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Literature Review

MECHANISMS OF PERIODONTITIS-INDUCED ATHEROSCLEROSIS

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ABSTRACT

Nowadays CVD become the most common cause of death in US and worldwide. Atherosclerosis plays an important role in CVDs pathogenesis. Atherosclerosis decreases the elasticity of the vascular. Atherosclerosis shares the same risk factor as CVD, in which obesity, hyperlipidemia, hypertension and lack of physical activity may initiate it. However, 50% of all CVD patients are lack of the usual causes of CVD. The purpose of this review is to reveal the mechanism of periodontitis-induced atherosclerosis. Inflammation and autoimmune disease might play an important role in initiate the CVD. Periodontitis is one of the oral diseases which can cause systemic inflammation and may induce the atherosclerosis. Porphyromonas gingivalis (Pg) which is the major cause of periodontitis can induce it by expressing protein gp130 in its fimbriae. Periodontics patients are prone to have bacteremia by daily routine oral hygiene activity. Chronic bacteremia may alter the endothelial physiology, which is resulted in neointima formation, EC dysfunction, and lipid accumulation. It is concluded that periodontitis may play an important role in initiation and progression of atherosclerosis.

Key words: *Pg's fimbriae, bacteremia, cytokines, endothelial dysfunction, atherosclerosis*

INTRODUCTION

In the 20th century, due to developments and inventories in medical field, the human's life expectancy was dramatically increased. There was a major shift in the causes of illness and death throughout the world. In 1950, infections were the most common causes of death. A century ago, CVD accounted for less than 10 percent of all deaths. Nowadays, CVD become the most common cause of death in US[1] and worldwide.[2,3] It causes global epidemic worldwide.[4] Approximately 30 percent of deaths worldwide are caused by CVD,[5] including nearly 40 percent in high-income countries and about 28 percent in low- and middle-income countries.[2] In 2006, it was reported that more than 81 million of US citizens got CVD.[6] Driven by industrialization, urbanization, and associated life changes; e.c smoking, high calories and lipid intake, these ongoing transition are occurring around the world of all races, ethnic groups, and cultures at an even faster rate than last centuries and may lead to cause CVD.[7] The risk of having CVD will increase in obesity, hypertension and impairment of lipid metabolism.[2,7]

Atherosclerosis is mainly caused by decreasing in vascular elasticity and lumen.[8,9] Atherosclerosis is known to share the same risk factors as CVD, which obesity, hyperlipidemic condition, hypertension and lack of physical activity may initiate it.[8] However, 50% of all patients with CVD were lack of known risk factors.[10] Autoimmunity[11] and systemic inflammation[12-16] were supposed to be possible to play a role ini CVD's initiation and progression. Infection and bacterial products may play an important role in atherosclerosis pathogenesis.[17,18] Immune response and inflammation factors, e.c. CRP, interleukin, and chemokines were suggested to be the causes and markers in atherosclerosis lesions.[19,20]

Atherosclerosis had been proven to be induced by periodontopathogen from periodontitis.[21-28] Inflammation in mouth may cause systemic inflammation, which is indicated by the elevation of CRP in the body,[29,30] which is functioned as markers,[31,32] predictors of CVD,[33,34] and

may induce atherosclerosis lesions.[35–38] Focal infection in mouth may induce atherosclerosis lesions by initiate systemic and humoral immune responses.[39]

Periodontopathogen bacteria may widely spread to another part of the body. Bacterial inoculation from atherosclerotic plaque have proven the presence of *periodontopathogen* bacteria such as *Porphyromonas gingivalis*, *Actinobacillus actinomycetem comitans*, dan *Bacteroides forsythus.*[39,40]

This article reviews the current state of knowledge concerning the direct role of periodontitis in developing atherosclerotic lesions. Better understanding of these diseases and long-term research will be needed to rehabilitate these lesions in the future.

