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RESEARCH ARTICLE

Interleukin (IL) 18 and Its Relation with Diabetes Mellitus and Chronic Periodontitis

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Abstract

IL-18 is a member of the IL-1 family of cytokines. IL-18 demonstrates a unique function by binding to a specific receptor expressed on various types of cells. Interleukin (IL)-18 was originally discovered as a factor that enhanced IFN-γ production from anti-CD3-stimulated Th1 cells, especially in the presence of IL-12. Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Chronic periodontitis, also known as adult periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tissues that support the teeth, i.e. the gingival, the periodontal ligament, cementum, and the alveolar bone. Chronic periodontitis can also play a role as a metabolic stress or for diabetes control. In this review article, we will focus on the unique features of Interleukin (IL) 18 and its relation with diabetes mellitus and chronic periodontitis.

Keywords: *Interleukin (IL) 18, Chronic periodontitis, Type 2 diabetes mellitus, Cytokines.*

Introduction

Interleukin (IL) 18 was first described as an interferon (IFN) -γ inducing factor which circulated during endotoxaemia in mice preconditioned with an infection of *Propionibacterium acnes* [1]. Because of its ability to induce IFN-γ, IL18 is by default a member of the T cell helper type I (Th1)-inducing family of cytokines(IFN-γ, IL2, IL12, IL15).

However, antibodies to IL18 also reduced the hepatotoxicity of endotoxaemia, IL18 was considered to possess other biological properties beyond that of inducing IFN-γ [2].It has become clear that IL18 is a proinflammatory cytokine and that its mechanism of action is independent of its ability to induce IFN-γ [3].

Diabetes is a widely studied condition associated with periodontal disease, and affects over 171 million people worldwide. Periodontitis is an infective condition attributable to certain pathogens, namely, Aggregatibacter actinomycetecomitans, Porphyromonas gingivalis, Bacteroides forsythus, Prevotella intermedia, Campylobacter rectus, Treponema denticola, Fusobacterium nucleatum and so on. Type 2 diabetes mellitus is a metabolic disorder characterized by insulin resistance and pancreatic ß-cell dysfunction, resulting in persistent hyperglycemia [4].

Insulin resistance occurs when cells in the body becomes less sensitive to insulin leading to elevated blood glucose levels which in turn triggers the need for more insulin secretion (hyperinsulinemia) in an attempt to transport glucose. The production of ever increasing amount of insulin eventually wears out ß cells [5].

TNF-α, sTNFR2, IL-6, CRP, IL-1, IL-18 are markers of insulin resistance [6]. Chronic, plaque-induced periodontitis is a specific inflammatory response to products of pathogenic bacteria, resulting in loss of connective tissue supporting teeth [7]. Biological factors involved in the etiopathology of periodontal disease are

present at the interface between hard tissue of tooth and soft tissue of periodontium. Bacterial biofilms are responsible for initiation of gingival inflammation and progression to periodontal tissue destruction in susceptible host.

Numerous cytokines mediate host immunoinflammatory response to overcome the microbial challenge [8]. Cytokines are involved in the initiation and effector stages of immunity and inflammation, in which they regulate the amplitude and duration of the response.

They are produced transiently, extremely potent, generally acting at picomolar concentrations and interact with specific cell surface receptors, which are usually expressed in relatively low numbers [9].IL-18 induces release of matrix metalloproteinase (MMP-9) and IL-1ß, which would have both proinflammatory and tissue degradation effects in rheumatoid arthritis [10].

Chronic periodontitis has an immunologic component, as its etiology and progression involves both cellular (Th1) and humoral (Th2) immune responses. Sites with periodontal inflammation contain plasma cells, T lymphocytes, and macrophages. T lymphocytes predominate in the stable lesion, the proportion of B cells and plasma cells are increased in the progressive lesion.

Location and Structure

IL-18 is synthesized as a precursor molecule(24 kD) without a signal peptide ,requires the IL-1ß converting enzyme (ICE, caspase-1) for cleavage into a 18-kD mature peptide [11].The Fas/Fas ligand system has been shown to be involved in the processing of IL-18 (processed in a caspase-1-independent manner) [12]. Metalloproteinase or proteinases 3 also process this cytokine. Nitric oxide (NO), which is a destructive molecule in the inflammatory reactions, directly inactivates caspase-1, thus regulating the secretion of mature IL-18 [13].

Despite its constitutive cytosolic presence in monocytes, IL-18 required lipopolysaccharide priming for the ATP induced release [14]. IL-18 is structurally similar to IL-1 family and functionally similar to IL-12.Like IL-1ß, IL-18 is, initially synthesized as a precursor that is cleaved by caspase-1 to form a mature protein.

In addition to the homology of the primary amino acid sequences, both share a common secondary and tertiary structure [15]. Elevated IL-18 plasma level has been observed in vivo in response to acute hyperglycemia in healthy volunteers and subjects with impaired glucose tolerance [16].

Similarities between Interleukin-1 and Interleukin-18

Interleukin-18 and IL-1 have long been recognized to be similar in many respects, although they share no significant sequence homology. Both cytokines lack the leader sequence, are processed by caspase-1, contain similar ß-sheets, which bind to receptors belonging to the same family, and use a common signal-transducing pathway leading to activation of NF-κB. However, there are some differences. IL-18 is constitutively expressed in macrophages, whereas IL-1 is inducible by stimuli such as lipopolysaccharide (LPS) [17].

Monocytes rapidly process and release both IL-1ß and IL-18 after exogenous ATP [18]. The human IL-18 gene is located on chromosome 11q22, whereas the IL-1 gene is on chromosome 2q13-21. Targeted disruption of the *MyD88* gene results in loss of IL-1 and IL-18 mediated function [19].

