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PRACA POGLĄDOWA

Periodontitis as a risk factor of stroke – literature review

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Abstract

Introduction and objective. Periodontitis is an inflammatory condition affecting tooth-supporting tissues that can interfere with the course of systemic diseases. Currently, the main interest has focused on the interaction between periodontal disease and cardiovascular diseases.

State of knowledge. The paper presents current views on the relationship between periodontitis and stroke, based on a search in the Medline and Pubmed databases from 2000–2016. Numerous studies have shown that periodontal inflammation may mediate the formation of ischemic stroke by promoting the growth of atherosclerotic plaque. Periodontitis was assumed to be an independent risk factor for stroke.

Conclusions. Prevention and treatment of periodontal disease might inhibit the development of the inflammatory process and consequently the formation of atherosclerotic plaque.

Key words

periodontitis, stroke, risk factors

INTRODUCTION

In 1996, Offenbacher introduced the concept of periodontal medicine, exploring the relationship between periodontal disease and systemic diseases [1]. During following 20 years, many studies were performed to discover the association between periodontitis and cardiovascular diseases, diabetes, pregnancy complications or rheumatoid arthritis [2]. Currently, the main interest is focused on the interaction between periodontal disease and cardiovascular diseases.

The two main forms of periodontal disease are gingivitis and periodontitis. Gingivitis is primarily caused by dental plaque, and affects gingival tissue only, while connective tissue attachment and alveolar bone remain intact. Conversely, periodontitis is a disease of multifactorial etiology with a complex clinical picture, manifested by the gradual, irreversible destruction of tooth-supporting tissues (gingiva, periodontal ligament, bone) which leads to the loss of teeth [2, 3]. Periodontitis disease is a common condition that affects about 90% of the world›s population [4]. Using the community periodontal index (CPI), one of the most frequent used indicators of periodontal disease, the incidence of periodontal disease can be evaluated. According to a recent study on the population of Europe, the distribution of CPI codes in the Polish population were as follows: CPI-0 (1.1%), CPI-1 (12.6%), CPI-2 (22.9%), CPI-3 (40.7%), CPI-4 (16.5%), with worse values present only in Germany and Croatia [5]. The average number of teeth in patients aged 65–74 in Poland was 6.7, compared to 18.7 in the USA and 17.6 in Switzerland [5]. The proportion of toothless individuals in Poland was 43.9%, 23.9% in the USA and 13.8% in Switzerland [5].

It is believed that periodontitis results from the interaction of genetic factors (host susceptibility) and environmental factors (microbial imbalance in the oral cavity, smoking) [4].

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In the course of periodontitis, there is a systemic increase in pro-inflammatory markers (IL-1, PGE_2, TNF, IL-6) as a result of an immune response against Gram-negative bacteria (periodontal pathogens), which is a common etiological agent for arteriosclerosis and periodontitis [6, 7, 8]. The complications of advanced atherosclerosis include myocardial infarction and stroke. Stroke is a sudden onset of focal or generalized brain dysfunction, lasting more than 24 hours, and due to only vascular reasons associated with cerebral blood flow [9]. Stroke in terms of the underlining mechanisms is divided into [10,11, 12]:

1) *ischemic stroke* – caused by arterial obstruction and reduced blood supply to the brain. This is due to atherosclerotic plaques in large and medium-sized arteries supplying the brain (p. Cervical, t. Cords), or large and medium cerebral arteries and changes in the small vessels of the brain (cerebral sinus);
2) *haemorrhagic stroke* – caused by intracerebral vessel rupture. A common cause of stroke is high blood pressure;
3) *venous stroke* – following vein thrombosis.

