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Review

The relationship of diabetes, periodontitis and cardiovascular disease

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ABSTRACT

Cardiovascular complications in diabetic patients comprise of interaction between traditional and non-traditional risk factors. This interaction is thought to play role in four-times increment of cardiovascular mortality risk in diabetic patients, compared to non-diabetics. Chronic inflammation is known to be one of atherosclerosis non-traditional risk factor and has a role on every phase of atherogenesis. Periodontitis is the most common cause of chronic inflammation in diabetic patient. Both periodontitis and diabetes have detrimental effect on each other in terms of alveolar bone destruction and poor metabolic control, by continuous inflammatory mediator activation. Defect of bacteria elimination ability and monocyte hyper-responsiveness in diabetic patients leads to persistent elevation of systemic inflammatory mediators. This process give rise to prolonged and augmented exposure to inflammatory cytokines. This exposure interacts with traditional risk factor could lead to initiation of endothelial dysfunction, the first phase of atherogenesis.

1. Introduction

Cardiovascular disease-related mortality increased by fourfold in diabetic patients [1] and this particular population has not yet benefited from traditional risk factor control as well as non-diabetic individuals [2–4]. The increment of cardiovascular risk in diabetic patients is influenced by complex interaction between traditional risk factors (hypertension, dislipidemia and obesity) and non-traditional risk factor non-traditional risk factors that play a role in the onset of atherogenesis involving endothelial dysfunction to emerging clinical outcomes [5]. One of the most important non-traditional risk factor is inflammation, and its relationship with atherogenesis is well-known [6]. Periodontitis is the most common chronic infection in diabetes worldwide [7,8] and in Indonesia [9,10]. Diabetes is a predisposing factor of periodontitis and periodontitis will exacerbate metabolic control of people with Diabetes Mellitus (DM). Periodontitis is also thought to play a role in cardiovascular complications in people with DM. Changes in oral flora, gingival mucosal changes, collagen regeneration disorders to immune system disturbances (including increased apoptotic monocyte ratios, cytokine dysregulation and monocyte hyper-reactivity) are the mechanisms that mediate chronic inflammation as well as bone and connective tissue damage, the underlying pathogenesis of periodontitis [11,12].

The evidence suggest that patients with periodontitis has fourfold risk of occurrence of coronary heart disease [13–15]. Endotoxinemia occurred during mastication, brushing test or even dental scaling in patients with periodontitis will cause systemic leakage of oral microbes that will induce the release of inflammatory mediators involved in atherogenesis [16]. The risk of bacteremia is increased by degree of severity of periodontitis [17].

2. Mechanism of periodontitis in diabetic patients

Periodontitis is chronic infection of dental supporting tissue caused by specific microorganism that leads to destruction of alveolar bone and periodontal ligament. Clinically, periodontitis is marked by pocket formation, recess or both. Periodontitis are classified into 3 categories: chronic periodontitis, aggressive periodontitis and periodontitis associated with systemic disease. Chronic periodontitis is the most common form of periodontitis.

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This slowly progressive type of disease is caused by plaque accumulation and calculus formation. Aggressive periodontitis on the other hand, is differed from chronic periodontitis by its fast progressing nature, occurred in healthy individuals without comorbidity without plaque or calculus formation. Genetic susceptibility may play a role in this type of periodontitis [18].

Periodontitis and diabetes has two-way relationship. Diabetes is a predisposing factor of periodontitis, and periodontitis will worsen metabolic control in diabetic patients. National Health and Nutrition Examination Survey (NHANES) III showed linear relationship between periodontal tissue destruction and severity of insulin resistance. Insulin resistance is also increase the risk of periodontal tissue destruction in population with obesity [13]. The growing theory suggests that pro-inflammatory cytokines expressed by gingiva in periodontitis leak into the systemic circulation and cause exacerbation of DM. Conversely, elevated levels of pro-inflammatory cytokines in DM can reach the gingiva and cause aggravation from existing periodontal disease [19].

Association between diabetes and periodontitis are explained by several mechanisms: (1) microvascular changes, (2) crevicular fluid changes, (3) collagen metabolism disturbance, (4) Altered host immune response, (5) subgingival floral changes, (6) genetic predisposition and (7) enzymatic glycation.