Gene Structure of Interleukin-18

The IL-18 gene is composed of seven exons, of which two exon 1 and 2 are noncoding. There are two promoters associated with IL-18 gene, located upstream of exon 1 and exon 2, which are unlike those of other cytokines, such as IL-2, IL-4, IL-5, and IL-6, TATA-less and Guanine rich cytosine poor.

An NF-κB recognition sequence is present in both promoter regions [20]. In addition, recognition elements for an IFN consensus sequence binding protein and a PU. One binding site is located in the upstream of exon1. The IL-18 gene is characterized by the lack of RNA-destabilizing element, which may suggest the prolonged secretion of IL-18 in the inflammatory reactions.

IL-18 gene expression is regulated by two independent promoters: p1 promoter (inducible promoter) and p2 promoter (constitutive promoter). Both promoters are TATA less, and IL-18 mRNAs are transcribed from multiple mRNA start sites located at both p1 and p2 promoters.

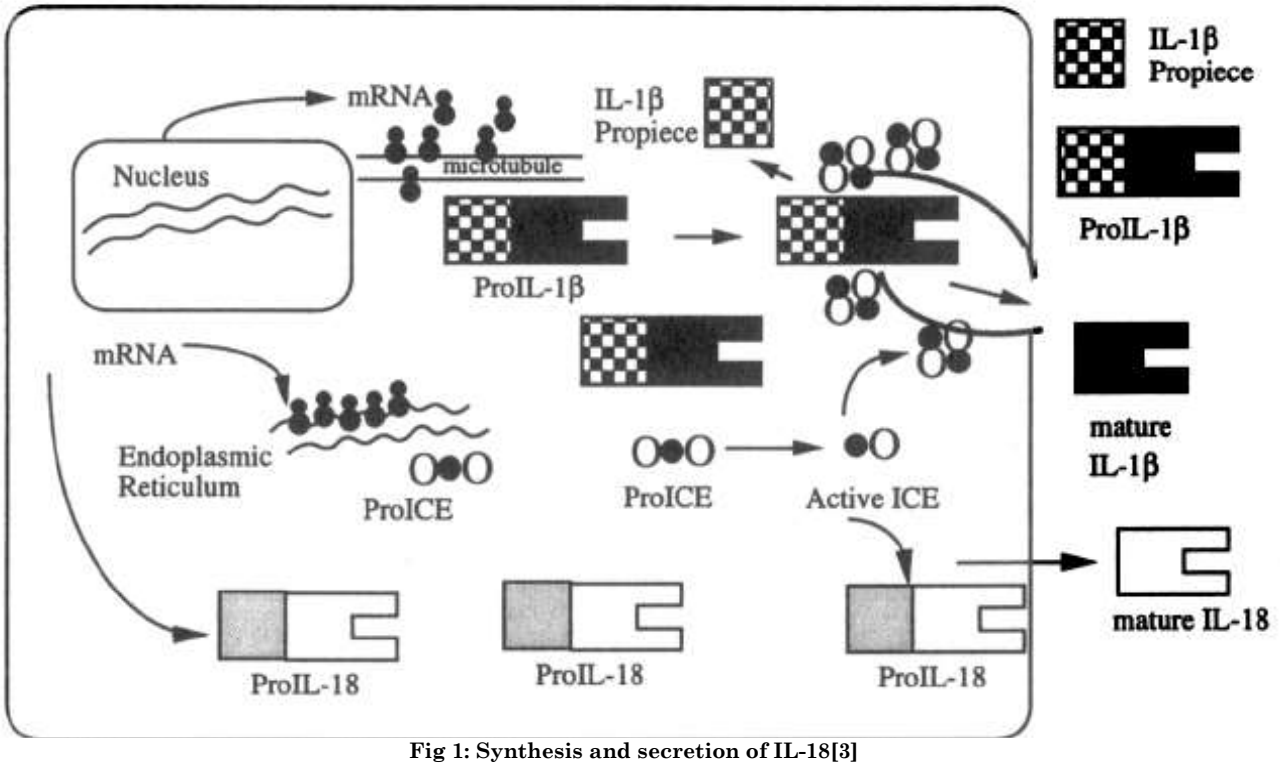

Fig 1: Synthesis and secretion of IL-18[3]

IL-18 Receptors

Torigoe et al [21].Described the purification and characterization of a human IL-18 receptor with the use of an antibody isolated from a panel of monoclonal antibodies directed against the human Hodgkin's cell line L428.Many of the cell lines of the hematopoietic lineage express IL-18R. Natural killer cells constitutively express functional IL-18R, and their cytolytic activity is rapidly augmented in response to IL-18.

Naive T cells apparently do not express IL-18R, but on stimulation with antigens and IL-12, they express IL-18R and develop into Th1 cells [22]. Both chains of IL-18 receptor (IL-18) are members of the IL-1 receptor family [23]. IL-18R is a hetero-complex composed of a constitutive ligand binding α chain, which is described as IL-1 receptor related protein (IL-1Rrp)and ß chain, which is named accessory protein-like (AcP).

IL-18Rα binds IL-18 with low affinity, whereas the ß chain dose not bind IL-18 but increases the affinity of the receptor and is involved in the signal transduction pathway [23]. IL-18 recognizes a heterodimeric receptor (IL-18R) comprising unique α (IL-1Rrp) and nonbinding ß (AcP) signalling chains [24].