LITERATURE REVIEW

Periodontitis is defined as an inflammatory disease of the supporting tissues of teeth caused by specific microorganism or group of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both.[41] Chronic periodontitis is the most common form of periodontitis, which is associated with plaque accumulation. It generally has a slow to moderate rate of disease progression, but periods of more rapid destruction may be observed. Systemic disease such as diabetes mellitus and HIV infection may influence the host defenses, and environmental factors such as cigarette smoking, and stress also may influence the response of the host to plaque accumulation.[41–44]

Although many factors may influence the onset of periodontitis, periodontopathogen bacteria play a key role in the onset and severity of periodontal diseases.[42,45,46] PG is an anaerob obligat,[47] non-motile,[48] pleiomorphic bacteria, and posses a capsul.[49] PG shows a strong proteolitic activity, grows in anaerobic environment, and shows dark pigmentation (brown, dark green, or black) on blood agar.[50] PG has fimbriae[51] which mediates adhesion.[52] The capsul serves a protection to prevent it from phagocytosis[53] and triggers the secretion of IL-1, IL-6, dan IL-8.[48]

The end products are various kinds of amino acid and endotoxin, haemolysin, collagenase and proteases which may damage immunoglobulins, complements, and heme-sequestering proteins: a protein which inhibits collagenase activities.[42,53,54] PG was shown to be able to invade epithelium,[51] soft tissue, inhibit PMN cell migration across the epithelium[55] and may cause cytokine degradation in mammal cells.[42,53]

Physiology of Blood Vessels

Arteries are strong, elastic vessels that are adapted for transporting blood away from the heart under high pressure to all parts of the body.[56] These vessels subdivide into progressively thinner tubes and eventualy give rise to the finer branched arteriolles.[56] The wall of an artery consists of three distinct layer, or tunics; tunica adventitia, tunica media and tunica intima as the innermost layer.[57-59]

Tunica adventitia is the outermost layer of the arterial wall. Researches were conducted, as it was known to have a potential role in homeostasis and pathological effects on the artery.[8] This outer layer is thin and chiefly consists of irregular connective tissue[57] and collagenous fibers.[8] Vasa vasorum and nerve endings are usually located on this outermost layer. This layer attaches the artery to the surrounding tissues.[57] Cell populations in this layer are relatively rare compared with those in the other layer.[8] This layer mainly consists of fibroblast and mast cell.[8] In clinical research with animal, this layer was suspected to induce atheroma and aneurysm lesions.[8]

Tunica media, located between tunica intima and tunica adventitia, is the thickest layer of the arterial wall.[57] The artery, especially the aorta, is surrounded by tunica media, which has SMC layer[57] and elastin as the extracellular matrix.[8] This structures make the artery very elastic and enable it to withstand against the force of blood pressure, and at the same time, tp stretch and accommodate the sudden increase in blood volume that accompanies ventricular contraction.[57] These structures are also important in maintaining the integrity of arterial branches.[8]

On the smaller artery; where the SMC in tunica media are not as strong as those in aorta; elastin are arranged in continuous layer, not in circular around the vessel wall.[8] On the capillaries, the tunica media becomes very thin, only single cell thick with some SMC's cells.[57]

Tunica intima is the innermost layer of the arterial wall.[8] The wall is covered with simple squamous epithelium attached to the basal lamina, fibrous connective tissue which is rich in elastic and collagen fibers,[57] known as endothelium.[56] In all newborn species, tunica intima is very thin.[8] However, in adult, its structure becomes more complicated and heterogen.[8] Thin endothelial layer is attached to basalis membrane which is contain non-fibril collagen e.c collagen type IV,[8] proteoglycan (chondroitin and dermatan sulphate), elastin, protein plasma,[9] laminin, fibronectin, and the other extracellular matrixes. As becoming older, the intimal layer will be developed more complicated, where it will be contained SMCs and fibril interstitial collagen, like tipe I and III. The more complex intimal layer are known as intimal thickening, which is the common characteristic in adult's vessels.[8]

Endothelial Cells (ecs)

ECs are the most important cells in tunica intima because they are fundamental to the maintenance of vessel wall homeostasis and normal circulatory function.[8,58] The endothelial lining of an artery provides a smooth surface that allows blood cells and platelets to flow through without being damaged.[57] ECs have five major role: 1) it is a metabolicaly active secretory tissue;[58] 2) to provide a smooth surface in the artery and secrete some anti-coagulants and anti-thrombotic agents;[8,57] 3) as a barrier

to the indiscriminate passage of blood constituents into the arterial wall;[58,61] 4) to help in controlling growth and elasticity of the vessels;[61] and 5) to adjust the vascular tone by strictly regulating the paracrin and autocrine.[61]

