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Association between apical periodontitis and risk of cardiovascular diseases – a review of the literature

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ABSTRACT
The aim of the study was to present views on the correlation between apical periodontitis (AP) and the risk of cardiovascular diseases (CVD) based on a review of the available literature. A review of PubMed for papers from the years 2011–2020 was conducted. Searched phrases included: apical periodontitis cardio-vascular diseases, apical periodontitis endothelial dysfunction, apical periodontitis myocardial infarction endodontic lesion CVD. Based on the literature review, it is suspected that there is a positive correlation between AP and the risk of CVD. Further studies are required to examine the prognostic impact of the treatment of AP on CVD.
Keywords: apical lesion; root canal treatment; cardiovascular risk; inflammation.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in Poland and across the world. In 2016, the standardized death rate from ischemic heart disease in the EU-28 was 119 per 100,000 inhabitants (source: Eurostat). Ongoing inflammatory processes in the body have been recognized as a factor leading to atherosclerotic plaque formation, which is the main cause of ischemic heart disease [1]. Finding risk factors confirmed by research can contribute to greater CVD control.

Apical periodontitis (AP) is the consequence of a bacterial infection of the endodontium (dentin and tooth pulp) and frequent pathological changes in the jawbone. These bones differ from other human bones due to the presence of teeth which form a direct path towards the bone marrow. At the same time, in both the maxilla and the mandible, there are no additional epithelial barriers protecting from the invasion of infectious and inflammatory factors induced by pathologically altered tooth pulp [2].

The inflammatory process of periapical tissues is initiated by an interaction between bacterial cell wall components and host cells. As a result of activation, the cells secrete a number of cytokines that promote the development of inflammation. This is a biological defense mechanism aimed at eliminating pathogenic substances, removing dead tissue, and initiating the healing process. Pro-inflammatory factors mainly include interleukin-1 (IL-1) and tumor necrosis factor (TNF) as well as IL-6, IL-11, IL-8 and chemokines [3, 4]. If the acute form of inflammation is not controlled, it can develop into a chronic form. In this case, the main inflammatory mediators are cytokines, chemokines, eicosanoids, growth factors, reactive oxygen species (ROS), and hydrolytic enzymes. In addition, the liver produces C-reactive protein (CRP) which facilitates the activation of the host's complement cascade by bacteria and dead cells. Mediators are continuously secreted to maintain the inflammatory response and, since they are present in peripheral blood, can serve as biomarkers of inflammation (BOIs) [4]. High-sensitivity C-reactive protein (hsCRP) levels can be used as an additional test to evaluate systemic inflammation in patients with AP [5].

The aim of the study was to present views on the correlation between AP and the risk of cCVD based on a review of available literature.

MATERIALS AND METHODS

A review of PubMed for papers from the years 2011–2020 was conducted. Searched phrases included: apical periodontitis cardio-vascular diseases, apical periodontitis endothelial dysfunction, apical periodontitis myocardial infarction, and endodontic lesion CVD. Literature reviews, case reports and studies without control groups were excluded. Polish and English-language papers based on human and animal studies were selected. Literature available in the text databases of the Medical University of Białystok library were used. Eleven references were selected.

RESULTS AND DISCUSSION

Aarabi et al. presented several hypothetical mechanisms of etiopathogenesis, atherosclerosis [2] and atrial fibrillation [6], which are based on the following processes: (1) low level bacteremia caused by oral bacteria entering the blood stream and

invading the arterial wall; (2) systemic inflammation induced by inflammatory mediators released from the sites of oral inflammation into the blood stream; (3) autoimmunity to host proteins caused by the host's immune response to specific components of oral pathogens; (4) pro-atherogenic effects resulting from specific bacterial toxins that are produced by oral pathogenic bacteria; (5) arrhythmic effects resulting from specific bacterial toxins that are produced by oral pathogenic bacteria.

Presence of bacteria

Infectious agents, particularly bacteria originating in the mouth or respiratory tract and their components, contribute to the development of the inflammation of atherosclerotic plaque, leading to its rupture and, consequently, to thrombus formation which closes the coronary vessel and blocks blood flow to the heart muscle. Pessi et al. evaluated bacterial DNA in thrombus aspirates from patients with ST-elevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention by means of real-time quantitative polymerase chain reaction (PCR). Bacterial DNA typical for endodontic infection, of which oral *viridans streptococci* was most prevalent, was detected in 78.2% of thrombi. Among a subgroup of 30 MI patients examined by panoramic tomography, a significant association between the presence of periapical abscesses and oral *viridans streptococci* DNA positive thrombi was found. The authors concluded that dental infection and oral bacteria, especially *viridans streptococci*, may be associated with the development of acute coronary thrombosis [7].