Annually, there are about 60,000 new cases of stroke in Poland. Stroke affects 177.3 men out of 100,000 and 125 women out of 100,000 in Poland [13]. Respectively, the mortality in patients with stroke is 106.4 per 100,000 in men and 78.7 per 100,000 in women [13]. According to current statistics, stroke is the third leading cause of death in Poland. Initial stroke diagnosis involves magnetic resonance imaging or computer tomography in order to determine the type of stroke [14]. Complications following a stroke include a number of dysfunctions, speech deficiencies, various type of paralysis and palsy [15]. The risk of recurrent stroke in patients after stroke is statistically higher [9].

The first case-control study indicating a link between periodontitis and a history of stroke comes from 1989 [16]. Since then, a series of case-control studies and cohort studies evaluating this relationship have been performed. It has been shown that both pathologies are social and have common risk factors. The in-depth exploration of these issues will allow

the implementation of appropriate preventive and curative measures in the field of periodontology and neurology.

STATE OF KNOWLEDGE

Atherosclerosis is a chronic inflammatory disease of the arteries. It is characterized by blood vessel wall inflammatory infiltration, lipid accumulation and fibrosis [9, 17]. The pathogenesis of atherosclerosis involves four stages:
1) damage to vascular endothelium;
2) release of mitogenic factors by the platelets and monocytes;
3) phagocytosis of lipids;
4) formation of atherosclerotic plaque [18].

Periodontal pathogens, such as, *Porphyromonas gingivalis* (P.g.), *Tannerella forsythia* (T.f.), and *Treponema denticola* (T.d.), may affect both the initial phase as well as the further development of atherosclerotic plaque [19, 20, 21]. Periodontal pathogens can enter the bloodstream by acting directly on the vascular endothelium. Transient bacteraemia may be associated with the act of chewing, tooth brushing or dental procedure [22, 23]. One of the factors affecting the development of atherosclerotic lesions is a lipopolysaccharide (LPS), which is released during the disintegration of bacteria. LPS triggers a metabolic cascade with an increase of PGE_2, TNF, IL-1, matrix metalloproteinases (MMP) and other proteolytic enzymes which, as a consequence, leads to the destabilization of atherosclerotic plaques and proliferation of smooth muscle cells in the arteries [19, 24, 25, 26, 27]. An ongoing inflammatory process in the periodontium increases TNF and IL-6 in the periodontal pocket fluid and in the serum. These cytokines stimulate the production of CRP in the liver, which in turn, is a risk factor for atherosclerotic plaques [28, 29, 30]. The bacteria *P. gingivalis* and *S. sanguis*, express on their surface a platelet aggregation-associated protein (PAAP), which initiates the adhesion and aggregation of platelets, regardless of calcium [25, 31, 32]. Another theory worth noting is a 'pathogen burden' which specifies that the risk of atherosclerosis is proportional to the number of infections with various microorganisms [33].

One of the latest concepts is the molecular mimicry, referring to an inappropriate immune response to bacterial HSP60 which results in host HSP60 destruction and damage to the vascular endothelium [33]. The risk factors for developing atherosclerotic plaque include cigarette smoking, low physical activity, elevated levels of LDL and triglycerides, low HDL levels, diabetes, obesity, high blood pressure and infectious agents, as well as non-modifiable risk factors, such as age over 45 and gender. Clinically, atherosclerotic plaque may initiate thrombus formation which is an embolic risk. Intraplaque haemorrhage leads to a sudden increase in its volume, narrowing the artery and causing myocardial infarction.

The consequences of the deposition of atheromatous plaques depend on their location. The formation of atherosclerotic plaques in the carotid arteries of the brain can lead to stroke [18]. Atherosclerosis, stroke and periodontitis possess common risk factors: age, male gender, cigarette smoking, diabetes and obesity (Tab. 1) [15, 34, 35, 36, 37, 38, 39]. So far, studies have allowed us to conclude that inflammation existing in the periodontium can lead to the development of atherosclerosis, both directly and indirectly. Studies