ECs may release vasoactive factors, which control the lokal vessel constriction and dilatation.[58] The vasodilator includes nitric oxide, prostacyclin, EDRF, and EDHF; and the vasoconstrictor includes endothelin, prostanoids and angiotensin II.[58,59,61] ECs are also able to secrete some procoagulants agents as factor VII, factor Va, factor von Willebrand's, tissue factor and PAI-1;[58,61] and also some fibrinolitic agents as thrombomodulin, tissue plasminogen activator, heparin sulfate proteoglycan, which acts like heparin as a co-factor for antithrombin III, a coagulation-inhibitor by binding and inactivating thrombin.[8]

NO is known as a potent EDRF[58] which inhibits vasoconstrictors' effects.[8] NO is also inhibit platelets aggregation and adhesion, leukocyte infiltration and adhesion, and also SMCs' migration and proliferation.[59] NO is also able to prevent LDL oxidation.[61,62] NO is produced in ECs by oxidating guanadino nitrogens L-arginine[58,61] which is catalyzed by eNOS enzyme in *caveolae*.[62] The presence of caveolin-1 proteins, which will bind the calmodulin, will inhibit the eNOS activity. Chemically bond of Ca^{2+} ion and calveolin will substitute caveolin-1 and thus increases NO production.[59,62] Some co factors like NADPH,[59,62] BH_4,[58,63] flavin nucleotide and oxygen molecule[64] are needed in NO synthesis. BH_4 is needed in electron transfer process from heme enzyme group in L-arginine to produce NO.[59,62]

In the atherosclerotic lesions, endothelium might be altered structurally and functionally. ECs may be more permeable to lipoproteins, hyperadhesive to leukocyte cells, and alter their homeostasis function in producing local pro- and antithrombotic, growth factor stimulator and inhibitor, and also vasoactive enzyme. These alterations are known as endothelial disfunctions, which have a big impact in initiation, progression and complications of atherosclerotic lesions.[9,60]

Smooth Muscle Cell (SMC)

SMCs have a lot of function in maintaining normal homeostasis vessels.[8] SMC's are responsible for vasoconstriction and dilation in response to normal or pharmacologic stimuli, homeostasis mechanisms to deliver blood to all parts of the body.[56,57] The arteries have more SMCs than the veins do, which makes the arterial wall much thicker. SMCs are innervated by simpathic nerves through adrenoreseptor with norepinepineprine as endogenous agonis. They also synthesize collagen, elastin, and proteoglicans; and elaborate growth factors and cytokines; which may alter morphology, proliferation rate and cell migration on the vessel's wall.[65,66]

SMCs are involved in pathogenesis of atherosclerosis and become a target in cardiovascular management therapy.[8] In big arteries with atherosclerotic lesions, SMC's contraction will cause vasospasm and impede the blood flow.[8] Normal SMCs synthezise a lot of extracellular matrix to maintain normal homeostasis, and prevent atherosclerosis.[65]

Normally, SMC's rarely proliferate. The rate of cell proliferation and necrosis are very low under the normal condition. Extracellular matrix will always be in homeostasis circumstances. Synthesis and dissolution are always the same rate; there will never be cell accumulation or atrophy.[8]

Under the pathologic condition, the cells may proliferate and migrate; thus may induce hyperplastic lesions such as atherosclerosis and re-stenosis.[8] SMCs' migration and proliferation are stimulated by PDGF, endothelin-1, thrombin, FGF, IFN-γ, and IL-1. On the contrary, NO, heparin sulphate and TGF will inhibit this process.[66]