Louhelainen et al. attempted to find out whether bacterial DNA can be measured in pericardial fluid, and if it correlates with pathologic-anatomic findings linked to CVD. Twenty-two pericardial aspirates were collected aseptically prior to forensic autopsy. The amounts of bacterial DNA were determined using real-time quantitative PCR with specific primers and probes for all bacterial strains associated with endodontic disease (*Streptococcus mitis* group, *Streptococcus anginosus* group, *Staphylococcusaureus/Staphylococcus epidermidis*, *Prevotella intermedia*, *Parvimonas micra*) and periodontal disease (*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nucleatus*, and *Dialister pneumosintes*). Of 22 aspirates, 14 (63.6%) were positive for endodontic-associated bacteria. Moreover, there was a statistically significant association between the amount of bacterial DNA in the pericardial fluid and the severity of CVD [8].

Liljestrand et al. evaluated the associations between endodontic lesions (ELs) and coronary artery disease (CAD) in 508 patients who underwent coronary angiography and extensive clinical and radiographic oral examinations. They recorded the number of teeth, carious teeth, poor filling margins, root remnants, pocket depth during probing, bleeding on probing, and the number of teeth with periapical lesions based on the periapical index (PAI) [9]. Widened spaces were scored as PAI = 3 and apical rarefactions as PAI = 4–5 [10]. Moreover, quantitative data of subgingival *P. endodontalis,* serum immunoglobulin A and G (IgA and IgG) levels against the whole cell antigen of *P. endodontalis,* and serum lipopolysaccharide activity were determined as potential mediators between ELs and CAD. The authors demonstrated an association between ELs and CAD, especially in acute coronary syndrome (ACS), which was independent of marginal periodontitis and its risk factors. The association between apical rarefactions and ACS was more evident in patients with untreated ELs. Endodontic lesions were associated with subgingival *P. endodontalis* and corresponding serum IgG levels, which, in the author's opinion, illustrates an imbalance in the oral biofilm and subsequent systemic immunologic response that may link ELs and CAD.

Assessment of biomarkers circulating in the blood

According to the ESC guidelines of 2016 regarding the prevention of CVD in clinical practice, biomarkers are classified into the following groups: inflammatory (e.g. CRP determined by high-sensitivity methods – hsCRP, fibrinogen), thrombotic (e.g. homocysteine, lipoprotein-associated phospholipase A2), glucose and lipid related (e.g. apolipoprotein), and organ-specific markers (e.g. renal, cardiac). One of the most intensively studied and discussed biomarkers is hsCRP. Prospective study results indicate that this protein integrates multiple lower-order metabolic and inflammatory factors with a relative risk value close to that of classic CVD risk factors [10].

Patoulias et al. summarized and critically appraised the most relevant evidence regarding the potential use of inflammatory markers in the field of CVD. They established that the main marker of inflammation is CRP, which yielded significant results for both primary and secondary prevention of CVD [11].

Van der Waal et al. pointed out the need to undertake carefully designed longitudinal studies on the systemic consequences of AP with traceability of specific BOIs. In the authors' opinion, the most important markers that indicate the transition of an acute inflammation to chronic inflammation are the cytokine IL-6 and the acute phase CRP. The episodic nature of certain chronic inflammatory diseases is accompanied by changes in the balance of the serum and other tissue fluids of pro-inflammatory cytokines such as: TNF, IL-1, IL-17A, IL-17F, anti-inflammatory cytokines transforming growth factor-beta (TGF-β), IL-10, IL-25 (IL-17E), cytokines involved in cell mediated immunity against intracellular pathogens (e.g. Interferon-gamma – IFN-γ) and soft tissue remodeling mediators, matrix metalloproteinases (MMPs), and particularly of notable bone turnover: soluble receptor activator of nuclear factor kappa B ligand (sRANKL), osteoprotegrin (OPG), c-telopeptide of type I collagen (ICTP) and osteocalcin, which also makes these useful molecules to consider as BOIs. In an intervention study design, a pre-solution could be evaluated successfully by the expression of BOIs or the lack thereof. It is essential to assess whether AP has an effect on the expression of particular BOIs as AP may contribute to the development of co-morbidities or exacerbate existing pathologies [4].