Oral manifestation found in diabetic patients comprise of cheilosis, dry mouth, burning mouth, less saliva flow and oral microflora changes dominated by *Candida albicans* and gram-positive coccus. These changes are seen prominently in patients with bad metabolic control. Diabetic patients also have tendencies to form gingival polyp, gingival hypertrophy, polypoid proliferation, abscess, periodontitis and tooth loss [20].

Oral cavity defect alongside with immune system disturbance and susceptibility to infection are predisposing factor for periodontal tissue destruction [20]. Immune system defect will alter Polymorphonuclear (PMN) cell function as a first line defence against bacteria. This condition followed by inadequate bacterial eradication, bacterial proliferation, and biofilm formation that eventually promote pro-inflammatory cytokine release [21,22]. Moreover, in patients with diabetes, there is alteration of collagen structure and function, that will further impair the reconstruction ability of periodontal tissue [20].

Immune system disturbance in diabetes occurred in all steps in inflammation process, from chemotaxis and adhesion disturbance, monocyte hyper-reactivity to premature PMN apoptosis. This will impair bacterial eradication ability of PMN and enhance pro-inflammatory activation (as a response of bacterial killing failure and monocyte hyper-reactivity) that will damage periodontal tissue [20]. Pre-existing dental plaque will lead to biofilm formation, putting diabetic patients vulnerable for periodontal infection [21,22].

Diabetic patients has more proinflammatory cytokine in gingival fluid than non-diabetics, on the same level of severity periodontitis [11]. Adhesion disturbance found in diabetics is caused by down regulation of Intracellular Adhesion Molecule 1 (ICAM-1) in vascular wall during inflammation. Aside from that, Advanced Glycosilation End Products (AGE) formed during hyperglycemia will alter formation of formyl-Met-Leu-Phe peptide, a PMN chemotactic regulator. Interaction between leucocyte and endothelial cell is also inhibited by sorbitol and Polyol pathway activation during hyperglycemia [23].

In diabetic patients, monocytes and PMNs are hyper-responsive to Lipopolysaccharide (LPS) exposure, leading to aggravation of cytokine release. AGE also plays a role in this hyper-reactivity by binding to monocyte receptor and activating Nuclear Factor Kappa B (NF-kB), which alter gene transcription of pro-inflammatory cytokines. This pro-inflammatory cytokines is continuously circulating in systemic circulation and causing tissue destruction [11]. This inflammation enhancement is also contributed by down regulation of anti-inflammatory cytokines such as Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-β1 (TGF-β1) and basic Fibroblast Growth Factor (bFGF). Anti-inflammatory cytokines such as TGF-β1 will activate Matrix Metalloproteinases (MMP)-2 in which inactivate monocyte chemoattractant-3 and halt inflammation process. Reduction of these growth factors resulted in loss of periodontal tissue ability to proliferate and heal after cytokine destruction [24].

Periodontal tissue also mediated by pathologic apoptosis occurs during chronic hyperglcemia state. During hyperglycemia; polyol, sorbitol, Protein Kinase C (PKC) and AGE will activate extrinsic apoptosis pathway mediated by Fas ligand and caspase, causing premature cell death of PMN, osteoblast, fibroblast and other extracellular-matrix-producing cells. Chronic hyperglycemia also induce pathologic apoptosis by Bcl-2 gene suppression [22,25].

Through the receptor Macrophage Scavanging Receptor (MSR) and Receptor for Advanced Glycemic End-Product (RAGE), AGE will be phagocyte by macrophages or endothelial cells that will induce monocyte proliferation, free radical release and activation of proinflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α). Proinflammatory cytokines will cause activation of B cells and T cells that play a role in tissue damage whereas free radicals can directly cause tissue damage [21]. This RAGE expression in lymphocyte and neutrophil cells in diabetic patients is increased. The AGE bond with its receptor will activate macrophages and neutrophils to produce proinflammatory, Reactive Oxygen Species (ROS) cytokines, and increase oxidative stress that all contribute to macro and micro vascular diabetic complications. AGE also has an adverse effect on bone formation and extracellular matrix [11].

3. The role of periodontitis in metabolic control of diabetes

As mentioned above, periodontal tissue and alveolar bone destruction in periodontitis is caused by pro-inflammatory cytokine release as a result of immune system activation by bacterial metabolite products, mainly LPS. These mediators however, also have significant role in affecting insulin resistance by several mechanisms: (1) modification of insulin receptor substrate, (2) increment of free fatty acid production and (3) reduction of nitric oxide (NO). These processes directly and indirectly interfere beta cell pancreas function by free fatty acid oxidation [26].

