

Is Resistin A Biomarker for Periodontitis - An Insight

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ABSTRACT

Resistin is a recently discovered adipocytokine, having a potent biomarker quality. Initially resistin was thought to be produced by adipocytes alone; however, emerging evidence suggests that it is also produced in abundance by various cells of the immunoinflammatory system, indicating its role in various chronic inflammatory diseases. Data suggests that resistin plays a role in obesity, insulin resistance, cardiovascular diseases, and periodontitis. Resistin derived its name from the original observation that it induced insulin resistance (*resist-in: resist insulin*) in mice and is downregulated in mature murine adipocytes cultured in the presence of insulin sensitizing drugs like thiazolidinediones. It is well recognized that obesity, is associated with insulin resistance and diabetes. Research shows incremental elevation of resistin with periodontal disease activity and a reduced level of resistin, after periodontal therapy. Thus resistin would 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.

Key words: Resistin, adipocytokine, periodontitis, obesity, biomarker.

INTRODUCTION

Periodontitis is a common oral disease of multifactorial etiology wherein microbial pathogens play an important role. Plaque bacteria and its products such as endotoxins elicit the host immunoinflammatory response. This immunoinflammatory response against the microbes, in an attempt to wall off the infection results in the local tissue destruction by producing various proinflammatory mediators such as prostaglandin E₂ (PGE₂), tumor necrosis factor (TNF) α and interleukin (IL) 1, IL 6 etc.¹ These proinflammatory mediators in addition to local tissue destruction also exert certain systemic effects.² Obesity which is another important risk factor for type 2 diabetes has also been linked to periodontitis.³ Obesity is characterized by increase in the adipose tissue which is an important source

for various proinflammatory cytokines such as TNF- α , IL, visfatin, adiponectin and resistin.⁴

Resistin is a cytokine involved in insulin resistance, inflammation, and immunity. Evidence suggests that resistin expression is elevated in diabetes and inflammatory diseases. Resistin is a recently identified adipocyte-derived hormone that has been shown to play a substantial role in the development of insulin resistance.⁵ Clinicians over the years have been working on different biological markers to establish a link between periodontal diseases and various systemic conditions and to determine which of those patients are at risk to develop the latter. Substances such as C-reactive protein (CRP), aspartate amino transferase (AST), tumor necrosis factor-alpha (TNF-5 α), and prostaglandin (PGE₂) have been extensively assayed for periodontitis leading to other

subclinical infection. This review is intended to give an insight into the biological action of resistin and its role in periodontitis influenced diabetes mellitus and diabetes induced periodontitis.

Resistin is produced by white and brown adipose tissues but has also been identified in several other tissues, including the hypothalamus, pituitary and adrenal glands, pancreas, gastrointestinal tract, myocytes, spleen, white blood cells, and plasma. It antagonizes insulin action, and it is downregulated by rosiglitazone and peroxisome proliferator-activated receptor agonists.^{6,7}

Initially it was thought that resistin is mainly produced by adipocytes. However, recent studies have shown that very little resistin is produced by adipocytes, whereas large amount of resistin is produced from cells of the immunoinflammatory system like PMNs, monocytes, and macrophages.⁸ Resistin is a member of a family of tissue-specific signaling molecules called as resistin-like molecules.

Action of Resistin

Immune system effects

Proinflammatory(- Activates NF- κ B dependent cytokine release and adhesion molecule expression (including TNF- α /IL-6)

Vascular Effects

Pathogenic - (Impairs bradykinin dependent vasorelaxations (NO and EDHF) No effect on acetylcholine dependent vasorelaxations (NO) VEGF and MMP up regulation.

Resistin and Inflammatory Diseases. Although resistin was firstly postulated to contribute to insulin resistance, more and more evidence indicated that it may also be involved in inflammatory process. Some proinflammatory agents, such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and lipopolysaccharide (LPS), can regulate resistin gene expression. Resistin mRNA was strongly increased by TNF- α in human peripheral blood mononuclear cells (PBMC).⁹

Recent studies have shown the regulation

of proinflammatory cytokine expression by resistin. Resistin strongly up-regulated IL-6 and TNF- α in human PBMC via NF- κ B pathway.¹⁰

Addition of recombinant human resistin protein to macrophages from both mice and humans resulted in enhanced secretion of proinflammatory cytokines, TNF- α , and IL-12.¹⁰ LPS was reported to induce resistin gene expression in primary human macrophages via cascade involving the secretion of inflammatory cytokines.¹¹

Another evidence linking resistin to inflammation is that plasma resistin levels were found associated with many inflammatory markers in some pathophysiological conditions. Resistin level was also positively associated with levels of inflammatory markers, including soluble TNF- α receptor- 2, IL-6, and lipoprotein-associated phospholipase A2 in atherosclerosis patients.¹²

Resistin and Chronic Periodontitis. Chronic periodontitis being a disease of multifactorial etiology is characterized by stimulation of host immune-inflammatory system in response to microbial deposits and their endotoxins produced. This results in a chronic low-grade subclinical inflammation. Host immune-inflammatory system, in an attempt to ward off the infections, causes the infiltration of periodontal tissues by various immune-inflammatory cells such as PMNs and monocytes, macrophages.^{12,13} These cells and the cytokines produced such as TNF- α , CRP, interleukins, prostaglandins, and resistin not only result in the local tissue destruction characterized by periodontal attachment loss and alveolar bone loss but also exert certain distant systemic effects such as increased risk for atherosclerosis, PTLBW, and increased insulin resistance.¹⁴

CONCLUSION

At present there are several biomarkers, studied in relation to periodontitis and diabetes. However, there are very few studies in the field of periodontics addressing the relation between chronic periodontitis and resistin, which acts as a biomarker "the connecting link between periodontitis, obesity, and diabetes." The currently

available literature suggests that the levels of resistin are increased in the patients with chronic periodontitis compared to the clinically healthy controls. Resistin induces insulin resistance, and large amount of resistin is secreted by adipocytes. Increased resistin levels in periodontitis may thus be considered to pose a risk for diabetes by decreasing the insulin sensitivity.

Thus, it can be observed that resistin can serve as one of the potential biomarkers for periodontitis with other systemic diseases such as diabetes and cardiovascular diseases. However, further long-term and interventional studies with larger sample sizes are warranted, to give a direct cause-effect relationship between resistin and chronic periodontitis and to determine the exact molecular mechanism involved in increased insulin resistance.

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