Table 1. Risk factor for stroke, atherosclerosis and periodontitis

Risk factor	Stroke	Atherosclerosis	Periodontitis
Age	+	+	+
Male	+	+	+
Black race	+		+
Genetic polymorphisms	+	+	+
Periodontal pathogens			+
Smoking	+	+	+
Diabetes	+	+	+
Obesity	+	+	+
Socioeconomic status		+	+
Stress		+	+
Hypertension	+	+	
Myocardial diseases	+		
Internal carotid artery stenosis	+		
Vascular diseases	+		
Increase fibrinogen levels	+		
Hypothyroidism	+		

confirmed that the thickness of the plaque corresponds to the severity of periodontal disease. In terms of the infection total load theory, the risk of atherosclerosis is proportional to the number of infections with various microorganisms [40]. Therefore, elimination of inflammation by treating periodontal disease may reduce the risk of the atherosclerotic plaque formation.

Cohort studies. Cohort (prospective) studies are based on the assessment of the incidence of a particular disease, depending on the exposure to the probable risk factor. From a total of eight cohort studies published from 2000–2016, four were included into the following analysis (Tab. 2). Studies were included if they fulfilled the following inclusion criteria:
1) stroke was diagnosed according to the internationally accepted criteria;
2) periodontitis as one of the outcomes of interest;
3) periodontitis fulfilling the definition of Tonetti and Claffey [41].

Survey-based studies have been omitted due to the limited credibility of the research.

Lafon et al., based on a four-year observation of 95 individuals, have stated that the inflammatory process occurring in patients with periodontal disease contributes to an increased risk of ischemic stroke [42]. In the study, various periodontal indices were measured, such as plaque index (PI), gingival index (GI), probing depth (PD), bleeding on probing (BoP), number of teeth and radiographic bone loss. The authors demonstrated a link between an increased BoP rates and bone loss and ischemic stroke [42]. Wu et al. conducted a 10-year study on a group of 9,962 individuals aged 25–74 [43]. They showed that the increase in the PD and number of teeth correlated with the risk of both haemorrhagic and ischemic stroke[43]. Jimenez et al. studied a group of 1,137 individuals over 24 years of age [44]. They examined the number of periodontal indices, including PI, GI and PD, and confirmed radiologically periodontal bone loss, showed that bone loss in men <65 years of age was significantly associated with the occurrence of stroke and transient ischemic attack

Table 2. Cohort studies

Author	Study population	Variable	Study parameters	Time after stroke	Type of stroke	Results	Duration of study
Lafon et al. (42) 2014	95 patients aged 18–80 48 – patients with ischemic stroke 47 – control group	Age, gender, education level, physical activity, smoking, alcohol consumption, hypertension, heart disease, atrial fibrillation, BMI, diabetes, CRP, total cholesterol, triglycerides, HDL, LDL, glucose, family history.	PI, GI, DMFT, BoP,PD, Radiographic bone loss	Month after stroke	Ischemic stroke	BoP and radiographic bone loss were significantly associated with ischemic stroke.	4 years
Soder et al. (14) 2015	1676 patients 39 – patients after stroke	Gender, age, smoking, level of education, income.	PI, GI,CL.I, Number of teeth	-	Stroke	Gingivitis over the years, contributes to the stroke.	26 years
Jimenez et al. (44) 2009	1137 men	Age, smoking, BMI, hypertension, diabetes, alcohol consumption, cholesterol, HDL, triglycerides, income, level of education, profession.	PI,GI, PD, number of teeth, radiographic bone loss		Ischemic stroke, Ischemic transient	Radiographic bone loss in males <65 years of age was significantly associated with the occurrence of stroke.	24years
Wu, et al. (43) 2000	9,962 patients aged 25 – 74	Age, gender, race, level of education, hypertension diabetes, smoking, alcohol consumption, cholesterol, BMI	PD, numer of teeth	-	Ischemic and haemorrhagic stroke	Periodontitis increased risk of cardiovascular disease, non-haemorrhagic stroke in males and females, white race and African- American.	10 years

[44]. To-date, the longest observation was performed by Soder et al. – over 26 years in a group of 1,676 patients – which demonstrated that in patients with gingivitis the risk of stroke rises significantly over the years [15]. Gingival index was significantly higher in patients with stroke, but no relationship between stroke and number of missing teeth were conducted [15].

