Review Article

Markers, Pathways, and Current Evidence for Periodontitis-associated Insulin Resistance: A Narrative Review

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Aims and Objectives: The aim of the present paper is to provide a narrative review of the markers and pathways of periodontitis-associated insulin resistance (IR).

Materials and Methods: Research papers published in peer-reviewed scientific journals from 2000 to 2021 were searched systematically in Online Cochrane Library, Google Scholar, and Medline/Pubmed database. The medical subject headings (MeSH) terms used for literature search were “diabetes AND periodontal disease,” “diabetes AND periodontitis,” “inflammation AND insulin resistance,” “Insulin resistance AND periodontal disease,” and “insulin resistance AND periodontitis.” Manual search for applicable work in review article peer-reviewed print journals, and latest editions of standard textbooks of pharmacology and pathology were searched for updated additional information. Relevant papers in English language on the topic and abstracts of pertinent articles after excluding the duplicates, animal studies, and in-vitro studies were also scrutinized thoroughly and finally included as required in this narrative review.

Results: Literature search in Medline/Pubmed with MeSH words mentioned above revealed 4,621, 4,993, 19,349, 414, and 434 papers, respectively. Seven out of 13 systematic reviews and a total of 18 randomized clinical trials to evaluate periodontitis-induced IR were short-listed to update current evidences. The current literature in the past two decades has evaluated the effect of periodontal therapy on various type-2 diabetes (T2D) biomarkers following periodontal therapy. These indicators of periodontal disease activity and surrogate biomarkers of T2D in periodontitis may be an important diagnostic tool for the early prediction of complications due to IR. This increased systemic burden of proinflammatory cytokines by periodontitis can be reduced by periodontal therapy, thus improving the patient’s overall systemic condition.

Conclusion: The inflammatory response in periodontitis is characterized by dysregulated secretion of host-derived mediators of inflammation and tissue breakdown that may lead to IR. It can be comprehended that periodontal disease is a recognized amendable risk factor for T2D.

Keywords: Cytokines, diabetes mellitus, insulin resistance, periodontitis

INTRODUCTION

Diabetes mellitus (DM) and periodontal diseases are among the most prevalent chronic diseases in the world. DM is speedily developing as one of

Received: 08-04-22
Revised: 26-07-22
Accepted: 16-08-22
Published: 31-10-22

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How to cite this article: Bains VK, Mahendra J, Mahendra L, Mittal M, Valli G. Markers, pathways, and current evidence for periodontitis-associated insulin resistance: A narrative review. J Int Soc Prevent Community Dent 2022;12:475-87.
the highest universal health challenges of the twenty-first century.\cite{3} Epidemiological studies have observed a rapidly increasing trend in DM epidemic mainly in Indian subcontinent countries.\cite{2,3}

DM, mainly type-2 diabetes (T2D) that accounts for 90% of all DM cases,\cite{4-6} is an intricate, chronic endocrinial disorder of metabolic imbalance in protein, fat, and carbohydrate metabolism produced by either resistance to insulin action or augmented compensatory insulin release, or in unison of both.\cite{7,8} Insulin resistance (IR) has evidently appeared as an important source of glucose intolerance leading to T2D.\cite{9,10} Chronic exposure to proinflammatory (PI) cytokines and/or oxidative stress (OS) mediators activates cytokine signaling proteins that eventually obstruct the activation of insulin signaling receptors in β-cells of pancreatic islets, thus producing IR.\cite{11-15}

Current evidence suggests that periodontitis being a low-grade infection is proficient enough to advance a low-grade systemic inflammation, thus able to impact the overall systemic health.\cite{16} However, literature providing the molecular mechanisms interlinking periodontitis-related DM in a single paper is scanty. Therefore, the present paper intends to provide a narrative review based on partial PRISMA guidelines for plausible molecular events, pathways, and current update interlinking the mechanism for periodontitis-associated DM.

**Materials and Methods**

Research papers published in peer-reviewed scientific journals from 2000 to 2021 were searched in Online Cochrane Library, EMBASE, Google Scholar, and MedLine/PubMed database. The medical subject headings (MeSH) terms used for literature search in MedLine/PubMed search engine were “diabetes AND periodontal disease,” “diabetes AND periodontitis,” “inflammation AND insulin resistance,” “Insulin resistance AND periodontal disease,” and “insulin resistance AND periodontitis” and revealed 4,621, 4,993, 19,349, 414, and 434 papers, respectively. Relevant papers in English language on the topic and abstracts of pertinent articles after excluding the duplicates, animal studies, and in-vitro studies were scrutinized thoroughly and finally included in this narrative review. Seven out of 13 systematic reviews and 18 randomized clinical trials that evaluated periodontitis-induced IR were included to update current evidences. Manual search for applicable work in review article from peer-reviewed print journals and latest editions of standard textbooks of pharmacology and pathology were searched for updated additional information [Figure 1].