Atherosclerosis

Atherosclerosis is disease where the artery loses its elasticity.[9,55,56] Atherosclerosis was defined as a chronic immunoinflamatory, fibroproliferative, disease which have been drived by lipids.[9] It affects primarily the intima of medium-sized and large arteries, resulting in intimal thickening, and may lead to luminal narrowing and inadequate blood supply.[9] Endothelial disfunction is the main cause of this disease.[56] Atherosclerosis forms atherosclerotic plaques,[56,66] which in turn, will cause lumen narrowing,[9] and obstruction;[66] weaken the big and medium-sized arterial structure;[9] impede the blood flow;[56] and reduce its elasticity.[56] As the name implies, mature atherosclerotic plaques consist typically of two main components: one is lipid-rich and soft (*athére* is Greek for 'gruel' or 'porridge') and the other is collagen-rich and hard (*skleros* is Greek for 'hard').[9,66] The flow-limiting potential of an intimal plaque may be modified by reactive changes in the underlying media and adventitia that may be attenuate (positive remodeling) or accentate (negative remodeling) the luminal obstruction and consequent hemodynamic impact of the plaque.[9] Furthermore, enhanced vasoconstriction and reduced vasodilator capacity associated with atherosclerotis can further contribute an additional dynamic component to luminal obstruction.[9]

The aggregation of lipoprotein on the tunica intima is considered as the early step of atherosclerosis. On this early step, atherosclerosis will apparent as a fatty streak consists of foam cells filled with lipid.[8,9,60,66,67] Lipoprotein will bind proteoglycan on the tunica intima where it will be stabilized on this layer. Proteoglycan-binded lipoprotein will be oxydated easier and undergo chemically alterations which were believed to be the early pathogenesis of atherosclerosis.[8,9]

The other researches showed that the increasing of endothelial permeability mainly caused LDL aggregation in the intima.[9] Some factors, i.e NADH/NADPH oxydase which is released by vascular cells; lypoxigenase that is released by infiltrating leukocytes; and myeloperoxidase may cause oxidative stress in the atheroma.[9]

Atherosclerosis lesions is also composed of leukocytes accumulation as a result of endothelial dysfunction.[8] Normal endothelial cells are able to prevent leukocytes

adhesion on their surfaces.[56] Eventhough in the inflamed area, leukocytes infiltration is started in venous, not in the artery.[9] In hypercholesterolemic condition, leukocytes adhere on the endothel and have a diapedisis on the EC junction into the tunica intima, where these leukocytes start lipid accumulation and become foam cells.[9,66] Besides the monocytes, lymphocytes T also tend to accumulate in atherosclerotic lesion in human and animals.[8,9] Accumulation of monocyte and lymphocyte T were stimulated by leucocyte adhesion melocule secreted by EC surfaces.[8,9,66,68]

DISCUSSION

In many epidemiological studies, periodontitis was proven to play important roles in initiation and progression of CVD,[69,70] by chronic infection on the blood vessels[20–29] or by the elevation of body's CRP level.[29–39] The prevalence of chronic periodontitis was very high among populations, especially in chronic form.[41–44,69–72] Chronic periodontitis is usually neglected and undetected, because it is lacked any clinical signs and symptoms.[41,42,71]

In chronic gingival and periodontal infection, the cappilarries are more fragile, which make it possible for microorganisms in plaque and calculus to be spread along with blood flow.[73] Chronic bacteremia from periodontitis may be easily happened from the daily activities e.c brushing, chewing,[73] and routine dental procedures like scaling and root planning, or the other treatments like endodontic, orthodontic and dental extraction.[74]

Many studies proved that atherosclerosis plaques contained numerous periodontopathogen bacteria,[3,40,76] especially PG.[39,40] Researches have demonstrated that PG induction may invade endothel and may initiate atherosclerosis in pigs.[75] The presences of PG in atheroma and human carotid aorta had been detected by immunostaining and PCR.[76,77] PG was known to have fimbriae, which allowed it to invade[51] and stimulate host response to produce citokynes,[52,78-81] and may be in latent phase[82] to cause chronic infection in EC and SMC.[75] Chronic infection was known to be able to cause endothelial dysfunction.[21–38]

PG's fimbriae secretes protein, called gp130,[83] which facilitate PG to invade EC and trigger celluler immune response.[84] The host will secrete TNF,[85] IL-1, IL-6, IL-10, and IL-12[86–88] by TLR's stimulation.[26,85,88–90] TLR is part of immune system, which will respond to PAMP.[91] Protein in PG's fimbriae may act as PAMP which triggers immune response by activating TLR, which, hence stimulate the host to produce cytokines.[86,91]