Among all follow-up studies, researchers took into account patients' age, gender, smoking habits and alcohol consumption. A large group of researchers assessed the physical activity of patients, their level of education, HDL and LDL levels, as well as genetic predisposition to cardiovascular disease. The authors showed that the subjects with a lower number of teeth, mostly men, were more likely to suffer a stroke [42, 43, 44]. In addition, all the subjects were smokers who admitted to low physical activity and increased alcohol consumption [42, 43, 44]. Lafon et al. showed that the level of CRP in patients after stroke with periodontal disease is significantly higher compared with the control group, and that treatment of periodontal disease reduces the level of CRP [42]. The cohort study performed by Soder et al. seems to be of the greatest importance, not only because of its durations (26 years) and sample size, but also because of the detailed documentation of periodontal status of the studied group which increases the reliability of the achieved results [15].

Case-control studies. Case-control (retrospective) studies are seeking for a relationship between the exposure and the onset of a disorder. From a total of 10 case-control studies published from 2000–2016, seven were included into the following analysis (Tab. 3). Studies were included if they fulfilled the following inclusion criteria:

1) stroke was diagnosed according to the internationally accepted criteria;
2) periodontitis as one of the outcomes of interest;
3) periodontitis fulfilling the definition of Tonetti and Claffey [41].

Survey-based studies have been omitted due to the limited credibility of the research.

Budin et al. demonstrated in the group of 160 patients that the oral hygiene index (OHI), PD and GI decayed-missing-filled teeth (DMFT) index were significantly higher in patients after stroke, compared to a control group [12]. The authors have shown that periodontitis is an independent risk factor for ischemic stroke. Abolfazli et al. showed that patients after an ischemic stroke had a greater loss of clinical attachment level (CAL) than the control group. At the same time, they found no relationship between ischemic stroke and gingivitis [45]. Hashemipour and Pradeep each studied an average number of patents [46,47]; in turn, Hashemipour et al. showed that moderate and advanced periodontitis occurred more frequently in patients after stroke, based on PI, GI and CAL examination [47]. Sim et al., based on a group of 479 patients, established a strong link between stroke and periodontal disease in patients with CAL> 6 mm. This relationship was significant in the patients under 60 years of age with normal blood pressure [48]. Research conducted by Dorfer et al., based on the assessment of DMFT, CAL, PD, GI, PI and radiological bone loss, demonstrated that patients who have had an ischemic stroke had an increased loss of CAL, compared to the control group [49]. The risk of ischemic stroke increased 7.4 times when CAL loss was > 6 mm, 18.3 times when GI was > 1.2, and 3.6 times when radiographic bone loss was present [49]. Grau et al., on the group of 771 individuals, showed that patients with advanced periodontitis where CAL was > 6mm were 4.3 times more likely to have an ischemic stroke. They also showed a greater relationship between ischemic stroke and advanced periodontal disease in men under 60 years of age [50].

Among the presented case-control studies, all authors, except Budin et al., evaluated the periodontal status based on the loss of CAL. Smin et al. performed measurements at six sites of each tooth present, while other researchers evaluated four sites [45, 46, 48, 49, 50]. All these researchers have confirmed that the risk of stroke increases proportionally to the loss of CAL. Case-control studies confirm that periodontal disease is an independent risk factor for stroke.