**Results**

Review of literature in the past few decades has revealed update in pathways, markers, and pathophysiology that connect IR with periodontitis. The summary of the findings from the pertinent literature can be divided into the following subheadings.

**Insulin Synthesis, Release, and Regulation**

Insulin is initially synthesized in the Golgi apparatus of beta-cells in pancreas as pre-proinsulin (110 amino acids) consisting of single polypeptide chain,
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B chain, C-peptide chain, and A-chain [Figure 2]. Insulin and C-peptide (31 amino acids) are stored in secretory granules and co-secreted in equimolar quantities by exocytosis from cell membranes.\textsuperscript{[17,18]} Insulin secretion and control are monitored by a well-synchronized interaction between nutrients (extracellular glucose, fatty acids, ketone bodies, and amino acids), gastrointestinal hormones (incretins, GIP and GLP-1), pancreatic hormones (glucagon and somatostatin), and autonomic neurotransmitters. Stimulation of alpha-2 receptors, e.g., by hypoxia, hypoglycemia, exercise, hypothermia, surgery, or severe burns, impedes insulin discharge, whereas β2 adrenergic and vagal nerve stimulation enhances insulin secretion.\textsuperscript{[19,20]}

Rorsman and Braun\textsuperscript{[19]} reviewed the regulation of insulin secretion from a pancreatic beta-cell in detail. The pancreatic beta-cell in a resting or fasting state is hyperpolarized. On entry into pancreatic beta-cells via glucose transporter-1 (GLUT-1) in humans, glucose is quickly phosphorylated producing G6P which enters the glycolytic pathway in mitochondria leading to elevation of ATP. This ATP binds to and inhibits Kir 6.2 subunits of the ATP-mediated K channel. Diminished K deportment results in depolarization of the local membrane and stimulation of Na\textsuperscript{+} and Ca\textsuperscript{2+} channels, and this increases the Ca\textsuperscript{2+} excitation of stored insulin exocytosis.\textsuperscript{[18,19]} Both acetylcholine and incretins activate the Gq-PLC-IP3-Ca-PKC pathway via M3 receptors and the Gs-AC-cAMP-PKa/EPAC2

Figure 2: Structure and function of insulin [modified from Maitra\textsuperscript{[17]}]
pathway via GPC receptors, respectively, resulting in increase in the exocytosis of insulin. Elevated levels of cAMP also further enhance the exocytosis by inhibiting ATP-mediated K channel, whereas somatostatin receptors SST2/3 with G_i/o re-instate cell membrane hyperpolarization [Figure 3].

**INSULIN SIGNALING AND ACTION**

Almost all mammalian cells express the insulin receptor forms; however, the liver, skeletal muscle, fatty tissue (adipocytes) as well as specific areas of the brain and the pancreatic islet are critical for the regulation of blood glucose. Insulin performs its...

![Figure 3: Insulin release and signaling mechanism (modified from Maitra[17] and Powers and D’Alessio 2018[18]).](image-url)
Insulin resistance (Glucose intolerance)

The measured quantity of glucose that is removed from the blood by a static dosage of insulin is known as insulin sensitivity, and the failure of normal amounts of insulin to elicit the expected response is referred to as IR. IR can be established by genetic and environmental factors and leads to impaired glucose tolerance. Defective signaling of insulin receptor at manifold levels is essential to the pathogenesis of T2D. Petersen and Shulman[21] summarized all linking putative mediators of IR and proposed that IR is triggered by rising nutrient-derived toxic metabolites (DAG, acylcarnitine, ceramide, branched-chain amino acids), overdoing nutrient consumption (oxidative and endoplasmic reticulum stress), or answering to nutrient stress-mediated cellular toxicity (inflammation). Various mechanisms proposed for developing IR are as follows:

1. Intramyocellular lipid metabolites trigger IR through activation of signal cascades of IR. Insulin binds to its receptor and triggers cascade of signaling events that stimulate intrinsic tyrosine kinase of the receptor dimer. This results in the tyrosine phosphorylation of the receptor’s beta subunits, and small numbers of specific substrates (IRS proteins, Gab-1 and Shc), and a caveolar pool of insulin receptor phosphorylates caveolin (Cav), adaptor protein with PH and SH2 domains (APS), and Cbl-associated protein (CAP) within the membrane. Crucial event in the target tissue is the translocation of GLUT-4 from intracellular vesicles to the plasma membrane, which is stimulated by both the caveolar and non-caveolar pathways. Insulin also stimulates the plasma membrane Na+ and K+-ATPase that enhances pump activity and a net accretion of K+ in the cell [Figure 3].[18,19]

