DOI : 10.35124/bca.2020.20.S1.2875

Biochem. Cell. Arch. Vol. 20, Supplement 1, pp. 2875-2878, 2020 | www.connectjournals.com/bca | *ISSN 0972-5075*

ELEVATION OF C-REACTIVE PROTEIN IN CHRONIC PERIODONTITIS PATIENT AS CARDIOVASCULAR DISEASE RISK FACTOR

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(Received 20 March 2020, Revised 9 May 2020, Accepted 11 May 2020)

ABSTRACT : Periodontal disease is an oral health problem with a high prevalence in Indonesian society about 96.58%. Chronic Periodontitis (CP) is an oral health problem, which if left untreated can lead to tooth loss, bone loss and cardiovascular disease risk factor. *Porphyromonas gingivalis* often found in patients with CP. *P. gingivalis* can produce endotoxin like Lipopolysaccharide (LPS) that can stimulate the release of pro-inflammatory cytokines such as Tumor Necrosis Factor-á (TNF-á), interleukin (IL-1â, IL-6 and IL-8) and indirectly can stimulate the liver to produce acute-phase proteins like C-Reactive Protein (CRP). CRP binds to damaged cells, healing phase, and activate neutrophils to the endothelium chemotaxis. The release of cytokines and CRP initiate the formation of atherosclerosis by circulating monocytes attached to the endothelium wall. Attachment endothelium is mediated Intercellular Adhesion Molecule-1 (ICAM-1), Endothelial Leukocyte Adhesion Molecule (ECAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1). Formation of Atheromatous Plaque (AP) can lead to blood vessel walls become thick so the lumen of blood vessels become narrow, resulting in increased blood flow. Thrombosis often occurs after the outbreak of the AP, occurred activation of platelets and the coagulation pathway. Platelets and fibrinaccumulation can cover the blood vessels causing tissue ischemia such as anginapectorisormy ocardialin farction. This narrative review describe the elevation CRP in CP as a cardiovascular disease risk factor. There was an increased level of CRP in CP patient. Elevation of CRP level in periodontitis can be a risk factor of cardiovascular disease.

Key words : Cardiovascular disease, C-reactive protein, chronic periodontitis, *Porphyromonas gingivalis*.

INTRODUCTION

Periodontitis is a widespread disease in the society (Nugraha *et al*, 2019). Periodontal disease is a dental and oral health problem which if left untreated can lead to tooth loss and even cause systemic diseases such as cardiovascular (Vieira, 2014). In Indonesia, periodontal disease is a dental and oral health problem with a high prevalence in Indonesian society at 96.58% (Tedjosasongko *et al*, 2019)

Periodontitis is an infectious disease in the tissue supporting the teeth, caused by bacteria, and causing damage to periodontal ligaments, alveolar bone, forming a pocket, recession, or both (Nugraha*et al*, 2019b; Sari *et al*, 2019; Prahasanti*et al*, 2020). One classification of this disease is the chronic periodontitis. Chronic periodontitis is aslow progressive typeof disease. It is an infectious disease that is generally caused by the bacteria *Porphyromonas gingivalis. P. gingivalis* acts as an antigen that stimulates inflammatory cells released to the capillaries to eliminate the antigens. Lipopolysaccharides (LPS) as endotoxin was released by *P. gingivalis* that can stimulate the secretion of inflammatory cytokine *e.g* Interleukin and Tumor Necrosis Factor-á (TNF-á) (Carranza, 2002; Rose and Mealy, 2004; Ridwan *et al*, 2018).

LPS of *P. gingivalis* and the others periodontal bacteria may stimulate the C-reactive protein (CRP) relseased from liver as acute inflammation response. The CRP can increase the deposit plaque in the injured blood vessel. CRP stimulate the healing and repair phase and activates chemotaxis of neutrophils especiallyinside the endothelium. Elevated serum CRP levels are a marker of systemic disease and are a risk factor for cardiovascular disease. The release of cytokines and CRP initiates the

formation of atherosclerosis by circulating monocytes attached to the endothelium, the attachment of this endothelium is mediated by Intercellular Adhesion Molecule-1 (ICAM-1), Endothelial Leucocyte Adhesion Molecule (ECAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) (Reyes *et al*, 2013; Boyapati *et al*, 2018).