This receptor is widely expressed on cells implicated in both innate and specific immune responses, and signals through a pathway that involves MyD88 (myeloid differentiation 88), IRAK (IL-1 receptor-associated kinase), TRAF6 (tumour necrosis factor receptor-associated factor 6) and NF-κB (nuclear factor kB) [13] IL-12 up-regulates IL-18 receptor expression on T cells, Th1 Cells, and B cells synergism with IL-18 for IFN-γ production [25]. IL-18 is functionally regulated by IL-18 binding protein, described as Ig-like cytokine receptor that strongly suppresses developing Th1 responses through IL-18 neutralization.

IL18 binding protein (IL18BP) functions as a natural inhibitor of IL-18 activity [26]. IL18BP binds IL18 with a high affinity (Kd of 400 pM) and, at equimolar ratios, inhibits 50-70% of IL18; at twofold molar excess, IL18BP neutralises nearly all IL-18 activity [27].L-18 binding protein increases spontaneous and IL-1-induced prostaglandin production via inhibition of IFN-γ [28].

Cells Expressing Interleukin-18

Monocytes/macrophages, dendritic cells(DCs), kupffer cells, keratinocytes, intestinal epithelial cells, rhematoid arthritis synovial cells, articular chondrocytes, lamina propria mononuclear cells, synovial fibroblasts and osteoblasts, airway epithelium, as well as within the adrenal cortex and pituitary gland [29].

Biological Actions OF IL-18

IL-18 enhances T cell and NK cell cytotoxicity and directly induces IFN-γ production by NK cells in combination with IL-12, enhances FasL on T cells and NK cells. IL-18 act directly on CD3+/4+ T lymphocytes and NK cells to initiate a chemotactic response [30].

IL-18 activates nuclear translocation of NFκB in T cells; induce monokine production by macrophages that constitutively express IL-18R. Commensurate with a putative early role in immune responses, IL-18 mRNA is widely distributed, facilitating rapid generation of cytokine if required [31]. IL-18 has direct proinflammatory properties.

In human unstimulated peripheral blood mononuclear cells (PBMC), it induces synthesis of IL-1ß, TNF-α, IL-6, IL-8, MIP-1α, and MCP-1 as well as enhances the production of adhesion molecules such as ICAM-1 [32]. IL-18 did not induce anti-inflammatory cytokines, IL-1Rα, or IL-10, although IL-18 induction of TNF-α was inhibited by IL-10. In the presence of IFN-γ, IL-18 induced TNF-α was enhanced and there was an increase in the mature form of IL-1ß [33].

IL-18 with IL-12 are capable to induce IL-6 and TNF-α production by mononuclear cells that might lead to an increase in IL-1Rα as well as to sIL-1RII secretion by neutrophils [34].Both cytokines are produced from activated macrophages, but the induction kinetics is different. IL-12 is readily inducible by mitogens, but constitutive IL-18 expression is detected in macrophages. IFN-γ itself or combination of IL-12 and IL-18 induced IFN- γ production from macrophages, demonstrating the unique pathways of autocrine macrophage activation.

In this case, IFN-γ induced IL-18 seems to have a critical role in autocrine activation in addition to paracrine activation of macrophages [35]. Virus infection activates IL-1ß and IL-18 production in human macrophages by a caspase-1-dependent pathway [36]. IL-18, when administered with IL-12, stimulates IL-4 and histamine release by basophils [37]. IL-18 serves as an effective modulator of the interaction between IL-1ß, sIL-1RII and IL-1Ra production by human neutrophils may be of significance in the inflammatory and other reactions mediated by IL-1ß. Understanding the complex inflammatory networks, involving IL-18 and IL-1ß as well as its regulatory proteins may provide novel strategies for augmenting or diminishing the early innate immune response [38]. IL-18 induces high levels of proinflammatory cytokine production and degranulation by tissue neutrophils. IL-18 can amplify acute inflammation through promoting neutrophil adhesion and migration, cytokine and chemokine production, granule release, and respiratory burst.

It induce neutrophil degranulation includes release of collagenase, cathepsin G, gelatinase, elastase, and phospholipase A2. Like IFN-γ, IL-18 suppresses IgE synthesis via induction of IFN- γ from B cell [39]. IL-18 blockade may evade host toxic effects of neutrophils but could simultaneously potentiate infections in which neutrophils are essential in host responses.

IL-18 bring about its effect on macrophage and DC functions may occur through direct, IFN-γ-independent pathways (via constitutive IL-18Rα expression), or indirectly through T-cell and NK-cell derived cytokine production [40]. Interleukin 18 together with interleukin 12 inhibits IgE production by induction of interferon-γ production from activated B cells [41].

Sustained IL-18 expression has been reported in a number of chronic inflammatory disease states such as, inflammatory bowel disease (crohn's disease), sarcoidosis, patients with systemic juvenile idiopathic arthritis, polycystic ovary syndrome, HIV lipodystrophy, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, Sjogren syndrome and rheumatoid arthritis, high plasma IL-18 levels, predicts the risk of developing cardiovascular diseases [42].

Signal Transduction Pathways of Il-18

Intracellular activation of caspase (caspase-1 or caspase-1-like enzymes) in antigen-presenting cells is mediated through Toll-like receptor (TLR) or Fas signaling, respectively. Caspase-1 and the extracellular serine esterase PR-3 induce activation of biologically active interleukinIL-18 (18 kDa) by cleavage of its precursor, pro-IL-18 (24 kDa) [43].