Garrido et al. examined healthy individuals with asymptomatic apical lesions of endodontic origin (ALEOs) and a control group without periapical pathologies aged 18–40 years. The authors performed oral clinical and radiographic examinations and determined the lipid profile, glycated hemoglobin, hsCRP, IgG, IL-6, IL-10, IL-12p70, MMP 8, soluble vascular cellular adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule 1 (sICAM-1), and soluble E-selectin blood samples. Significantly higher hsCRP levels were found in ALEO patients vs. control, whereas the pathobiological determinants of atherosclerosis in youth score was comparable among the groups. As well as this, the levels of IL-6, MMP 8, and soluble E-selectin were significantly higher in ALEO patients. The researchers concluded that ALEO is associated with a systemic inflammatory burden and cardiovascular risk determined by hsCRP, supporting the argument that there is a mechanistic link to CVD in young adults [12].

The impact of chronic AP on overall health seems particularly interesting in the context of the decrease in the level of inflammatory markers after properly executed endodontic treatment. Kimak et al. conducted a study with an aim to determine the concentration of inflammatory mediators, hsCRP and lipoprotein phospholipase A2 (LpPLA2), in the peripheral blood of 26 patients with diagnosed chronic AP (based on radiographic imaging) before endodontic treatment and 1 year after treatment. The subjects were divided into 2 groups: above and below 50 years of age. Patients with AP who had no marginal periodontitis, known liver disease, kidney disease, diabetes, cancer, history of stroke or acute cardiovascular events qualified for the study. The results of this study showed that people under 50 had a statistically significant reduction in hsCRP and LpPLA2 levels 1 year after endodontic treatment compared to baseline, suggesting a reduction in the risk of CVD. Due to the fact that increased LpPLA2 levels are associated with an increased risk of ischemic heart disease and MI, and hsCRP has value in predicting acute cardiovascular events, the authors of the cited study concluded that endodontic treatment can play an important role in general prophylaxis as well as preventing secondary vascular events (MI, stroke) [13].

Proatherogenic effect

Hernández-Ríos et al. found that chronic periapical inflammation is associated with an increased risk of atherogenesis and, to a lesser degree, CVD [14]. The potential mechanisms linking these diseases are detailed in the processes described below. During endodontic infection, ligation of Toll-like receptors (TLRs) on the surface of phagocytes triggers activation, phagocytosis, synthesis of ROS, activation of humoral and cellular responses, and production of inflammatory mediators, such as cytokines and MMPs. The incremental increase in ROS perturbs the normal redox balance and shifts cells into a state of oxidative stress. Reactive oxygen species induce molecular damage and disturbed redox signaling, which results in the loss of bone homeostasis, increased pro-inflammatory mediators, and MMP overexpression and activation, leading to a breakdown of apical tissue. Oxidative stress has also been found to be strongly involved in the pathogenesis of atherosclerosis, where a chronic inflammatory process develops in the arterial wall.

Endothelial dysfunction

The basis of the development of CVD, including hypertension, is vascular endothelial dysfunction. In terms of hypertension, endothelial dysfunction (ED) mainly relates to impaired vasodilation but is also associated with the severity of the atherosclerotic process and the development of thrombosis [15]. Bergandi et al. evaluated vascular and molecular markers of early ED before and after endodontic treatment (2 and 12 months) in 21 young adults with chronic AP diagnosed through clinical and radiological examination. Twenty subjects without AP served as a control group. An assessment of endothelial flow reserve (EFR) was performed via an endothelial function test. Moreover, the following plasma markers were evaluated: IL-1, IL-6, and tumor necrosis factor alpha (TNF-α); vasoconstrictor ED marker endothelin (ET-1), circulating endothelial adhesion markers, ICAM-1/CD54 and sVCAM-1/CD106; soluble CD14; and the endothelial leukocyte adhesion molecule (E-selectin) [16].

The authors demonstrated that AP was associated with increased serum levels of ET-1, ICAM-1, E-selectin, IL-1, and sCD14, suggesting early vascular ED, with no macroscopic evidence of a reduction in EFR. Whereas in the control group, root canal treatment ameliorated inflammation and early ED, lowering plasma levels of IL-1, sCD14, ET-1, ICAM-1/CD54. Their findings suggested that AP may intensify early vascular ED, while endodontic therapy of AP reduces the risk of early ED [16].

Cotti et al. evaluated whether subjects with AP were more exposed to the pathogenetic indices of an atherosclerotic lesion. Forty men (20 with AP and 20 as a control) between 20–40 years old, free from periodontal disease, CVD, and traditional cardiovascular risk factors were enrolled in the study. All subjects underwent dental examination and complete cardiac assessment: physical examination, electrocardiogram, conventional and tissue Doppler echocardiography, and the measurement of EFR. The following laboratory parameters were tested: IL-1, IL-2, IL-6, TNF-α, and asymmetrical dimethylarginine (ADMA). Patients with AP presented significantly higher blood concentrations of IL-1, IL-2, IL-6, and ADMA and a significant reduction of EFR. The authors claimed that increased ADMA levels and their relationship with poor EFR and increased IL-2 might suggest the existence of an early ED in young adults with AP [17].

