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Resistin: A New Link in the Old Tale

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Abstract: ***Adipocytokines are cytokines secreted mainly by adipose tissue that play an important role in various metabolic functions such as short and long term energy homeostasis. Resistin is one of the most important adipocytokines implicated in insulin resistance. Chronic inflammation mediated by resistin can lead to some metabolic disease such as obesity, atherosclerosis, and cardiovascular diseases. Recent studies have shed light on the correlation between obesity and periodontitis and resistin has been suggested on the molecular link connecting periodontitis, obesity and diabetes mellitus. An online search was conducted for relevant literature published in English between 2000 and 2018 using MEDLINE/Pubmed database. Resistin, obesity, insulin resistance, periodontal disease and periodontitis were the search terms used. The relevant articles were chosen and compiled. This literature review provides an insight into the possible role played by resistin in linking periodontitis and various systemic diseases/conditions.***

Keywords: Resistin, Insulin Resistance, Diabetes Mellitus, Periodontitis

1. Introduction

Resistin is recently discovered adipocytes –secreted polypeptide that has been implicated as a potential link between obesity and insulin resistance (IR). [1, 2] Steppan et al for the first time described unique signaling molecule secreted by adipocytes which induce insulin resistance in mice and named it 'resistin' (for resistance to insulin).[1] It is a cysteine-rich protein found in inflammatory zone[3]. Resistin is a member of family of tissue–specific signaling molecules called resistin –like molecules. There are four members in the mouse RELMS family; resistin, RELMα, RELMβ, RELMγ. Only two counterparts are found in humans; resistin and RELMβ[4].

Data suggests that resistin has a role in association between obesity, insulin resistance and Type 2 diabetes mellitus.[5] Resistin can also be a part of disturbances beyond dysglycemia like atherosclerosis ,cardiovascular disease, non-alcoholic steatohepatosis and some autoimmune disorders[5].The association of resistin and periodontitis has been recently investigated and a positive correlation with clinical signs of periodontitis was observed;[6, 7, 8] this could provide a biological link between periodontitis and obesity-related systemic diseases and conditions.

2. Materials and Methods

An online search was conducted for relevant literature published in English between 2000 and 2018 using MEDLINE/Pubmed database. Resistin, obesity, insulin resistance, periodontal disease and periodontitis were the search terms used. The relevant articles were chosen and compiled.

Resistin in obesity

Obesity is defined as a Body Mass Index≥30.0kg/m2.[9] Obesity is characterized by increased adipose tissue which is an important source for various pro-inflammatory cytokines such as resistin, tumour necrosis factor-α (TNF- α), visfatin and adiponectin[10]. In humans, plasma levels of resistin, TNF-α, visfatin, adiponectin, C-reactive protein are closely related to obesity.[11] Obesity is characterized by presence of chronic subclinical inflammation with increased concentration of above mentioned pro inflammatory cytokines. In obese animals, resistin expression was increased in adipose tissue and resistin levels in plasma was also elevated.[1] A correlation between obesity and the level of resistin has been reported in humans.[12, 13] They noted that more severe the obesity, the higher the level of resistin in humans.[14]

Resistin in diabetes mellitus

Skeletal muscle is the major site of glucose uptake induced by insulin.[15] One of the key processes in the adjustment of the plasma glucose level is the regulation of hepatogluconeogenesis and disturbed glucose production in the liver is the central characteristic in type 2 diabetes mellitus.[16]Under normal conditions, hepatic glucose production was inhibited by insulin action and resistin has been shown to decrease the insulin effects by promoting increased plasma glucose levels. It seems that increase in rate of gluconeogenesis in liver is crucial step of resistin action in patients with type 2 diabetes mellitus.[17]

Serum and polymorphism assessments confirm that resistin could have critical role in type 2 diabetes mellitus and could be known as important risk factor for the disease.[18,19] One of the proposed factors that affect the levels of adipocytokine in biological fluids is the presence of functional polymorphism in the promoter and intron regions of their corresponding genes.[20,21] Recently the effects of resistin gene (RETN) polymorphisms on type2 diabetes mellitus have become focus of interest to researches.[22]

Study done by Cho et al demonstrated that the SNP-420 C/G in the promoter region of RETN plays a critical role in resistin gene expression and determination of plasma resistin concentration in humans.[23]

Fawzy et al suggested that SNPS of RETN and increased resistin levels may be associated with increased IR and consequent susceptibility to type2 diabetes mellitus in offsprings of diabetic mellitus patients.[24]

Fontana et al reported that levels of serum resistin could be related with mortality risk in patients with type 2 diabetes mellitus. Increased levels of resistin could be associated with progression of type 2 diabetes mellitus.[18]

Resistin in atherosclerosis

Resistin may promote the initiation or perpetuation of atherosclerotic state by activating vascular endothelial cells. Verma et al found that resistin promoted endothelial cell

activation by promoting endothelin-1 release, partly by inducing endothelin-1 promoter activity. Furthermore, resistin up regulated vascular cell adhesion molecule-1(VCAM-1) and monocyte chemotactic protein (MCP-1) and down regulated TNF-receptor associated factor -3.[25.]