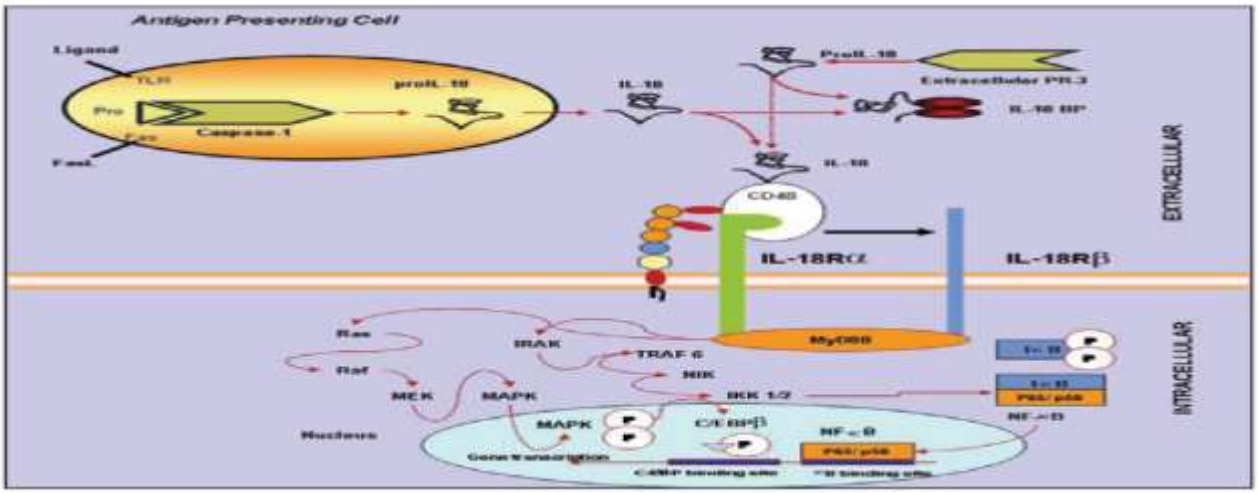

Fig 2: Signal transduction pathway of IL-18 [43]

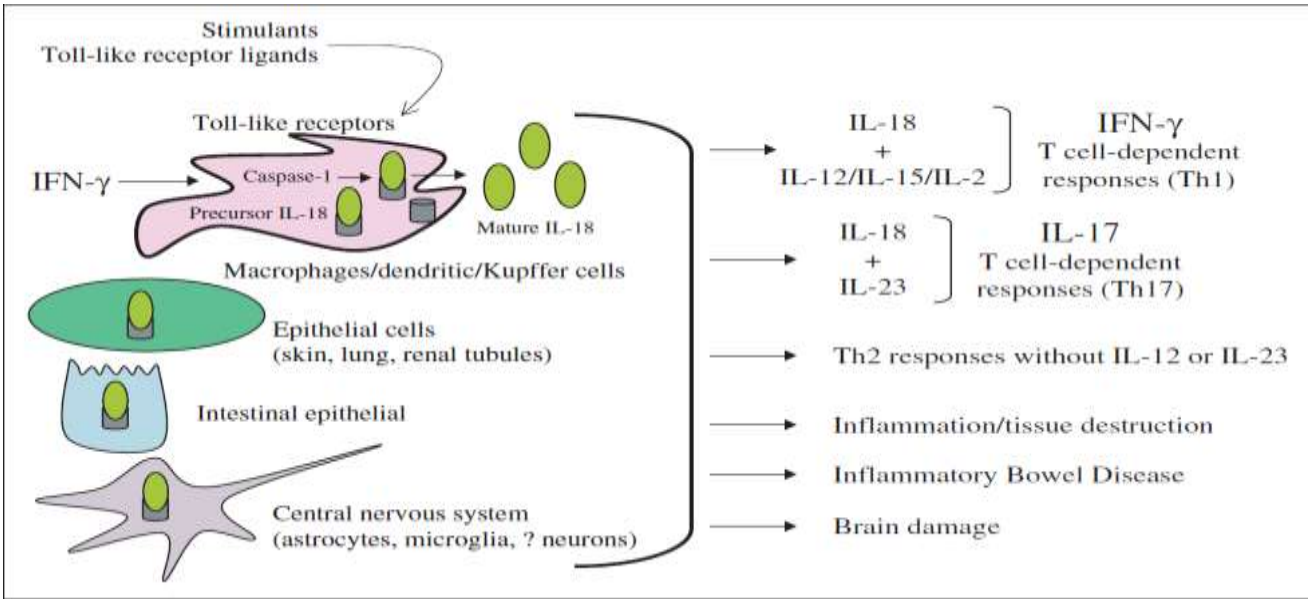

Fig 3: Cell sources of IL-18 precursor [44]

Chronic Periodontitis

The initial immune response in chronic periodontitis occurs following colonization of the gingival sulcus by periodontopathic bacteria. The presence of the bacteria induces the production of cytokines and chemokines by the gingival epithelium. This results in the expression of adhesion molecules, increased permeability of gingival capillaries and chemotaxis of polymorphonuclear neutrophils through the junctional epithelium and into the gingival sulcus.

The specific cytokines and chemokines produced by this initial response lead to a perivascular T-cell / macrophage dominated inflammatory infiltrate in the connective tissues. If this cell-mediated immune response does not control the bacterial challenge, progression to a B-cell / plasma-cell lesion occurs. The effectiveness of this response varies among individuals and appears to be important in determining disease susceptibility [45].

Immune Regulation in Chronic Periodontitis

The immune response in periodontal disease is governed by the net effect of Th1 and Th2 cytokines. Th1 cytokines include interleukin-2 and IFN-γ and promote cell-mediated immunity, while the Th2 cytokine, interleukin-4, suppresses cell-mediated responses and enhances humoral immunity. Th17 cells, a new subset of T-helper cells, characterized by the production of interleukin-17, have both destructive and protective effects in periodontal diseases.