The role of insulin on glucose transport rests on the stimulation of phosphatidylinositol 3-kinase (PI3K), which is triggered after interaction with IRS proteins. This generates phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3] that further controls the action of downstream kinases [PKB (Akt), protein kinase C (PKC), and mTOR]. PKB (or Akt) is the collective name for a set of three serine/threonine-specific kinases that mediate its effector functions via phosphorylation-dependent events and plays a role in multiple cellular processes, e.g., glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration. Insulin’s action on a target cell that mediated via insulin binding to the tetrameric receptor activates “insulin receptor substrate-phosphoinositide 3-kinase/Akt” (IRS-PI-3-kinase/Akt) signaling. Akt phosphorylates and inhibits the function of the tuberous sclerosis complex proteins, leading to activation of the downstream mammalian TOR (mTOR) complex which enhances protein synthesis. Akt also inhibits the function of Forkhead box O (FOXO) protein, which, in turn, reduces glucose synthesis, whereas inhibition of glycogen synthase kinase 3 (GSK3) enhances glycogen production [Figure 3]. Akt also enhances intracellular glucose uptake by translocation of GLUT-4 vesicles to the cell membrane.[17-20]
Table 1: Processes, signaling pathways, and mediators involved insulin metabolism and resistance\[^{[14,22-42]}\]

| Process/Pathway | Mediator/Molecule |
|----------------|------------------|
| AMP-activated protein kinase (AMPK) |  |
| Autophosphorylation |  |
| Chemokines-induced IR: CCL2, CCL3, and CCR5 and its ligand MCP-1 |  |
| c-Jun N-terminal kinases (JNKs) |  |
| Endoplasmic reticulum stress |  |
| Forkhead box O (FOXO) proteins |  |
| Glucolipotoxicity (glucotoxicity and lipotoxicity) |  |
| IL-1-beta |  |
| IL-6 |  |
| Inhibitor kB kinase (IKK) and protein kinase C (PKC) |  |
| Inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) |  |
| Mitogen-activated protein kinase (MAPK or MAP kinase) |  |
| Myeloid differentiation primary response 88 (MyD88) |  |
| Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) |  |
| Phosphatidylinositol 3-kinase (PI3K) |  |
| PI3K/AKT/mTOR pathway |  |
| Protein kinase A (PKA) AKT [also known as protein kinase B (PKB)] |  |
| Protein Kinase C (PKC) |  |
| TNF-alpha |  |
| Toll-like receptors (TLR-2 and -4) |  |
| Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP) |  |
| Toll-interleukin-1 receptor-domain (TIR)-containing adapter-inducing interferon-β (TRIF-β) |  |
| TRIF-related adaptor molecule (TRAM) [also known as TIR-containing adaptor molecule (TICAM)-2] |  |

Quantifying insulin sensitivity is the direct method of estimation of IR. Table 2 shows various biological, clinical, and surrogate makers of IR.\[^{[44-47]}\]

**Pathogenesis of Periodontitis**

Periodontitis is a chronic multifactorial inflammatory disease linked with dysbiotic plaque biofilms and is characterized by progressive destruction of supporting structures of teeth. Case definition of periodontitis by World Workshop 2017 is as follows: “Interdental clinical attachment loss (CAL) that is detectable at more than equal to 2 non-adjacent teeth, or buccal or lingual CAL of more than equal to 3 mm with pocketing of more than 3 mm is detectable at more than equal to 2 teeth.”\[^{[48]}\]

Virulent factors of periodontal pathogens in forms of toxins, lipopolysaccharides (LPS), and lipoteichoic acid pose significant challenges to the patients who exacerbated the host immune-inflammatory response. LPS secreted from periodontal pathogens is located in the outer membrane of Gram-negative bacteria that are recognized by TLR-4 and interact with CD14/TLR-4/MD-2 receptor complex on immune cells such as macrophages, monocytes, dendritic cells, and B cells, with resulting release of PI mediators and inflammatory mediators such as prostaglandin E2 (PGE2), resistin, and CRP from these cells. Lipoteichoic acid, a component of Gram-positive cell walls, stimulates immune responses through TLR-2. Alveolar bone loss as a protective mechanism to prevent bacterial invasion of the bone ultimately leads to tooth mobility and its loss. Multinucleated osteoclasts cause bone resorption after activation by a variety of mediators such as PI cytokines, oncostatin M, bradykinin, thrombin, and various other chemokines via the RANK/RANL/OPG signaling pathway.\[^{[49]}\]

These host-mediated products are released to the circulation. Loos\[^{[51]}\] hypothesized “possibly daily episodes of a bacteremia originating from periodontal lesions are the cause for the changes in systemic markers in periodontitis; the cumulative size of all periodontal lesions in the untreated severe periodontitis patient may amount to 15 to 20 cm\(^2\)”.