Periodontitis and atherosclerosis have potential pathogenic mechanisms. Both diseases have complex and multifactorial etiology. Periodontitis is a chronic inflammation that is preceded by microorganism plaque can induce the atherosclerosis. Atherosclerosis can decrease the blood vessel flow. Eventually, atherosclerotic lesions may split and/or rupture, resulting in narrowing of the arteries. Thrombosis often follows platelet activation and coagulation pathways. Accumulation of platelets and fibrin can cover blood vessels that lead to tissue ischemia such as angina pectoris or myocardial infarction (Li *et al*, 2017; Söder *et al*, 2016).

Chronic periodontitis

Chronic periodontitis (CP) is a chronic inflammation of the tooth-supporting tissue (periodontium). The CP can cause destructive periodontal tissue. *P. gingivalis, Prevotella intermedia* and *Bactoriodes forsytus* are pathogenic bacteria as the etiology of chronic periodontitis (Benachinmardi *et al*, 2015). The systemic factors, such as diabetes mellitus, smokers, or stress were known as CP risk factor as well. Diabetes mellitus as systemic disease can interrupt and disturb the host immunity response, delay wound healing and alveolar bone remodeling (Rezkita *et al*, 2020). In addition, there was a degeneration of tissue and cells in the diabetes mellitus patient (Narmada *et al*, 2019; Suciadi *et al*, 2019).

The pathogenic bacteria accumulation and activity that attached on the surface can induce the host immunity reaction that lead to formation of periodontal pockets and alveolar bone loss (Ridwan *et al*, 2019). The CP diagnosis sometimes is quite complicated to identify because no symptoms or complaints from the patient. The detection of associated risk factor is recommended to minimalize the CP morbidity. The course of CP has been explained as the consequence of interactions between genetic, environmental, microbial and host factors (Carranza, 2002; Arutyunov *et al*, 2020).

Periodontitis is a disease caused by several factors or multifactorial. The main factor in the occurrence of periodontitis is the presence of plaque accumulation in the teeth and gingiva. Several factors contribute to an increased risk of developing the disease, including (1) Local factors. The accumulation of plaque on the teeth and gingiva at the dentogingival junction is the initial initiation of the agent in the etiology of chronic periodontitis. Bacteria usually have a local effect on cells and tissues in the form of inflammation. (2) Systemic factors: most chronic periodontitis occurs in patients who have systemic diseases that affect the effectiveness of the host immunity response. Diabetes mellitus is an example of a disease that can increase the severity of this disease; (3) The environment and smoking behavior can increase the morbidity or severity of this disease. In smokers, there is more loss of attachment and bone, more furcation, and deepening of the pocket. (4) Genetic. Usually, periodontal disease often occurs in a family, this might indicate the presence of genetic factors that influence chronic periodontitis (Van Dyke, 2009).

Characteristics found in chronic untreated periodontitis patients include supragingival and subgingival plaque accumulation, inflammation or swelling in the gingiva, bleeding in the gingiva, periodontal pocket formation, attachment loss of periodontal ligament, alveolar bone loss, suppuration. The dental plaque or dental calculus accumulation can be found in CP patient (. In addition, loss or changes of gingiva stippling into blunt and flat (crater papilla), discolor of gingiva from coral pink into red pale or magenta also can be found.The periodontal pocket depth, and bone loss both vertical and horizontal, tooth mobility wasoccurred in the CP. The examination of chronic inflammatory changes may help to diagnose the CP beside the presence of periodontal pockets and attachment loss (Armi and Cullinan, 2010; Nath and Raveendran, 2011).

At the beginning of periodontitis, pathogenic periodontal tissue bacteriacolonized and accumulate in the gingival sulcus, known as chronic inflammatory plaque or biofilm that trigger chronic inflammation response. As plaques mature, plaque and bacteria become more pathogenic and the inflammatory response changes from an acute to a chronic phase (Ridwan *et al*, 2018).

