

Relationship between General and Oral Diseases: Literature Review

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Abstract The aim of the study was to define the relationship between oral health and widespread general pathology – diabetes mellitus and cardio-vascular disease. PubMed, EMBASE, MedLine, eLibrary and CyberLeninka databases were used to search publications on the issue of the relationship between general and oral diseases. Complex diabetes mellitus consequences for oral health were described. In patients with diabetes mellitus the incidence of dental caries, periodontal and oral mucosa diseases, disorders of saliva production, bone metabolism and teeth eruption were common. Cardio-vascular diseases promote oral pathology development. Cardiac patients have high prevalence of caries, dental erosion, periodontal disease, etc. It was revealed that poor oral health increase the risk of infective endocarditis, metabolic disorders, deterioration and complications of diabetes mellitus and cardio-vascular disease course. The need of coordination and interaction between cardiologists, endocrinologists and dental professionals is highlighted.

Keywords Oral health, Diabetes mellitus, Cardio-vascular disease

1. Introduction

Poor oral health can affect systemic health and general diseases can cause the development of various types of oral pathology. To understand the relationship between oral and general health is very important for dental and general practitioners, oral health workers. Diabetes mellitus and cardio-vascular diseases are well known general pathologies, which have high and increasing prevalence in the world and are one of the main causes of mortality and morbidity. So it is important to study their interactions with oral health in children and adults.

2. Materials and Methods

Databases of PubMed, EMBASE, MedLine, eLibrary and CyberLeninka were used to search publications on the issue of the relationship between general diseases (diabetes mellitus and cardio-vascular diseases) and oral health. Seventy three published works including reviews and the results of clinical studies were selected for subsequent analysis.

3. Results of the Study

Diabetes mellitus is one of the most urgent medical and social problems of the modern society affecting both children and adults, urban and rural population of the planet. The problem is caused by the high level of diabetes mellitus incidence, the necessity of its continuous treatment with medicines, a strict diet, a certain lifestyle and serious late complications [1,2,3].

At present, a group of metabolic diseases caused either by deficient insulin production, disturbance in insulin action or a combination of both factors is considered under the name of “diabetes mellitus”. Diabetes mellitus is characterized by hyperglycemia, glucosuria, polydipsia and metabolic disorders of lipids, protein and minerals [4].

Chronic hyperglycemia associated with diabetes mellitus provokes the response of actually all inner organs and systems of the body. Microvascular complications such as nephropathy, polyneuropathy, diabetic foot syndrome and aggravating macrovascular diseases (ischemic heart disease) that develop due to diabetes mellitus are the main causes of disability. The symptoms of diabetes mellitus are well-known to people: thirst, increased appetite, unquenchable hunger, frequent urination. The progress of the disease is characterized by dryness in the mouth, itching of the skin and mucous membranes, fatigue, weakness, irritability, vision disorders, and persistent inflammatory lesions of the skin that are resistant to medical treatment [5].

Classical symptoms are not typical of type 2 diabetes mellitus which prevails on the territory of the Russian Federation, as well as in all countries, so the disease may not be diagnosed for a long time. An increased level of blood

glucose may be revealed by chance during the patient's examination for a disease that may often be combined with diabetes mellitus. While considering case history, the symptoms are revealed retrospectively and the patient might not have paid attention to them [5].

Diabetes mellitus also affects patients' oral health. Studying the structure and incidence of dental diseases in children with autoimmune diabetes mellitus, Ivchenko and Domenyuk stated that the severity of oral pathology depends on endocrinopathy severity [6]. The obtained data correspond to the research conducted by Twetman et al. [7], who studied the dental status of children and young adults with type 1 diabetes mellitus. As Orekhova et al. reports, the incidence of dental diseases (caries, periodontitis, oral mucosa lesions) is a few times higher in the patients with diabetes mellitus and pregnant women. The authors also provide the data on dental pathologies affecting patients' general health [8]. Patients suffering from diabetes may have early eruption of permanent teeth that occurs more often in girls. The process of teeth eruption is followed by gingivitis [9].

Vascular abnormalities that are typical for diabetes mellitus result in disordered trophic and slow down the formation of the jaw alveolar bone, complicate orthodontic teeth transfer and bones remodeling, aggravate periodontal status of orthodontic patients [10].

