatic model assessment of β cell function; BMI- Body mass index; WC- Waist circumference; WBC- White blood cells; PSS – Perceived stress scale.

Clinical implications and future directions

The essence of existing evidence is a prelude to the critical association between periodontitis and insulin resistance. This warrants further long term and multicentric trials to elucidate the true nexus of pathophysiology of this bidirectional relationship. Animal studies help to an extent in understanding the cellular mechanisms in the pathogenesis but these findings cannot be extrapolated to humans with certainty.[7]

Parameters defining periodontal disease burden, need to be more explicit in the experimental studies. Clinical parameters can be supplemented with radiographic assessment as well as other biologic phenotypes determining the periodontal pathogenesis.[39] One such adjunctive and simple tool to quantify the amount of inflammatory burden is Periodontal inflamed surface area (PISA).[41] This gives the cumulative surface area of all periodontal lesions in a patient. Studies should be conducted quantifying PISA and insulin resistance to substantiate the association.

Conclusion

Insulin resistance may be a key component in the pathogenesis of multiple disorders. It acts as a common denominator in the interrelation between periodontal disease, diabetes and obesity. Therefore, it calls for further investigation and extensive research to analyze the reciprocal link between periodontal disease and insulin resistance. Clearly much progress has to be made in terms of aligning the contributions of medical and dental professionals in controlling the pernicious effects of both these pathologic conditions.[40]

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