The cytokine family consists of pro-inflammatory cytokines, of which tumor necrosis factor -α (TNF-α) and interleukin (IL)-1 are best known, and anti-inflammatory cytokines, including IL-10. IL-12 and IL-18

are cytokines with proinflammatory properties. They share many biological activities, and synergistically induce the production of interferon (IFN)-γ [45]. The early / stable lesion of chronic periodontitis is dominated by macrophages and T-cells, suggesting that Th1 cytokines are important in the development of this response, while the advanced / progressive lesion of chronic periodontitis, which is characterized by B-cells and plasma cells, is dependent upon Th2 cytokines [46].

Diabetes Mellitus

Diabetes is an endocrine/metabolic disorder characterized by alterations in the metabolism of carbohydrates, proteins and lipids. However, chronic hyperglycaemia underlies the incidence and the progression of diabetes related microvascular complications, as well as the main etiopathogenic mechanism in periodontal disease.

Type 2 diabetes is characterized by dual faults of impaired insulin action (insulin resistance) and pancreatic dysfunction that include progressive loss of ß-cell functions, loss of insulin secretion and loss of ß-cell mass. Pancreatic islets from Type 2 diabetes patients present with amyloid deposits, fibrosis and increased cell death. Cytokines and chemokines are released from islets exposed to metabolic stress, partly because of IL-1ß signalling.

These events are typically associated with an inflammatory response, and therefore it was hypothesized that the pancreatic islet in type 2 diabetes is associated with immune cell infiltration. The characteristic of insulin resistance is the failure of insulin to suppress hepatic glycogen production or stimulate glucose uptake by peripheral tissues, and this, in turn, causes hyperglycemia, hyperinsulinemia and dyslipidemia .It typically begins at around middle age (40 years) and may be treated by dietary modification, oral hypoglycaemic agents or may require insulin therapy in uncontrolled cases**.**

Patients with long standing diabetes frequently experience pathologic changes in many tissues and organs and the extent of diabetic complications is related to the degree of metabolic control. The major complications of diabetes, which include retinopathy, nephropathy, neuropathy, and vascular degeneration, are the result of hyperglycaemia. Both types of diabetes are risk factors for periodontitis, which is now a recognized complication of diabetes mellitus. Abnormalities in PMN function can be markedly improved with insulin therapy and meticulous control of the disease. This may explain why well-controlled diabetics are not at increased risk for periodontitis [47]. The chronic state of the infection and inflammation accumulated over time has been associated with insulin resistance and worse glycemic control in patients with type 2 diabetes and periodontitis.

It has been shown that if the infection and inflammation reduced, this may have a positive impact on glycaemic parameters [fasting plasma glucose and glycated haemoglobin (HbA1c)]. The complications of hyperglycemia have been correlated to advanced glycosylation end products. The hyperglycemia causes increased formation of non-enzymatic advanced glycosylation end-products [48].

Accumulation of advanced glycosylation end-products is a measure of cumulative metabolic and oxidative stress, are predictors of long-term complications for diabetes. Treatment of ß-cells with advanced glycosylation end-products results in the production of reactive oxygen species and apoptosis [49].

Rosenthal evaluated the relationship of inflammatory periodontal disease to the diabetic status of the insulin-dependent diabetes mellitus (IDDM) patient. There was a greater % of ketoacidosis, retinopathy and neuropathy in the periodontitis group. IDDM patients with neurological complications or a history of chronic infections had a significantly higher gingival index score than those without the complication (<0.05) [50].

Emrich *et. al.* studied the relationship between Type 2 diabetes and periodontal disease in 1342 Pima Indians: there was a higher prevalence of periodontitis in diabetic subjects at all age groups under 55 years. However, this study gave no information about the subjects level of diabetic control [51]. Miller *et al* the effects of mechano-chemical periodontal therapy on the metabolic state of nine poorly controlled diabetic patients was evaluated. A control group was not included in the study. Each

subject was treated by mechanical therapy followed by a 14 day course of doxycycline (100 mg BD). The study duration was two months, after which time HbA1c levels were not significantly different from baseline. In five of the nine subjects, there was a statistically significant reduction in HbA1c, but there were no changes in gingival inflammation or bleeding on probing [52]. Taylor *et al* carried out a longitudinal study on 100 Pima Indians, found that poorly controlled diabetics had more severe periodontitis than controlled diabetics, and that subjects with type 2 diabetes and periodontitis had increased risk of poor glycemic control, the first report of this in the literature.

However, when evaluating the studies on Pima Indians, one needs to consider that this population is not representative of other groups [53]. Arthur B. Novaes Jr *et al.* evaluated whether type 2 non-insulin dependent diabetes mellitus (NIDDM) changes the pattern of evolution of periodontal disease.

The glycosylated hemoglobin test was more reliable than the fasting glucose analysis [54]. Bridges RB *et al.* conducted a prospective, cross-sectional study and compared the periodontal status of 118 diabetic men and 115 age-matched non-diabetic men. Plaque and gingival indices, bleeding scores, probing depth, loss of attachment, and number of missing teeth were measured in a blinded manner.

Smoking status, glycemic control, socio-economic status, and previous dental care were also assessed. These parameters were significantly higher in diabetic than non-diabetic men. These studies indicate, for this study group, that diabetes significantly affects all measured parameters of periodontal status [55].