**Mechanism of Periodontitis-associated Insulin Resistance**

The normal pathway of insulin functioning commences with attachment of insulin to insulin tyrosine kinase receptor. The insulin receptor phosphorylates IRS-1 which in turn phosphorylates PI3-kinase. PI3-kinase then phosphorylates PIP2, which then activates Akt/protein kinase B (PKB), eventually leading to GLUT4 translocation to the plasma membrane of skeletal muscle cells and adipocytes, thus allowing the cell to absorb extracellular glucose, lowering interstitial glucose levels and thus plasma glucose concentration.\[^{[17]}\]

Peroxisome proliferator-activated receptor-gamma (PPAR-γ) complements insulin signaling and has been shown to regulate adipocyte differentiation, FA storage, and glucose metabolism. PPAR-γ agonist improves IR by opposing the effect of tumor necrosis factor (TNF)-α in adipocytes and by enhancing the expression of a number of genes encoding proteins involved in glucose and lipid metabolism.\[^{[19]}\]
The inflammatory response in periodontitis is characterized by dysregulated secretion of host-derived mediators of inflammation and tissue breakdown. Important PI biomarkers characteristically increased in periodontitis are interleukin (IL)-1β, IL-6, PGE2, and TNF-α. Other mediators most extensively investigated in periodontitis are PGE2, RANKL, high-sensitive C-reactive protein, resistin, and matrix...
metalloproteinases (MMPs) (particularly MMP-8, MMP-13, and MMP-9), along with T cell regulatory cytokines (e.g., IL-12, IL-18) and other chemokines. Pertinent data from the articles reviewed have been summarized in Table 3.\textsuperscript{[53-70]} Among them, the most significant cytokine concerned to be related with the commencement and development of IR is TNF-α. Increase in TNF-α resulted in the development of IR by (a) modification in intracellular insulin signaling by inhibiting tyrosine kinase activity of the insulin receptor (IRS), (b) reduction in insulin-responsive glucose transporter synthesis, and (c) macrophage-dependent pancreatic islets cytotoxicity in diabetes.\textsuperscript{[12,71,73]} Constant elevations of IL-1β/TNF-α resulting from longstanding chronic inflammation and infection result in pancreatic β-cell destruction.\textsuperscript{[12,74]} Increase in L-1β enables PKC activation leading to apoptotic pancreatic β-cell demolition. Further, IL-6 significantly targets

### Table 3: Randomized and non-randomized clinical trials\textsuperscript{a} showing markers in serum used to evaluate periodontitis-induced insulin resistance

| Year | Author | Population studied | Sample size | Parameters investigated |
|------|--------|--------------------|-------------|-------------------------|
| 2020 | Montero et al.\textsuperscript{[53]} | Spain | 63 | High-sensitivity C-reactive protein (hsCRP), cytokines, markers of prothrombotic states, carbohydrate, and lipid metabolism |
| 2019 | Nishioka et al.\textsuperscript{[54]} | Japan | 71/74 | Fasting or post-load serum glucose and insulin, body mass index (BMI), HOMA-IR, HOMA-β, and Matsuda index |
| 2019 | Javid et al.\textsuperscript{[55]} | Ahvaz, Iran | 43 | Fasting blood glucose, insulin, serum levels of fasting insulin and insulin resistance (homeostasis model assessment of insulin resistance), TGs |
| 2018 | D’Aiuto et al.\textsuperscript{[56]} | London, UK | 264 | HbA1c |
| 2017 | Zare Javid et al.\textsuperscript{[57]} | Ahvaz, Iran | 43 | Fasting blood glucose, insulin, insulin resistance (homeostasis model assessment of insulin resistance), TGs |
| 2017 | Bizzarro et al.\textsuperscript{[58]} | Amsterdam, The Netherlands | 110/110 | Waist circumference, systolic/diastolic blood pressure (BP), HDL-cholesterol, triglycerides, glucose |
| 2017 | Hayashi et al.\textsuperscript{[59]} | Meikai University Hospital, Japan | 12 | Total protein, albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (GGT), urea nitrogen, creatinine, uric acid, IgG, IgM, IgA, IgD, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in blood samples were measured by the commercial laboratory (BML Inc.) |
| 2017 | Mammen et al.\textsuperscript{[60]} | Kerala, India. | 40 | Fasting serum C-peptide, Homeostasis Assessment (HOMA) Index-Insulin Resistance, and HOMA-Insulin Sensitivity |
| 2017 | Joseph et al.\textsuperscript{[61]} | Kerala, India | 60 | HbA1c, FBG, lipid profile, HbA1c |
| 2013 | Bharti et al.\textsuperscript{[62]} | Tokyo, Japan | 29 | Glycated hemoglobin (HbA1c), hsCRP, TNF-α, IL-6, adiponectin, leptin, and resistin |
| 2012 | López et al.\textsuperscript{[63]} | Santiago, Chile | 165 | Serum lipoprotein cholesterol, glucose, body mass index (BMI), C-reactive protein (CRP), and fibrinogen concentrations |
| 2012 | Moiintaghabi et al.\textsuperscript{[64]} | Mashhad, Iran | 40 | Fasting plasma glucose (FPG), HbA1c, total cholesterol (TC), triglyceride (TG), and cholesterol levels |
| 2011 | Sun et al.\textsuperscript{[65]} | Zhejiang University, China | 190 | Adiponectin, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), lipid profile, glucose, insulin, homeostasis model of assessment-insulin resistance (HOMA-IR), and homeostasis model assessment of β-cell function (HOMA-β) |
| 2010 | Kardeşler et al.\textsuperscript{[66]} | Izmir, Turkey | 25 | Serum levels of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, C-reactive protein (CRP), soluble intercellular adhesion molecule-1, adiponectin, and leptin |
| 2009 | Dağ et al.\textsuperscript{[67]} | Dicle University, Turkey | 45 | HbA1c value and circulating TNF-alpha |
| 2009 | Matsumoto et al.\textsuperscript{[68]} | Gakkocho-Dori Niigata, Japan | 27 | Adiponectin |
| 2005 | Promsudthi et al.\textsuperscript{[69]} | Bangkok, Thailand | 52 | FPG and HbA1c |
| 2005 | Kiran et al.\textsuperscript{[70]} | Isparta, Turkey | 44 | Fasting plasma glucose (FPG), 2-h post-prandial glucose (PPG), glycated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), HDL-cholesterol, LDL-cholesterol, and microalbuminuria |
liver (hepatic glycogenolysis and gluconeogenesis), resulting in an amplified inflammatory response with impaired insulin signaling and action and resulting in diminished insulin production.[75,76]