Asymmetrical dimethylarginine plays an important role in the pathogenesis of numerous diseases, the common denominator of which is the ED of blood vessels which indicates an unfavorable prognosis in diseases of the cardiovascular system [18].

Chauhan et al. attempted to determine whether chronic infections of endodontic origin might predispose one to the onset of CVD; 120 men (60 subjects with AP and 60 controls) were included in the study, aged between 20–40 years, free from periodontal disease, CVD, and traditional cardiovascular risk factors. All subjects underwent a complete physical and dental examination, echocardiography, ultrasound assessment of flow-mediated dilatation (FMD) of the right brachial artery, and carotid intima-media thickness (c-IMT). The study showed that FMD was significantly impaired in patients with AP compared with healthy controls. The study also showed

statistically significant differences between the c-IMT of the AP patients and the control group. Impaired FMD and greater c-IMT in subjects with AP suggests a potential association between endodontic infection and CVD [19].

Animal studies

The effect of AP on the body was also analyzed using animal models. In addition to observing the level of inflammatory mediators, this allowed for an assessment of possible pathological changes in individual organs based on histopathological examination.

Zhang et al. induced AP in 36 rats. They then measured serum levels of CRP, IL-2 and IL-6 by enzyme-linked immunosorbent assays at different time intervals (0, 6, 12, 24, 48, and 96 h and 1, 2, 3, 4, 5, and 6 weeks) after pulp exposure. Multiple organs (the aortic arch, myocardium, liver, and spleen) were collected for histological observation. At each time point, blood was collected from 3 rats, followed by organs for histological evaluation. The group assessed at "0 hours" was the control group. Serum levels of CRP, IL-2, and IL-6 were significantly elevated at all time points assessed after 6, 24, and 96 h, respectively. The peak values of serum cytokines were reached at 1, 4, and 2 weeks respectively, followed by a decline. Time-dependent reversible histopathological changes were detected in the aortic arch, myocardium, and spleen, whereas irreversible changes were found in the liver. Based on the study, the authors claimed that AP may trigger a systemic immune response, impair remote organs, and affect a patients' general health. However, pathological changes in distant organs may have been caused by increased levels of cytokines and CRP in the blood serum but could also be a consequence of the systemic spread of microorganisms or immune complexes [20].

Samuel et al. evaluated whether the presence of single or multiple AP alters blood cell counts and cytokine production. Thirty rats were divided into 3 groups: a control group comprising rats without AP, a group called 1AP comprising rats with AP in 1 tooth, and a group called 4AP comprising rats with AP in 4 teeth. Endodontic infection was induced by pulp exposure of the 1st right maxillary molar in the 1AP group or by exposing the 1st and 2nd right maxillary and mandibular molars in the 4AP group. Blood count and cytokine levels were obtained 30 days after infection by collecting blood via cardiac puncture. A significant increase in leukocytes, lymphocytes, and TNF-α was observed in the blood of 4AP compared with the control and 1AP groups. In addition, a significant decrease of IL-4 in groups 1AP and 4AP was observed when compared with the control. The authors concluded that, in the rat model, the presence of multiple AP can affect systemic health by increasing lymphocyte and TNF-α levels in the blood [21].

The prevalence of AP among the adult population in the world varies between 27–70% and increases with age [22]. It is suggested that there is a 2-way relationship between infections of dental origin and problems with general health. The effect of periodontal disease on CVD development is well documented and often mentioned in the literature [10, 23, 24], whereas the contribution of AP to the emergence and development of CVD is unclear and ambiguous. However, there has been an increasing amount of research in recent years and the conclusions drawn suggest that there is a connection between endodontic infection and cardiological diseases, which may encourage scientists to explore this issue. Further understanding of other risk factors and the cooperation of cardiologists and dentists may contribute to improving health in society [25].

There are also some limitations of the analyzed publications from 2011–2020, for example a wide age range of patients, comorbidities and lack of long-term observations.

CONCLUSIONS

Based on the literature review, it is suspected that there is a positive correlation between AP and the risk of CVD. There are 4 main mechanisms of AP and CVD association: subclinical bacteremia, changes in the level of proinflammatory mediators, the host's autoimmune reactions and proaterogenic effect stimulated by bacterial toxins. Further studies are required to examine the prognostic impact of the treatment of AP on CVD.

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