Papapanou found a significant association between diabetes and periodontitis. Diabetes also may increase the risk of experiencing continued periodontal destruction over time. A two-year longitudinal study demonstrated a fourfold increased risk of progressive alveolar bone loss in adults with type 2 diabetes compared with that in adults who did not have diabetes [56]. Sandberg GE *et. al.* conducted a controlled cross-sectional study with the aim of studying oral health in patients with type 2 diabetes was carried out in a health care district in Sweden. The study included 102 randomly sampled diabetic patients and 102 age and gender matched non-diabetic subjects from the same geographical area, variables associated with glycemic control were extracted from medical records. The authors established that periodontal disease was more advanced among individuals with type 2 diabetes than among controls [57]. Iwamoto and colleagues found that periodontal treatment resulted in a significant reduction in serum levels of TNF-α that was accompanied by a significant reduction in mean HbA1c values (from 8.0 to 7.1 percent).

The improvement in HbA1c values was correlated strongly with the reduction in serum TNF- α levels across the patient population. This suggests that a reduction in periodontal inflammation may help decrease inflammatory mediators in the serum that are associated with insulin resistance, thereby improving glycemic control [58].

Beikler *et. al.* found glucose levels in blood sampled after bleeding on periodontal probing had a high correlation with blood samples taken from fingertips. This work suggests that the general dentist could use gingival blood samples in glucose self monitoring devices as a simple screening method to detect undiagnosed diabetics and identify patients with poor metabolic control [59].

Campus G *et. al.* conducted a case-control study to evaluate the possible association between non–insulin-dependent diabetes (T2DM) and clinical and microbiological periodontal disease among adult Sardinians. A total of 212 individuals participated in this study: 71 T2DM patients aged 61.0 ±11.0 years and 141 non-diabetic controls in good general health aged 59.1 ± 9.2 years. They arrived at results as T2DM patients showed a significantly lower number of teeth present and concluded that patients with T2DM undoubtedly have susceptibility for more severe periodontal disease [60].

Stephen L *et. al.* conducted a study to compare the periodontal status of a group of diabetic coloured and black communities of South Africa with a non-diabetic group. Sixty-seven type 2 diabetics (mean age: 49.3 ± 8.97) and

67 non-diabetics (mean age: 47.6 ± 8.85) were examined. Since advanced periodontal disease ultimately leads to tooth loss, lower number of teeth in diabetics than non-diabetics is an expected finding. This study showed that diabetics had more severe and a higher prevalence of periodontal disease [61].

Preshaw et al determined the prevalence of periodontitis in an urban population of Sri Lankans with Type 2 diabetes (T2DM) and recorded the duration of diabetes, blood pressure, percentage glycosylated haemoglobin, fasting blood glucose level, total cholesterol, triglycerides, low and high-density lipoproteins and it was concluded that subjects with T2DM demonstrated a compromised periodontal status compared with non-diabetic controls [62].

Kim *et al* investigated the effect of IL‐18 on the expression of Type I and collagen genes in dermal fibroblasts. Their results suggested that IL -18 down‐regulated collagen production in human dermal fibroblasts via extracellular signal regulated kinase pathway [63]. Fawad Javed Cytokine profile in poorly controlled type 2 diabetic patients with periodontitis may differ from the GCF cytokine profile in systemically healthy individuals with periodontitis.

Ten studies were included in this literature review. Two studies reported GCF concentrations of interleukin (IL-6) to be higher in patients with periodontitis and Type 2 diabetics compared to systemically healthy patients with periodontitis [64].

Corbella investigate whether non-surgical periodontal treatment reduces glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels in diabetic patients in a systematic review and meta-analysis.The meta-analysis showed that non-surgical periodontal treatment improves metabolic control in patients with periodontitis and diabetes [65].

JE Botero (2016) studied effect of periodontal treatment on glycaemic control in patients with diabetes and periodontitis. Thirteen (13) systematic reviews/meta-analysis were included for qualitative synthesis. Only three studies separated the use of adjunctive antibiotics and found a reduction of 0.36 percentage points but the difference was not statistically significant.

However, longer term studies having sufficient sample size do not provide evidence that periodontal therapy improves glycaemic control in these patients [66]. Khushboo Yamima Nand compare the prevalence of chronic periodontitis among individuals with and without type 2 diabetes, aged 35-65 years from a rural block in Vellore, Tamil Nadu and to assess risk factors for chronic periodontitis among individuals with diabetes.

Individuals with Type 2 diabetes have a higher prevalence of periodontitis. As poor oral hygiene is a strong risk factor for periodontitis, there is a need for targeted education regarding dental hygiene to reduce this preventable condition [67]. "The Perio Diabetes Symposium": Consensus Report of the Indian Society of Periodontology and Research Society for the Study of Diabetes in India a joint event on Periodontitis and Diabetes (2019) has given the 7 conclusive points of agreement [68].

Effect of Periodontal Disease on Diabetes

Diabetic patients with periodontal disease may have increased risk of diabetic complications. In a separate analysis including over 600 subjects periodontal disease is suggested as a significant risk factor for myocardial infarction and stroke as well as diabetes. The patients with severe periodontitis have 2.3 times high death rate from ischemic heart disease as compared to rate in subjects with no or mild periodontitis. Thorstensson H (1996) conducted case-control study which consisted of 2 parts, a baseline study and a follow-up study. 39 case-control pairs were selected.

They were adult, long-duration, insulin-dependent diabetics matched according to sex, age and diabetes duration. One individual in each pair (CASE) exhibited severe periodontal disease while the other (CONTROL) exhibited gingivitis or only minor alveolar bone loss. The median age of the cases was 58 years (range 36 to70 years) and of the controls 59 years (range 37 to 69 years). The median disease duration in cases and controls was 24 years and 25 years, respectively. The median follow-up time was 6 years. The medical variables analysed were weight, insulin dose, systolic and diastolic blood pressure, vibratory threshold,

triglycerides, total-cholesterol, HDL-cholesterol, creatinine, HbA1c, proteinuria, ECG, retinopathy, stroke, transient ischemic attacks (TIA), angina, myocardial infarct, heart failure, hypertension, intermittent claudication, foot ulcer, death, cause of death, and smoking habit. Biochemical analyses and clinical variables used as a routine in the monitoring of diabetics failed to differentiate between diabetics with severe and minor periodontal disease.