Periodontal disease as a Risk Factor for cardiovascular disease

There was a correlation between oral health and systemic health based on previous study. The periodontitis and cardiovascular disease may have an association. Cardiovascular disease generally starts with atherosclerosis. Risk factors such as the presence of local infection periodontitis which is a chronic inflammatory reaction have become one of the mechanisms that can cause atherosclerosis (Hegde and Awan, 2019; Li *et al*, 2017).

The pro-inflammatory cytokines might have secreted

during the periodontitis. Those pro-inflammatory cytokines such as TNF-α andIL-1β (Miranda *et al*, 2019). LPS that secreted by *P. gingivalis* in the subgingival plaque in severe CP can enhance the pro-inflammatory cytokine level which play an important role in the atherosclerotic heart disease risk factor either through direct action on blood vessel walls or indirectly by means of induce the liver to secrete acute phase of protein such as CRP (Kurita-Ochiai and Yamamoto, 2014).

Periodontitis and atherosclerosis both have complex and multifactorial etiology. Atherosclerosis is a thickening of the arteries, occurs in the inner lining of blood vessels, thickening under the intima layer consisting of smooth muscle, collagen, and elastic fibers. LPS of *P. gingivalis* cause stimulate infiltration of inflammatory cells into arterial walls, the proliferation of smooth arteries, and intravascular coagulation. This change is identical to the events that can be observed in atheromatosis. Periodontal disease causes chronic systemic infections, the bacteriemic state begins the body's response by affecting coagulation, endothelial and integrity of blood vessel walls, platelet function, this causes atherogenic changes and the thromboembolic occurs (Kurita-Ochiai *et al*, 2015; Ketabi *et al*, 2016).

These periodontal microbes stimulate pro-inflammatory cytokines and tissue growth factors in arterial walls such as increased fat accumulation, Low-density lipoprotein (LDL) by stimulating macrophage receptors or LDL receptors. The periodontal pathogenic bacteriasin directly influence the growth and development of atherosclerosis with systemic effects without directly damage the endothelial blood vessels, *i.e.* by releasing endotoxins and lipopolysaccharides into the circulation which can indirectly damage the arterial endothelial arteries or their immune responses and produce abnormal lipid forms that affect the occurrence of atherosclerosis or can affect the arterial environment into procoagulant levels produced in acute thrombus above the blood vessel plaque susceptible to injury and can cause acute ischemia (Hedge and Awan, 2019; Boyapati *et al*, 2018).

LPS of *P. gingivalis* can enhance the LDL to form the large foam cells. The Foam cells is an important characteristic of cardiovascular disease (Kim *et al*, 2018). In addition, LPS recruit the pro-inflammatory cells to the blood vessel and activate the cascade of the inflammatory through the secretion of IL-1β and TNF-α in the vascular endothelium directly and increase the proliferation of smooth muscle, aggregation of platelet, degeneration of fat and plaque deposition on the blood vessel walls surface. Those events can lead to the narrowed and constriction of blood vessel (Boyapati *et al*, 2018). In addition, coagulation factor X, prothrombin, CRP tend to increase induced by the large quantities of proteolytic enzymes from *P. gingivalis*. Previous study has been found that dental plaque might entered the bloodstream during the bacteremia that may directly induce the systemic inflammation. Platelet activation and aggregation can have activated by LPS of *P. gingivalis* that may contribute to hypercoagulability, thrombosis, thromboembolic (Kurita-Ochiai and Yamamoto, 2014). In addition, the pathogenic periodontal bacteria presence in the bloodstream may increase the thrombus formation and embolus risk (Karnoutsos *et al*, 2008). The CP might contribute to the mechanism of atherosclerosis directly or indirectly. Chronic inflammation has an important role in the development of atherosclerosis, both directly and indirectly (Ketabi and Meybodi, 2016).

CONCLUSION

Based on this narrative review, the elevation of C-Reactive Protein level in the Chronic Periodontitis patient can be the risk factor of cardiovascular disease. Dentist and physician should collaborate together to overcome these problems.

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