Diabetes mellitus contributes to the diseases of hard teeth tissues. So, Akpata et al. reported that children with type 1 diabetes mellitus have more carious lesions, both in primary and permanent dentition [11].

Among adult patients suffering from type 2 diabetes mellitus caries also prevails over those who do not have diabetes in their history [12]. Garton and Ford stated that in adults with type 2 diabetes mellitus dental caries occurs significantly more often than in the patients of dental clinics who do not suffer from diabetes [13].

In men with diabetes CFE (Caries Filling Extraction) index and probability of all teeth extraction is higher than in men with no diabetes in their history. CFE indices in patients with diabetes mellitus correlate with high HbA1c level [14,15].

Special literature provides the data on a significant increase of caries incidence and its complications resulting in apical periodontitis, a larger number of periapical foci of infection and endodontically treated teeth in patients with diabetes mellitus comparing to dental patients with no diabetes [16,17,18]. Jawed et al. takes the view that the risk of caries development in diabetes mellitus is caused by changes in saliva pH and decreased optimal calcium content in saliva which leads to teeth demineralization [19].

In diabetes mellitus patients salivary glands undergo structural changes. Salivation disorder causes xerostomia (dry mouth) and further development of complications: multiple caries, candidiasis, halitosis [20]. It was proved that salivary glands disfunction in diabetes mellitus provokes biochemical changes in saliva composition and leads to pH changes, lowered production of saliva, decreased content of

calcium compared to the same data in people having no diabetes in their history [19].

Healthy life style is taught to children at early age. If children with diabetes mellitus do not have preventive habits to take care of their oral health, in pubertal period they will ignore oral hygiene and brush their teeth irregularly [21,22,23].

According to some researches, oral hygiene is not a priority for diabetic adults, either: they are less informed about their dental health, seldom visit a dentist or brush their teeth twice a day compared with non-diabetic people [24,25]. Over half of the people suffering from diabetes do not possess flossing skills [26]. Cinar et al. provide the data that most 40-70-year-old adults with diabetes mellitus in their history brush their teeth only once a day, 77% of them do not know their level of HbA1c, 42% are overweight and one third of them suffer from obesity [27].

Diabetes mellitus is characterized by systemic depression of the immune system resulting in opportunistic oral infections, mostly candidiasis, after the treatment of infections in diabetic patients with antibiotics; periodontitis is accompanied by multiple periodontal abscesses, the reparation period after operative interventions are longer. Halitosis, unpleasant smell from the mouth, is also typical for diabetic people. As a result of chronic immune suppression in diabetes mellitus patients, recurrent aphthous stomatitis of bacterial, viral or fungous origin, and lichen ruber planus are often diagnosed; pathologic changes and diseases of lips and oral mucosa may develop [28,29,30].

Neurologic disorders are typical for diabetes mellitus and also have their manifestations in dental patients. Patients feel burning tongue or mouth, their taste changes. Dysgeusia develops and contributes to hyperphagia and obesity, impossibility to keep to a diet. As a result control of glycemia decreases. Lasting stomatalgia results in the difficulties in using a toothbrush and disturbed oral hygiene [31].

Microbial picture changes, pathognomonic for diabetes mellitus, leads to a vicious circle: pathogenic flora of the periodontium increases the tissue resistance to insulin, thus deteriorating the metabolic control of glycemia. At the same time, a high concentration of glucose in the gingival fluid of diabetic patients provokes the increase of pathogenic microorganisms. The persistence of subgingival microflora promotes disturbances in chemotaxis and phagocytosis which is characteristic of diabetes mellitus [32].

It was stated that in controlled diabetes mellitus the content of microflora is identical to that in periodontitis and in uncontrolled diabetes mellitus the content of microflora changes. The percentage of colonies of such pathogenic microorganisms as TM7, *Aqreqatibacter*, *Neisseria*, *Gemella*, *Eikenella*, *Selenomonas*, *Actinomyces*, *Capnocytophaga*, *Fusobacterium*, *Veillonella* and *Streptococcus* genera increases. Revelation of a significantly larger amount of *Porphyromonas*, *Filifactor*, *Eubacterium*, *Synergistetes*, *Tannerella* and *Treponema* genera decreases. Phylotypes of *Fusobacterium nucleatum*, *Veillonella parvula*, *V. dispar* and *Eikenella corrodens* is the evidence of

aggressive course of parodontosis in diabetes mellitus patients [33]. These research results correlate with the data reported by Alexandrov [34].