In the follow-up study, significantly higher prevalence of proteinuria and cardiovascular complications such as stroke, TIA, angina, myocardial infarct and intermittent claudication were found in the case group. An association between renal disease, cardiovascular complications and severe periodontitis seems to exist [69]. Saremi A In a prospective longitudinal study of 628 subjects aged ≥35 years, the effect of periodontal disease on overall and cardiovascular disease mortality in Pima Indians with type 2 diabetes were examined.

Periodontal disease is a strong predictor of mortality from IHD and diabetic nephropathy in Pima Indians with type 2 diabetes. The effect of periodontal disease is in addition to the effects of traditional risk factors for these diseases [70]. Amiri et al 2014 evaluated the frequency of periodontal disease in patients with type 2 diabetes mellitus (DM) and how this was related with the presence of diabetic retinopathy (DR). Periodontal disease in diabetic patients can compromise a patient's ability to maintain a proper metabolic control and may be associated with diabetic complication. Study concluded that the patients with diabetes retinopathy appear to show increased periodontal disease susceptibility [71].

B.R. Chrcanovic (2014) Diabetes and Oral Implant Failure: A systematic review investigated whether there are any effects of diabetes mellitus on implant failure rates, postoperative infections, and marginal bone loss. The difference between the patients (diabetic vs. non-diabetic) did not significantly affect implant failure rates (p = 0.65), with a risk ratio of 1.07 (95% confidence interval = 0.80, 1.44) [72]. Filippo Graziani (2017) in a systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes gave following results.

Healthy individuals with periodontitis exhibit a poor glycaemic control and a higher risk of developing diabetes. Individuals affected by diabetes show a deterioration of glycaemic control if also affected by periodontitis and significantly higher prevalence of diabetes-related complications. Limited evidence is available on gestational diabetes and type 1 diabetes. Periodontitis has a significant impact on diabetes control, incidence and complications [73].

Mechanisms by Which Periodontitis May Influence Diabetes-Related Inflammatory State and Insulin Resistance

Roberta Santos Tunes, Nogueira-Filho stated that the inflammatory mediators originating from periodontal sources can interact systemically with lipids, free fatty acids and advanced glycation end products (AGEs), all of which are characteristic of diabetes. This interaction induces or perpetuates activation of the intracellular pathways, such as the I-kappa-B (IκB), I-kappa-B kinase-ß (IKKß), nuclear factor kappa B (NF-kß) and the protein c-Jun *N*-terminal kinase (JNK) axes, all of which are associated with insulin resistance.

The activation of these inflammatory pathways in immune cells (monocytes or macrophages), endothelial cells, adipocytes, hepatocytes and muscle cells promotes and contributes to an increase in the overall insulin resistance, which makes it difficult to achieve metabolic control in patients with both type 2 diabetes and periodontitis [74].

Role of Il-18 in Diabetic Mellitus

Chronic low-grade inflammation plays an important role in the development of diabetes vascular complications.IL-18 produces proinflammatory cytokines and upregulates various adhesion molecule expressions. These processes could lead to the development of diabetes vascular complications including atherosclerosis.

Indeed, serum IL-18 levels can be a strong predictor of death in patients with cardiovascular diseases and is associated with nephropathy and atherosclerosis in type 2 diabetic patients. IL-18 concentrations are reported to be elevated in patients with type 2 Diabetes mellitus, in obese individuals with the metabolic syndrome.

Infusion of glucose into normal volunteers and patients with impaired glucose tolerance induces an acute increase in serum IL-18 concentrations. It has been therefore hypothesized that the increased IL-18 concentrations have a pathophysiological role in insulin resistance and lipid deposition. It was also reported that serum IL-18 levels were increased during the early developing stage of type 1 diabetes [75]. Ishida *et al* examined whether interleukin-18 affects natural killer (NK) cells' migration and matrix metalloproteinases (MMPs) production.

This study demonstrated that chemotaxis of human NK cells through basement membrane-like Matrigel was augmented by IL-18. IL-18 stimulation induces the production of activated forms of matrix metalloproteinase-2 (MMP-2) and the production of pro-MMP-2 from NK cells. This study results demonstrated that MT1-MMP expression on human NK cells, which is a major activator of MMP-2, was induced by IL-18 stimulation coordinated with MMP-2 activation [76].

Thorand investigated prospectively the association between serum levels of interleukin IL-18 and the risk of type 2 diabetes in a case-cohort study conducted in middle-aged men and women. Elevated levels of IL-18 are associated with a considerably increased risk of Type 2 diabetes. This association is independent of a generalized proinflammatory state, but subjects with elevated levels of several inflammatory markers are particularly prone to develop Type 2 diabetes [77].

M. Bosch Serum IL-18 levels might be a sensitive marker of the chronic inflammatory process underlying insulin resistance, in contrast to other cardiovascular risk markers such as serum CRP or IL-6 concentrations that depend mostly on obesity. IL-18 has recently been described as one of the factors which, in addition to insulin resistance, also contribute to atherosclerosis [78].

Orozco Cytokines are of major importance in periodontal disease progression. IL-12 stimulates interferon-γ production by T helper type 1 (Th1) cells while IL-18 induces Th1 responses when present with IL-12 but Th2 responses in the absence of IL-12. IL-1ß has been correlated with periodontal disease destruction.