Usually, obesity is considered as a recognized cause of both T2D and periodontitis. Adipokines released from adipocytes result in low-grade chronic inflammation through inflammatory mediators. Periodontal disease further can aggravate hyperlipidemia, abnormal fat metabolism, and consequent inflammatory changes in adipose tissue, which upsurge the serum PI cytokines and adipokines, thus worsening periodontal inflammatory status.[72,77,78] In disparity with the aforesaid nearby connotation between periodontitis, obesity, and T2D, Song et al.[77] observed that normal waist circumference or non-abnormally obese volunteers with IR were more expected to have severe periodontitis. However, variation for IR associated with severe periodontitis, among “at risk” obese, metabolically healthy, but obese (MHO), metabolically obese, normal-weight (MONW), and metabolically healthy (MH),[79] is still awaited.

OS due to imbalance in redox balance of innate immune response to periodontal pathogens resulted in the damage of supporting local tissues in chronic periodontitis.[80,81] Reactive oxygen species (ROS) overproduced mostly from mitochondria and peroxisomes of hyperactive neutrophils and monocytes (innate immune cells) in periodontitis may characteristically result in increased metabolites of lipid peroxidation, DNA damage, mitochondrial dysfunction (mitochondrial fission), and protein damage that may be responsible for pancreatic beta-cell dysfunction, IR, and T2D.[16] ROS causes IR in the marginal tissues by distressing insulin receptor signal transduction (due to the production of NADPH oxidase, GLUT4 is transported to lysosomes for degradation rather than to the plasma membrane). ROS also directly stimulates NF-kB, JNK, and p38 MAPK, resulting in mitochondria-induced stress responses characterized by mitochondrial fission subsequently, resulting in actions on the insulin receptor pathways [Figure 4].[82]

**DISCUSSION**

Reviewing the pertinent literature revealed that inflammatory cytokines and mediators originating from periodontal resources can interact systemically with lipids, free fatty acids, and advanced glycation end products (AGE) in diabetic patients. Potentially environmental host threats (ROS, AGEs, PI cytokines fatty acids, etc.) are recognized by cell components of innate immune cells via PRRs. This interaction induces activation of intracellular pathways like JNKs, NF-KB, IKKβ, IkB (a cytosolic inhibitor of NF-KB), as well as downregulation of PPAR-γ. This results in phosphorylation of IRS-1 and IRS-2 at serine and threonine residues (instead of tyrosine kinases) by kinases like JNKs leading to suppression of insulin signaling and thus results in downregulation of Akt/PKB.[16] IKKβ causes IR via transcripational activation of NF-κB that induces immune inflammatory genes for the release of cytokines, growth factors, adhesion molecules, and acute phase proteins. Activation of IKKβ also results in phosphorylation of IκB, freeing NF-κB to translocate into nucleus that regulates target genes for IR.[43]

Highly specific and sensitive indicators of periodontal disease activity and surrogate biomarkers of T2D in periodontitis may be an important diagnostic tool for early detection of IR. This, increased systemic burden of PI cytokines by periodontitis, can be reduced by periodontal therapy, thus improving the patient’s overall systemic condition.[45] Studies have assessed the effect of periodontal therapy on various T2D biomarkers following periodontal therapy.[52,83,84] In initial systematic review, Esteves Lima et al.[85] concluded that scientific evidence cannot affirm a positive association between periodontitis and gestational DM due to heterogeneity in substantial clinical, methodologic, and statistical analysis, among the studies. Pushparani[86] in a narrative review outlined physiologic mechanisms, clinical studies, and scientific evidences that reveal the interrelationship between zinc and DM with periodontal disease and suggested that disturbance in the zinc micronutrient and increased OS in T2D may bring down IR and formation of diabetic complications. Nibali et al.,[87] Martinez-Herrera et al.,[88] Daudt et al.,[89] and Gobin et al.[90] in systematic reviews suggested an association between metabolic syndrome or obesity and periodontitis and concluded that patients suffering from periodontal disease should be screened for metabolic syndrome and vice versa. They further suggested that individuals unveiling features of metabolic syndrome must maintain their oral health. Similarly, Alvarenga et al.[91] in a systematic review suggested a low grade of association of diabetic retinopathy and periodontitis. Systematic reviews hypothesized that association may have occurred due to IR developed in response to persistent source of inflammatory mediators as a result of chronic bacterial challenge.[87,91]