The relationship between inflammation and insulin resistance lies in the axis of c-JUN N-terminal Kinase (JNK1) and Inhibitor of Nuclear Factor Kappa-B Kinase (IKKβ)/NFκB. Inflammation will inhibit post-receptor signal transduction, especially Insulin Receptor Substrate (IRS) 1 and 2. Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1 activate serine kinase molecules such as IKKβ, JNK1 and ribosomal S6 kinase (p70S6K), this will inhibit signal transduction through IRS 1 and 2. NF-kB will inhibit Peroxisome Proliferator-Activated Receptor (PPARg) molecules that act as the co-repressor genes that make up Catabolite-bound Activator Protein (CAP) and IRS-2. Both CAP and IRS-2 genes play a role in Glucose Transporter Type 4 (GLUT-4) translocation (by insulin mediation) to the cell membrane [19].

The breakdown of free fatty acids in diabetics is also one of the mechanisms of insulin resistance mediated by inflammatory mediators. Ectopic fat depletion due to excessive acid breakdown activates PKC and through activation of serine kinase, will inhibit signal transduction mediated by IRS 1 and 2. TNF-α may also inhibit adiponectin production in adipocyte cells. Adiponectin is a molecule produced by adipose cells that have anti-inflammatory and insulin sensitizing effects. Adiponectin will activate Adenosine

Monophosphate Dependent Kinase (AMPK). PPAR-α and other signal transduction pathways that are not yet known and play a role in enhancing insulin sensitization. Adiponectin has antagonistic effects with TNF-α and vice versa TNF-α will decrease insulin secretion by adipose cells [19].

4. Relationship of periodontitis and cardiovascular complication in diabetes

Colonization of bacteria in dental plaque accompanied by immune system disorders that occur in diabetes leads to a continuously activated inflammatory condition. The mechanisms underlying bacterial colonization of plaque against insertion and worsening atherosclerosis are activation of the immune system, bacteremia, direct involvement of bacterial activated inflammatory mediators, pro-inflammatory cytokine involvement and predisposing factors that can be found in both periodontitis and atherosclerosis [27].

Inflammation plays a role in all stages of atherogenesis, from initiation, evolution to rupture of atheromic plaque. Periodontitis contributes to atherogenesis by exposing the vascular wall with bacterial LPS and pro-inflammatory cytokines continuously. Periodontitis increases the risk of bacteremia. Gingival ulceration in the periodontal pocket will cause bacterial translocation to the systemic circulation, supported by evidence of P. gingivalis found in atherosclerotic plaque [28]. Gentle mastication, tooth brushing and simple dental intervention could promote endotoxinemia and bacteremia in periodontitis [17,29]. Locally produced proinflammatory cytokines such as TNF, IL-1β and IL-6 may enter the systemic circulation and induce an acute phase response characterized by increased hsCRP, which can then promote atherogenesis [28]. These low-grade bacteremia may favor systemic inflammatory processes and lead to activation of the coagulation system, inducing platelet aggregation and endothelial activation. The inflammatory response to plaque accumulation is certainly different, in some individuals of good immunity, excessive plaque accumulation does not always result in extensive alveolar tissue and bone damage.

On the other hand, a person with an immune system disorder may show extensive tissue damage in the presence of minimal plaque accumulation or small bacterial colonies. Some individuals may exhibit hyper-reactivity to the bacterial challenge, especially individuals who exhibit a monocyte/macrophage hyper-inflammatory phenotype (MØ +). Patients with the MØ + phenotype will release pro-inflammatory cytokines such as IL-1, TNF-α and Prostaglandin E2 (PGE2) in greater numbers than patients without this phenotype. The phenotype of hyper-responsive monocyte/macrophage is found in one of these patients with DM [30]. Bacteremia and systemic inflammatory markers are more common in severe periodontal tissue damage and/or periodontitis with extensive tissue involvement, thus the presence of such hyper-responsiveness increases the risk of bacteremia and systemic inflammatory responses, contributing to atherogenesis.