Resistin in rheumatoid arthritis

A study conducted by Healthy Naval Medical Research Institute (NMRI) mice intra –articularly injected with recombinant mouse resistin in the knee joints showed arthritis compared with mice injected with albumin. These mice showed infiltration of synovial tissue with leucocytes in several cases associated with hypertrophy of synovial lining layer and pannus formation. In human study, synovial fluid from patients with rheumatoid arthritis (RA) showed significantly higher level of resistin compared with control samples. Moreover, resistin level in RA synovial fluid positively correlated with synovial leukocyte count and Interleukin (IL)-6 levels.[26]

Resistin in chronic kidney disease (ckd)

Few studies in the literature address the role of adipocytes hormones in CKD. Yaturu et al conducted a study to compare the levels of resistin, adiponectin and other inflammatory markers in subjects with CKD with those of the control subjects. The results of the study demonstrated the relationship between resistin and TNF-α in subjects with CKD and suggests that resistin may play a role in the sub-clinical inflammation associated with CKD.[27]

Resistin as a Link Between Periodontal Diseases and Systemic Diseases /Conditions

Recently role of adipokines have been identified in inflammation related diseases. 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. Host immune-inflammatory system ward off infections causing the infiltration of periodontal tissues by various immune-inflammatory cells such as PMNs, monocytes and macrophages.[28,29]Lipopolysaccharides produced by periodontal pathogens are shown to induce resistin gene in macrophages via cascade involving the production of pro–inflammatory mediators.[30] Currently available literature suggests that levels of resistin are increased in patients with chronic periodontitis.[31]

Saito T et al conducted a study to assess the circulating serum adipokine levels in women with periodontitis. They have concluded that an increased serum resistin level in middle-aged Japanese women with periodontitis may affect systemic health.[6]

Furugen R conducted a study to clarify the relationship between serum levels of adipokines and periodontal conditions in elderly Japanese people with and without periodontitis. They have concluded that serum resistin levels and total leukocyte counts in subjects with periodontitis were higher than in control subjects.[7]

Zimmermann et al conducted a study to evaluate the local and circulating levels of adipocytokine (resistin, adiponectin, leptin, TNF-α, and IL-6 in individuals who are obese and individuals who are normal weight (NW) with chronic periodontitis. They have concluded that periodontitis mainly influenced the circulating levels of resistin and adiponectin, whereas both obesity and periodontitis affected the circulating levels of leptin in favor of pro-inflammation. In addition, obesity up regulated the local levels of TNF-α.[8]

Resistin also exert certain distant systemic effects such as increased risk for atherosclerosis, increased IR which may explain the link between periodontal diseases and various systemic diseases /conditions.

Rao R M et al conducted a study to correlate the serum and saliva resistin levels and its association in obese individuals with chronic periodontitis. They suggested that resistin probably may bear similar features of a proinflammatory cytokine and could play a role in inflammatory diseases like periodontitis. They also concluded that resistin can be considered as a potential mediator linking obesity and periodontal disease.[32]

Suresh S et al conducted a study to assess and compare the GCF resistin levels in obese subjects with periodontal health and disease and to correlate the disease severity with GCF resistin levels. They reported that obese subjects with periodontitis have more GCF resistin levels compared to non-obese subjects with healthy periodontium[33].

Patel et al. conducted a study to assess the concentration of resistin in serum and gingival crevicular fluid(GCF) and to compare the levels between subjects with and without periodontitis and type 2 diabetes mellitus and to further correlate the resistin levels with the single-nucleotide polymorphism (SNP) at −420.They have concluded that the resistin levels in GCF and serum from patients with periodontitis or diabetes mellitus related periodontitis (controlled or uncontrolled) were higher than that of healthy subjects.[34]

Ingles et al. conducted a clinico-biochemical study to estimate and compare the levels of resistin in the gingival crevicular fluid (GCF) in health, chronic periodontitis, and Type 2 diabetes mellitus. They have concluded that resistin levels are increased in chronic periodontitis and Type 2 diabetes mellitus. Hence, GCF resistin levels may be considered as a potential inflammatory marker for periodontitis with Type 2 diabetes mellitus.[35]

Lahariya et al. conducted a study to determine the role of adipokines in periodontal disease with diabetes mellitus and without diabetes mellitus. They have concluded that periodontal disease and diabetes mellitus are closely associated and are highly prevalent chronic diseases with many similarities in pathobiology. Diabetes can lead to several health complications, including periodontal disease.[36]

Resistin levels were shown to correlate with periodontal disease activity and severity as well as the hyperglycemic state of patient recruited. This highlights the role that resistin could potentially play in the etiopathogenesis of both local and systemic inflammatory conditions as evidence in chronic periodontitis and diabetes mellitus there by

translating into its utility as a potential marker of inflammation in periodontal disease and Type 2 diabetes mellitus.

3. Conclusion

The role of resistin in obesity and other inflammatory diseases is going through extensive research. Resistin modulate inflammation in chronic periodontal disease and may be used as surrogate measure to identify subjects at risk for periodontitis. Resistin may serve as a possible mediator linking periodontal disease with other systemic inflammatory conditions like obesity, diabetes mellitus, and rheumatoid arthritis. Future studies will be needed to determine the cause effect relationship between resistin and chronic periodontitis and to understand the exact molecular mechanism underlying the pathogenesis.

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