**STRENGTH AND LIMITATIONS**

The biggest strength of this narrative review is that it is focussed on highlighting the mediators and
pathways to better understand the role of periodontitis in the pathogenesis of IR in a single paper. However, extraction of data as required in systematic review and meta-analysis could not be performed due to nature of the paper and is the limitation of the paper.

**Future direction**

From the current evidence, it can be comprehended that periodontal disease is a well-known modifiable risk factor for T2D. Further, besides conventional periodontal therapy, novice future treatment strategies including...
IL-1 receptor antagonist, salicylates, polyphenols, anti-TNF approaches, anti-chemokine approaches, pharmaceutical chaperons, and thiazolidinediones need to be focussed for better outcomes. Understanding factors and molecular mechanism involved in the development of IR may serve as the basis for developing target strategy for the management of T2D. It becomes more imperative when recent studies are reporting IR markers’ association with early signs of periodontal breakdown among adolescents. However, it has often been ignored to be an imperative element of “interprofessional collaborative management approach” for T2D. Therefore, oral and non-oral (medical) health professionals should line up efforts in the management of T2D-susceptible subjects with periodontitis.

ACKNOWLEDGEMENT
The authors would like to thank Saraswati Dental College & Hospital, Lucknow and MAHER University, Chennai for supporting the preparation of this manuscript.

FINANCIAL SUPPORT AND SPONSORSHIP
Self-funded by authors.

CONFLICTS OF INTEREST
None to declare.

AUTHORS’ CONTRIBUTIONS
Conception or design: VKB, JM
Acquisition, analysis, or interpretation of data: VKB, JM
Drafting the work or revising: VKB, JM, LM, MM, GV
Final approval of the manuscript: VKB, JM, LM, MM, GV

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT
Not applicable.

PATIENT DECLARATION OF CONSENT
Not applicable.

DATA AVAILABILITY STATEMENT
Data presented in this paper is procured from original articles and all the relevant data is included in the manuscript.