Tunica Intima Thickening

Atherosclerosis may emerge from physiologic changes in EC. In early phase, atherosclerotic lesions is started by thickening of tunica intima (neointima).[8] Epidemiologic studies reported a positive relationship between PG infection and the formation of neointima.[92] Mechanism of PG infection and neointima thickening was remained unclear. It was supposed that TNF stimulation by protein gp130[83] might facilitate lymphocyte and monocyte adhesion[85] and also stimulate cytokines and growth hormone in host cells.[86–93] Neointima formation is mainly caused by accelerating proliferation rate, inhibiting apoptotic process, and increasing SMC migration to the neointima layer.[8]

In EC, PG invasion may accelerate TNF[94] and IL-6 synthesis,[68] which in turn may initiate atherosclerosis lesions by accelerating SMC proliferation,[68] stimulating tissue factor,[95] increasing platelet aggregation[95] and increasing the level of fibrinogen in blood.[93] TNF may initiate neointima hyperplation through p55 pathway.[94] TNF was also known to induce FGF and NFκB secretion, SMC proliferation and neointima formation.[96]

NFκB may inhibit apoptotic process[97–99] by suppressing the activity of gen p53,[100] which is responsible to induce the apoptotic process.[101] Its mechanism was remained unclear, but it was assumed to have the same mechanism as gen IE from CMV. Gen IE was able to bind gen p53 and disturb transcription process by extracting this gen from nucleus by cytoplasmic sequestration process.[102]

Growth hormone, from TNF induction may increase proliferation rate.[96] Rupture endothel will secrete MCSF,[103,104] which will increase fibroblast proliferation rate, increase the production of IL-1,[105] induce the synthesis of vasoactive factors, growth factor, vascular adhesion molecules, and chemokines.[106] Infection may increase the production of FGF and PDGF almost twice higher.[68] MCSF and IL-1 induction in proliferation process of fibroblast and SMC were supposed to be performed via cyclooxygenase pathway.[68,107]

The formation of neointima mass is also caused by SMCs migration from tunica media and tunica adventitia into the tunica intima.[8–10] Infections may increase PDGF reseptors sensitivity which result in SMC thickening in tunica intima. Besides FGF and PDGF, there some factors are known to play roles in SMC migration, they include endothelin-1, thrombin, IFN-γ, TGF and IL-1.[8,9,58,59,61,66] Whereas NO, heparat sulphate, and TGF-β will act as antagonists to inhibit SMC migration.[8,9,61,62]

Injured ECs[68] and the presences of either TNF[108] or CRP[109] may trigger the synthesis of cell adhesion molecules e.c VCAM-1 and ICAM-1.[68] VCAM-1 will interact with VLA-4, which is exclusively sinthezised by monocyte, T cell, and leukocyte accumulated in atheroma.[8] VCAM will facilitate monocyte adhesion[8] and infiltration into injured arterial wall and may increase SMCs proliferation rate.[66,109]

ICAM-1 is immunoglobulin secreted by ECs surfaces. The role of this molecule is remained unclear as it is produced only in very small amount, and the leukocyte which will be bound is remained unknown.[8] It was supposed that ICAM-1 will increase VCAM-1 production.[110]

Once the leukocyte binds the EC, it needs a signal to penetrate into EC and enter the arterial wall.[8] Leukocyte

migration would be impossible without the presence of protein molecules known as chemoattractant cytokine or chemokines. At the early phase of atherosclerosis, chemokines attract monocyte into the atheroma.[8] MCP-1 facilitate monocyte chemotactic into the arterial wall.[8,66] MCP-1 is a kind of chemokines produced by ECs as a response to CRP,[111] MCSF,[68] and oxidized lipoprotein, and the other stimulus.[112,113]

The disturbances in local blood flow may result in some physiologic changes, which are responsible for predilection lesion of atherosclerosis.[8,9,58,66] Atheroma may act as an obstacle in local blood flow and causes local blood turbulances that will inhibit ECs to produce superoxide dismutase enzyme and eNOS, which are known to have a protective effect against the atherosclerosis.[58,62,66,101] Superoxide dismutase enzyme is able to reduce oxidative stress by catalyzing catabolic reaction on reactive superoxide anion into oxygen and hydrogen peroxide, where this hydrogen peroxide will be converted to be water and oxygen.[58,101]

eNOS produces NO as an endogenous vasodilator.[62] Besides as vasodilator, it also suppresses VCAM-1 production from inflammation-induced ECs.[8,114] NO may also act as anti-inflammatory agent by increasing IκBα production,[115] an intracellular inhibitor, which will disturb the NFκB transcription process.[8,115,116] NFκB regulates various genes, which are responsible in inflammatory process and especially in atherosclerosis.[8,114-116]