The MMP enzyme produced by neutrophil activation and macrophages will degrade the vascular extracellular matrix which results in weakened collagen crosslinking and impairing elastin. Both of the above mechanisms are accompanied by endothelial impairment due to ROS contributing to the role in decreasing vascular distensibility, which is the initial stage of atherosclerosis [31].

Bacteria have properties that can damage periodontal tissue and stimulate the host immune system. LPS found in gram-negative bacteria will stimulate the immune system by binding to Toll-Like Receptor-4 (TLR-4) or TLR-2, which will stimulate the Major Histocompability Complex II (MHC II) via CD80/CD86 co-receptor. This MHC-II activation will trigger the differentiation of naive t cells into T helper 1 (Th1). The peptidoglycan also activates the nonspecific immune system by binding to TLR-2. Some bacteria such as *P. gingivalis* can secrete Vascular Cell Adhesion Molecule-1 (VCAM-1), ICAM-1, and TNF-α. These subgingival bacteria can penetrate into the blood circulation and induce low-grade systemic inflammation [27]. Activation of this pro-inflammatory cytokine will cause endothelial damage that initiates atherogenesis [32].

In inflammation process, there is a change in production of "housekeeping" proteins by the liver. At this stage, the production of fibrinogen and Plasma Activator Inhibitors (PAI) will increase, which can promote the occurrence of thrombosis. The increased production of amyloid A will also alter the function of High Density Lipoprotein (HDL) as an exporter of cholesterol in atherosclerotic plaque, in addition to the declining amounts in inflammatory conditions [32]. In the early stages of atherogenesis, there is an increase of VCAM-1 produced by the endothelium due to stimulation of the cytokine that will attract T lymphocytes and monocytes into the tunica intima media. In tunica intima media, monocytes undergo maturation into macrophages that will express scavenger receptors that have an important role in Low Density Lipoprotein (LDL) internalization and foam cell formation. This macrophage will also secrete pro-inflammatory cytokines that can attract T lymphocytes and other monocytes into nascent atherosclerosis plaque [33].

Macrophages also play a role in the complications of thrombosis from atherosclerosis. Macrophages produce MMP-1, MMP-8 and MMP-13 enzymes that degrade collagen and disrupt atheromic plaque stability. This can lead to thrombosis ending in tissue ischemia [33].

5. Conclusion

Periodontitis and DM are interrelated and affect each other. Oral mucosal changes accompanied by eradication of bacterial disorders will increase the risk of bacterial accumulation in dental plaque. On the other hand, in people with DM, hyperreactivity of immune cells is acquired due to LPS exposure produced by gram negative bacteria in dental plaque in periodontitis patients. Both of these will result in the release of proinflammatory cytokines and large inflammatory mediators that contribute to endothelial dysfunction underlying atherosclerosis.

Consent for publication

All authors consent to publish this manuscript and this review has not been published before.

Conflicts of interest

None conflict of interest was declared.

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List of Abbreviations

DM	Diabetes Mellitus
NHANES	National Health and Nutrition Examination Survey
PMN	Polymorphonuclear
ICAM	Intracellular Adhesion Molecule
AGE	Advanced Glycosilation End Products
LPS	Lipopolysaccharide
NK-kB	Nuclear Factor Kappa B
PDGF	Platelet-Derived Growth Factor
TGF-β1	Transforming Growth Factor-β1

bFGF	basic Fibroblast Growth Factor
MMP	Matrix Metalloproteinases
PKC	Protein Kinase C
MSR	Macrophage Scavanging Receptor
RAGE	Receptor for Advanced Glycosilation End Products
IL	Interleukin
TNF-α	Tumor Necrosis Factor- α
ROS	Reactive Oxygen Species
JNK1	c-JUN N-terminal Kinase
IKKβ	Nuclear Factor Kappa-B Kinase
IRS	Insulin Receptor Substrate
PPAR	Peroxisome Proliferator-Activated Receptor
CAP	Catabolite-bound Activator Protein
GLUT-4	Glucose Transporter Type 4
AMPK	Adenosine Monophosphate Dependent Kinase
PGE2	Prostaglandin E2
TLR	Toll-Like Receptor
MHC	Major Histocompability Complex
Th1	T helper 1
VCAM	vascular cell adhesion molecule
PAI	Plasma Activator Inhibitors
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein

Appendix. ASupplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2019.03.023.

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