REFERENCES
1. Morino K, Petersen KF, Shulman GI. Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. Diabetes 2006;55(Suppl. 2):S9-S15.
2. Bains VK, Chandra H, Jamaluddin K, Bains R. Awareness among health care professionals regarding interrelationship between diabetes mellitus and periodontal diseases: A step towards interprofessional collaborative practice. Asian J Oral Health Allied Sci 2020;10:10.
3. Singh M, Bains VK, Jhingran R, Srivastava R, Madan R, Maurya SC, et al. Prevalence of periodontal disease in type 2 diabetes mellitus patients: A cross-sectional study. Contemp Clin Dent 2019;10:349-57.
4. Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA 2017;317:2515-23.
5. Wang S, Liu J, Zhang J, Lin J, Yang S, Yao J, et al. Glycemic control and adipokines after periodontal therapy in patients with type 2 diabetes and chronic periodontitis. Braz Oral Res 2017;31:e90.
6. Klokkevold PR, Mealey BL. Influence of systemic conditions. In: Newman MG, Klokkevold PR, Takei HH, Carranza FA, editors. Carranza’s Clinical Periodontology. 13th ed. New York: Elsevier; 2018. p. 186-201.
7. Soi S, Bains VK, Srivastava R, Madan R. Comparative evaluation of improvement in periodontal and glycemic health status of type 2 diabetes mellitus patients after scaling and root planing with or without adjunctive use of diode laser. Lasers Med Sci 2021;36:1307-15.
8. Afable A, Karingula NS. Evidence based review of type 2 diabetes prevention and management in low and middle income countries. World J Diabetes 2016;7:209-29.
9. International Diabetes Federation. IDF Diabetes Atlas. 7th ed. Available from: https://diabetesatlas.org/idfwp/resource-iles/2012/07/IDF_diabetes_atlas_seventh_version_en.pdf. [Last accessed on 22 December 2021].
10. Fève B, Bastard JP. The role of interleukins in insulin resistance and type 2 diabetes mellitus. Nat Rev Endocrinol 2009;5:305-11.
11. Hotamisligil GS. Inflammatory pathways and insulin action. Int J Obes Relat Metab Disord 2003;27(Suppl. 3):S53-5.
12. Moller DE. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol Metab 2000;11:212-7.
13. Akash MS, Shen Q, Rehman K, Chen S. Interleukin-1 receptor antagonist: A new therapy for type 2 diabetes mellitus. J Pharm Sci 2012;101:1647-58.
14. Rehman K, Akash MS. Nutrition and diabetes mellitus: How are they interlinked? Crit Rev Eukaryot Gene Expr 2016;26:317-32.
15. Kawazoe Y, Naka T, Fujimoto M, Kohzaki H, Morita Y, Narazaki M, et al. Signal transducer and activator of transcription (STAT)-induced STAT inhibitor 1 (SSI-1)/suppressor of cytokine signaling 1 (SOCS1) inhibits insulin signal transduction pathway through modulating insulin receptor substrate 1 (IRS-1) phosphorylation. J Exp Med 2001;193:263-9.
16. Gurav AN. Periodontitis and insulin resistance: Casual or causal relationship? Diabetes Metab J 2012;36:404-11.
17. Maitra A. The endocrine system. In: Kumar VK, Abbas AK, Aster JC, Turner JR, editors. Robbins and Cotran Pathologic Basis of Disease. 10th ed. International Edition. New York: Elsevier; 2021; p. 1097-112.
18. Powers AC, D’Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In: Brunton LL., Hildal-Dandan R, Knolllmann BC, editors. Goodman and Gilman’s: The Pharmacological Basis of Therapeutics. 13th ed. New York: Elsevier; 2018. p. 863-906.
19. Rorsman P, Braun M. Regulation of insulin secretion in human pancreatic islets. Annu Rev Physiol 2013;75:155-79.
20. Manning BD, Toker A. Akt/Pkb signaling: Navigating the network. Cell 2017;169:381-405.
21. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev 2018;98:2133-223.
22. Jager J, Grémeaux T, Cormont M, Le Marchand-Brustel Y, Tant JF. Interleukin-1beta-induced insulin resistance in...
adipocytes through down-regulation of insulin receptor substrate-1 expression. Endocrinology 2007;148:241-51.
23. Abbatecola AM, Ferrucci L, Grella R, Bandinelli S, Bonafè M, Barbieri M, et al. Diverse effect of inflammatory markers on insulin resistance and insulin-resistance syndrome in the elderly. J Am Geriatr Soc 2004;52:399-404.
24. Hwa V, Nadeau K, Wit JM, Rosenfeld RG. STAT5B deficiency: Lessons from STAT5B gene mutations. Best Pract Res Clin Endocrinol Metab 2011;25:61-75.
25. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. Mol Med 2008;14:222-31.
26. Aguirre V, Uchida T, Yenush L, Davis R, White MF. The c-Jun NH2-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). J Biol Chem 2000;275:9047-54.
27. Chen G, Goeddel DV. TNF-R1 signaling: A beautiful pathway. Science 2002;296:1634-5.
28. Sartipy P, Loskutoff DJ. Monocyte chemoattractant protein 1 in obesity and insulin resistance. Proc Natl Acad Sci USA 2003;100:7265-70.
29. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005;436:356-62.
30. Xu L, Kitade H, Ni Y, Ota T. Roles of chemokines and chemokine receptors in obesity-associated insulin resistance and nonalcoholic fatty liver disease. Biomolecules 2015;5:1563-79.
31. Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 2004;306:457-61.
32. Kim JJ, Sears DD. TLR4 and insulin resistance. Gastroenterol Res Pract 2010;2010:212563.
33. Towler MC, Hardie DG. AMP-activated protein kinase in metabolic control and insulin signaling. Circ Res 2007;100:328-41.
34. Musi N. AMP-activated protein kinase and type 2 diabetes. Curr Med Chem 2006;13:583-9.
35. Weir GC. Glucolipotoxicity, β-cells, and diabetes: The emperor has no clothes. Diabetes 2020;69:273-8.
36. Maffeì A, Lembo G, Carnevale D. PI3 kinases in diabetes mellitus and its related complications. Int J Mol Sci 2018;19:4098.
37. Lee S, Dong HH. FOXO integration of insulin signaling with glucose and lipid metabolism. J Endocrinol 2017;233:R67-79.
38. Liu T, Zhang L, Joo D, Sun SC. NF-kB signalling in inflammation. Signal Transduct Target Ther 2017;12:17023.
39. Yung JHM, Giacca A. Role of c-Jun N-terminal Kinase (JNK) in obesity and type 2 diabetes. Cells 2020;9:706.
40. Bazi A. Toll-like receptors and targeted therapy in diabetes mellitus. Int J Basic Sci Med 2017;2:71-2.
41. Yehualashet AS. Toll-like receptors as a potential drug target for diabetes mellitus and diabetes-associated complications. Diabetes Metab Syndr Obes 2020;13:69788-91.
42. Rajpoot S, Wary K, Ibbott R, Liu D, Saqib U, Thurston TLM, et al. TIRAP in the mechanism of inflammation. Front Immunol 2021;12:69788.
43. Hoedson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.
44. Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World J Diabetes 2010;1:36-47.
45. Dina R, Dobrétia A, Rădulescu R, Dina C, Dinu F, Moța M. Clinical and biological markers of insulin resistance. Roman J Diab Nutr Metab Dis 2010;17:177-85.
glycosylated hemoglobin levels in pre-diabetic patients with chronic periodontitis. World J Diabetes 2017;8:213-21.