This study determined the local concentrations of these cytokines in sites of gingivitis and periodontitis. These results suggest that there is an association between severity of periodontal disease and levels of IL-1, IL-12 and IL-18 [79]. Zilverschoon (2008) obese individuals and patients with Type 2 diabetes mellitus exhibit increased circulating concentrations of IL-18. IL-18 resistance may represent an important mechanism of the increased susceptibility of these patients to a number of infections [80].

C. M. Figueredo measure the levels of Interleukin-18 in inflamed shallow sites and inflamed deep sites in patients with periodontitis and to compare the data with results from inflamed shallow sites in patients with gingivitis. The presence of similar levels of red complex species in gingivitis sites from periodontitis patients and from gingivitis patients suggested that the higher levels of IL-18 were not associated with a different microbial challenge [81].

Turkoglu assessed levels of cathelicidin LL-37 and Interleukin-18 in patients with chronic periodontitis. No correlation was found between the total amount of GCF IL-18 and clinical periodontal parameters at the sampled sites ($P > 0.05$) [82]. Pradeep GCF IL-18 and MCP-1 concentrations increased in periodontal disease compared to health and correlated positively with the severity of disease. In this study, it can be proposed that IL-18 may promote an inflammatory response by the induction of MCP-1 production and the subsequent recruitment and activation of circulating leukocytes at the inflammatory site [83].

Ozcaka patients with chronic periodontitis exhibit different salivary and/or plasma concentrations of interleukin IL-17 and IL-18 compared with clinically healthy subjects. The healthy control group exhibited significantly lower values in all clinical periodontal measurements ($p < 0.001$). The salivary concentration of IL-17 was significantly lower, and that of IL-18 significantly higher, in patients from the chronic periodontitis group compared with healthy control subjects ($p = 0.025$ and $p = 0.009$, respectively). Plasma IL-17 and IL-18 concentrations were similar in the two study groups [84].

Sanchez-Hernandez compare the levels of (IL-12) and IL-18 in gingival tissue and

serum between patients with chronic (n = 18) or aggressive periodontitis (n = 12) and healthy subjects (HS) (n = 9). Gingival tissue biopsies and serum were obtained from all study subjects. Patients with chronic periodontitis showed significantly elevated levels of serum IL-18 compared with Healthy subjects. The patterns of IL-12 and IL-18 are different in chronic and aggressive periodontitis; this finding suggests distinctive mechanisms of immunopathogenesis between these forms of periodontitis [85].

Campos evaluated the effectiveness of the non-surgical periodontal treatment in reducing the gingival crevicular fluid (GCF) levels of IL-18 from inflamed periodontal sites. This study showed that non-surgical treatment was effective in reducing GCF levels of IL-18 from inflamed periodontal sites [86]. S. Thirumalai compared the levels of Interleukin-18 in chronic periodontitis and aggressive periodontitis.

This study illustrated that there is no significant correlation between the levels of IL-18 and clinical parameters such as PI, GI, PPD, and CAL in chronic periodontitis and aggressive periodontitis [87]. Banu examine the level of toll like receptor-4 (TLR-4), Interleukin-18 (IL-18) and uric acid as a marker of the inflammatory host response along with routine biochemical parameters such as fasting glucose, insulin, total cholesterol, High density lipoprotein (HDL), Low density lipoprotein (LDL), triglycerides, fasting glucose, alanine transaminase (AST), aspartate transaminase (ALT) in the plasma and saliva of healthy individuals and periodontitis patients.

They also checked whether the patients with chronic periodontitis exhibit different modulations in salivary and/or plasma concentrations of these parameters compared with clinically healthy individuals. Study concluded that TLR-4, IL-18 and uric acid could have a role in the inflammatory pathology of periodontitis, are suggested to be useful in the prognosis and diagnosis of chronic periodontitis [88]. Esfahrood assessed the levels of IL-18 in unstimulated whole saliva and GCF samples among patients with chronic periodontitis and individuals with healthy periodontium. Levels of IL-18 among study groups suggested that levels of IL-18 in saliva and GCF cannot be used as a predictable biomarker for early diagnosis of periodontal disease [89]. Vineet Nair elucidated the level and role of IL-18 in the gingival crevicular fluid (GCF) and serum of individuals with healthy gingiva, chronic gingivitis, chronic periodontitis, and aggressive periodontitis before and after periodontal therapy.

Post treatment groups showed reduction in the mean IL 18 concentration in both GCF and serum. As the inflammation increased, there was a concomitant increase in the level of IL 18 and vice versa following periodontal therapy [90]. Emanuela Zaharieva Interleukin-18 (IL-18) is an inflammatory cytokine found to be elevated in obesity, metabolic syndrome and Type 2 diabetes as a part of the chronic low grade inflammatory process in these states. IL-18 was analyzed through enzyme-linked immunosorbent assay , the IL-18 serum level was higher in T2D and LADA than that in control subjects, but did not differ between both diabetic groups, even when they were BMI matched. Correlations with lipid, glycemic and inflammatory parameters were present in Type 2 Diabetes [91].

Conclusion

IL-18 demonstrates a unique function by binding to a specific receptor expressed on various types of cells. Diabetes mellitus and periodontitis share common risk factors. Numerous clinical trials have established a bidirectional relationship between diabetes mellitus and periodontitis. Increase in severity and progression of periodontal disease could be observed in Type 2 diabetes. It may be concluded that an association exist between levels of IL-18 with glycemic control in type 2 diabetes mellitus and chronic periodontitis.

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