Table 3. Case-control studies

Author	Study population	Variable	Study parameters	Time after stroke	Type of stroke	Results
Sim et al. (48) 2008	479 patients 265 – non-fatal stroke 214 – control group	Age, gender, income, alcohol consumption, education level, smoking, hypertension, diabetes, BMI, family history	CAL, DMFT	From 3 months to a year	Non-fatal ischemic and hemorrhagic stroke	Periodontitis is significantly associated with occurrence of stroke in patients <60 years.
Abolfazli et al. (45) 2011	200 patients 100- patients with ischemic stroke 100 – control group	Age, gender, hypertension, smoking, diabetes, atrial fibrillation, obesity, cardiovascular disease family history	CAL, GI	About 3 days after	Ischemic stroke	Periodontitis is an independent risk factor for ischemic stroke in men.
Dorfer et al. (49) 2004	603 patients aged 18 – 75; 303 patients with ischemic stroke; 300 – control group	Age, gender, hypertension, smoking, diabetes, atrial fibrillation, cardiovascular disease, alcohol consumption, body mass index, family history, level of education	CAL, PD, PI, GI, DMFT, radiographic bone loss	3 days after	Ischemic stroke	With the growth of CAL increased risk of ischemic stroke.
Grau et al.(50) 2004	771 patients aged 18 – 75; 303 ischemic stroke, transient ischemic; 468 – control group	Age, gender, hypertension, smoking, diabetes, hyperlipidemia, heart disease, atrial fibrillation, alcohol consumption, level of education, family history	CAL, GI, PI, DMFT, radiographic bone loss	One week after	Ischemic stroke	Periodontitis increases the risk of ischemic stroke in men <60 years.
Pradeep et al. (46) 2009	200 patients aged 33–68	Age, gender, diabetes, hypertension, smoking, alcohol consumption, cholesterol, level of education, family history, diet	PI, GI, PD, CAL	About 5 days after	Ischemic stroke	Periodontitis is an independent risk factor for ischemic stroke.
Budin et al. (12) 2014	160 patients 80 – patients after stroke 80 – control group	Hypertension, heart disease, diabetes, hyperlipidemia, kidney disease	PD, GI, OHI, DMFT	-------	Stroke	Periodontitis occurred more frequently in patients after stroke.
Hashemipour et al.(47) 2013	200 patients 100- patients after stroke 100 – control group	Age, diabetes, hypertension, atrial fibrillation, kidney disease, smoking, cardiovascular disease	GI, CAL, PI	About 3 days after	Stroke	Periodontitis occurred more frequently in patients after stroke.

CONCLUSIONS

Four cohort studies and seven case-control studies were analyzed in the present review. All the research confirmed that periodontitis is an independent risk factor for stroke. The studied groups differed in size from 95–29,584 individuals. The European population was analyzed in the two cohort studies [5, 14] and two case-control studies [49, 50]. To our knowledge, no studies in this field has been performed in the Polish population. In terms of the quality of the evidence, cohort studies seem more valuable than case-control studies, as the observation of the subject is long-term and risk precedes the effect. However, the majority of the cohort studies, which were not included in the present analysis, were based on the surveys or decay-missing-filled (DMFT) index only, thus reducing the reliability of data and overestimating the real prevalence of periodontal disease in the cohort.

Conversely, diagnosis of periodontal disease was usually well-documented in the case-control studies. The authors performed clinical (gingival index, BoP, probing depth, CAL) and radiological (bone loss) periodontal examinations [12, 45, 46, 47, 48, 49, 50]. The methodological differences were also demonstrated at the level of stroke diagnosis. Some researchers focused on ischemic stroke, binding its occurrence to the formation of atherosclerotic plaque [45, 46, 49, 50]. Other researchers mentioned only a history of stroke in their patients [12, 14, 47, 48].

Recent meta-analysis that analyzed five case-control and three cohort studies showed a statistically significant association between periodontitis and ischemic stroke in both cohort pooled relative risks at 2.52 (1.77–3.58), and case-control studies pooled relative risks at 3.04 (1.10–8.43) [51]. Although interventional studies in stroke are lacking, the available results suggest that adequate prevention and treatment of periodontal disease can reduce the incidence of stroke.

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