62. Bharti P, Katagiri S, Nitta H, Nagasawa T, Kobayashi H, Takeuchi Y, et al. Periodontal treatment with topical antibiotics improves glycemic control in association with elevated serum adiponectin in patients with type 2 diabetes mellitus. Obes Res Clin Pract 2013;7:e129-38.

63. López NQ, Quintero A, Casanova PA, Ibietta CI, Baelum V, López R. Effects of periodontal therapy on systemic markers of inflammation in patients with metabolic syndrome: A controlled clinical trial. J Periodontol 2012;83:267-78.

64. Moeintaghavi A, Arab HR, Bozorgnia Y, Kianoush K, Alizadeh M. Non-surgical periodontal therapy affects metabolic control in diabetics: A randomized controlled clinical trial. Aust Dent J 2012;57:31-7.

65. Sun WL, Chen LL, Zhang SZ, Wu YM, Ren YZ, Qin GM. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. Intern Med 2011;50:1569-74.

66. Kardesler L, Buduneli N, Cetinkalp S, Kinane DF. Adipokines and inflammatory mediators after initial periodontal treatment in patients with type 2 diabetes and chronic periodontitis. J Periodontol 2010;81:24-33.

67. Dağler L, Buduneli N, Cetinkalp S, Kinane DF. The effect of antimicrobial periodontal treatment and maintenance on serum adiponectin in type 2 diabetes mellitus. J Clin Periodontol 2009;36:142-8.

68. Promsudthi A, Pimapansri S, Deerochanawong C, Matsumoto S, Ogawa H, Soda S, Hirayama S, Amarasena N, Ak, Kaplan A. The role of inflammation. Ann Periodontol 2001;6:125-37.

69. Panjmurthy K, Manoharan S, Ramachandran CR. Lipid peroxidation and antioxidant status in patients with periodontitis. Cell Mol Biol Lett 2005;10:255-64.

70. Bains VK, Bains R. The antioxidant master glutathione and periodontal health. Dent Res J (Isfahan) 2015;12:389-405.

71. Hurrel S, Hsu WH. The etiology of oxidative stress in insulin resistance. Biomed J 2017;40:257-62.

72. Santos Tunes R, Foss-Freitas MC, Nogueira-Filho Gd R. Impact of periodontitis on the diabetes-related inflammatory status. J Can Dent Assoc 2010;76:a35.

73. Mohan M, Jhingran R, Bains V, Madan R, Rizvi I, et al. Impact of scaling and root planing on C-reactive protein levels in gingival crevicular fluid and serum in chronic periodontitis patients with or without diabetes mellitus. J Periodontal Sci 2014;44:158-68.

74. Esteves Lima RP, Cyrio RM, de Carvalho Dutra B, Oliveira da Silveira J, Martins CC, Miranda Cota LO, et al. Association between periodontitis and gestational diabetes mellitus: Systematic review and meta-analysis. J Periodontol 2016;87:48-57.

75. Pushparani DS. Zinc and type 2 diabetes mellitus with periodontitis—A systematic review. Curr Diabetes Rev 2014;10:397-401.

76. Nibali L, Tatarakis N, Needleman I, Tu YK, D’Aiuto F, Rizzo M, et al. Clinical review: Association between metabolic syndrome and periodontitis: A systematic review and meta-analysis. J Clin Endocrinol Metab 2013;98:913-20.

77. Martinez-Herrera M, Silvestre-Rangil J, Silvestre FJ. Association between obesity and periodontal disease. A systematic review of epidemiological studies and controlled clinical trials. Med Oral Patol Oral Cir Bucal 2017;22:e708-15.

78. Daudt LD, Musskopf ML, Mendez M, Remonti LLR, Leitão CB, Gross JL, et al. Association between metabolic syndrome and periodontitis—A systematic review. Curr Dent Pract 2016;7:e108-15.

79. Alvarenga MOP, Miranda GHN, Ferreira RO, Saito MT, Fagundes NCF, Maia LC, et al. Association between diabetic retinopathy and periodontitis—A systematic review. Front Public Health 2020;8:550614.

80. Thouvenot K, Turpin T, Taille J, Clément K, Meilhac O, Gonthier MP. Links between insulin resistance and periodontal bacteria: Insights on molecular players and therapeutic potential of polyphenols. Biomolecules 2022;12:378.

81. Ladeira LLC, Leite FRM, Nascimento GG, Saraiwa MDC, Bredoni MA, Moreira ARO, Ribeiro CCC. Precursors of insulin resistance underlying periodontitis in adolescents aged 17–18 years. Oral Dis 2022. doi: 10.1111/odi.14283.