Endothelial Dysfunction

Prolonged infection in blood vessels may result in endothelial dysfunction.[8-10,17,59-62] Normal ECs posses an antithrombotic effect, which make them able to release and synthezise substances as heparin sulphate PGI_2 , NO, plasminogen activator, and thrombomodulin.[8,9,59-62] Infectious agent may change ECs phenotype, from anticoagulant in usual, to be procoagulant.[8-10,62,66,117] Bacteria and its product, endotoxin, may cause endothel to produce tissue factor which in turn it will activate extrinsic blood clotting cascade,[117] increase thrombin formation, and platelets aggregation and at the same time these infections may suppress the synthesis of PGI_2, and thrombomodulin.[8,9] Inhibition of prostacyclin happened as the presence of CRP which is suppressed PGI_2 production which may cause disturbance in TBB_2/PGI_2 ratio.[35] The disturbance in the ratio of TBB_2/PGI_2 may facilitate platelets aggregation.[35]

The other important role of EC is to have a local vasodilatation.[8-10] A pilot study had demonstrated that infection might disturb local endothelial vasodilatation response. This dysfunction is mainly caused by the disturbance in NO and non-NO pathways. Disturbances in NO pathways automatically will increase platelet aggregation, leucocyte adhesion and SMCs proliferation.[61] Decreased NO production will increase LDL oxidation, where oxidated LDL may increase caveolin-1 production and inhibit NO synthesis by inactivating eNOS.[62] Macrophage is also able to produce ROS[10] which will inactivate NO[118,119] and destroy BH_4.[62]

Vascular damage was believed to induce atherosclerosis and be responsible for its progression.[8–10,66] In in-vitro study, it was found that PG was able to adhere and invade on vascular wall,[52,78–81] which was indicated that PG may cause vascular damages.[82] Endothel damage may cause ECM, beneath it, become exposed. Platelets may have a direct contact to ECM on that area which makes them active.[117] Activated platelets will stimulate intrinsic pathway of coagulation cascade and activate fibrin-forming process.[117]

Lipid Accumulation

The presence of infection may facilitate lipid accumulation. Infection was known to be able to reduce cholesterol ester hydrolytic activity[120,121] and increase the scavenger reseptor susceptibility.[122] Infection on human SMCs may increase LDL oxidation mediated by scavenger reseptor. Foam cells accumulation and the level of cholesteryl ester will dramatically increase if infected macrophages are incubated in an area with a high LDL level.[122]

ROS may cause LDL oxidation in arterial wall, and then the oxidated LDL,[62] mediated by scavenger receptor, will be absorbed by macrophage and form foam cells.[123] MCSF may increase cholesterol uptake by macrophage and delayed the apoptosis process, which may cause foam cells forming.[68]

It was summarized that atherosclerosis may be periodontically induced. PG, one of the periodontopathogens, was supposed to induce atherosclerosis via bacteremia. Pg with its fimbriae may invade and stimulate various kinds of cytokines, which are caused neointima proliferation, endothelial dysfunction, and lipid accumulation. These were facilitated with endothelial physiologic switching that tends to be pro-thrombotic; lipoprotein accumulation, especially LDL; chemically altered LDL via oxidation; monocytes and platelets adhesion on the vessel's wall; and also the inflammation factors released from platelets and macrophages.

This review was not subjected to prove that periodontitis was the main cause of atherosclerosis. It was supposed to increase awareness of periodontitis as a risk and a predisposing factor for atherosclerosis. Although this issue had not been clinically proven, but in my opinion it was important to reduce any oral-origin infection as our effort to maintain healthy mouth and reduce the risk factors for atherosclerosis, otherwise we might miss a chance to help our patients suffering from cardiovascular disease.

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