The development or progressive course of periodontal disease is typical almost for all patients with metabolic syndrome or diabetes mellitus. Children and teenagers at the age of 12-18 develop a severe form of gingivitis with the defects in epithelial attachment of gingiva alongside with the first signs of periodontitis. Every fourth child with diabetes in their history suffers from an aggressive course of periodontitis at 15-19 years of age [35,36].

In diabetic adults defective epithelial attachment of the gingiva is revealed 3 times more often compared to other people, loss of the alveolar part of jaws is also recorded more often; periodontitis develops 2.9 times more often due to the anti-inflammatory response of the immune system; inflammatory diseases of periodontium are characterized by deeper gingival pockets and the increased number of extracted teeth [18]. These data correlate with the research results by Zharkova *et al.*, who determined a direct correlation between the severity of inflammatory-destructive processes in the periodontium and the course of insulin-dependent diabetes mellitus [37].

Unsatisfactory control of glycemia in adults with diabetes mellitus 1 or 2 type correlates with higher prevalence of gingivitis and periodontitis. In patients with bad glycemic control dental diseases are manifested by a large number of grave clinical symptoms, extensive periodontitis, deep destruction of alveolar bone, a large number of extracted teeth, and unfavorable prognosis of dental implants [38,39].

Analyzing the interrelation between diabetes mellitus and periodontitis, many researchers came to the conclusion that these diseases influence each other. It is suggested that the impact of diabetes on the periodontium condition may occur due to the formation of the end products of deep glycation (AGE) as a result of hyperglycemia / hyperlipidemia. These products, connecting to macrophages receptors, reproduce various inflammatory cytokines, such as interleukine-1, interleukine-6 and tumor necrosis factors (TNF, α -factor), which may be responsible for periodontitis development. A.M. Schmidt *et al.*, 1996, also considered oxygenation stress in gingiva caused by end products of progressive glycation (AGEs) as a potential mechanism underlying a rapid development of periodontitis in diabetes mellitus patients [40].

Albrecht *et al.* noted a higher prevalence of potentially malignant disturbances in patients with diabetes mellitus 2 compared to the people with no diabetes. The obtained data were explained by progressive atrophy of oral mucosa which developed due to xerostomia that increased permeability of the oral mucous membrane for carcinogens. On the other hand, it was suggested that the increased level of blood glucose in diabetes mellitus patients results in excessive formation of free radicals and decreases antioxidants activity which causes oxidative damage to DNA and promotes carcinogenesis [41]. These data correlate with the research results by Saini *et al.* [42].

Thus, the scientific literature presents a vast amount of information on the specific character of oral pathologies developing in patients with type 1 and type 2 diabetes. It shows how diabetes affects the course of dental diseases in children and adults. The analysis of the data confirms the topicality of the problem of interdisciplinary approach to medical treatment of patients with diabetes mellitus and dental diseases.

Besides diabetes mellitus, cardio-vascular diseases also affect oral health. Blood circulation impairment which develops in diabetes mellitus and hypertension increases the risk of stroke and cardiac infarction – the most common causes of death around the world. Cardiovascular diseases are one of the major causes of disability and mortality in the world and are being found more and more often among able-bodied people. For this reason, their early diagnosis and elimination of aggravating factors are most urgent [43,44].

The aspects of cardiovascular pathology effects on oral health are various. Sivertsen *et al.* revealed that in 5-year-old children with congenital heart defects the prevalence of caries and erosion was significantly higher than in general population. Moreover, in children with congenital heart defects erosion prevalence was significantly higher than caries prevalence. The authors concluded that many children with congenital heart disease have impaired oral health which may increase the risk of systemic hazardous consequences [45].

In another study, higher prevalence of periodontitis, dental decay and Lactobacilli colony counts in saliva in children with congenital heart disease compared to their healthy peers was described; however the differences were not significant statistically [46].

Good oral health is known to be crucial for children with congenital heart diseases. However, the knowledge of parents about caries and periodontal disease connection with general health is not sufficient and children do not receive oral disease prevention according to the newest guidelines. Current studies highlight the need for coordination between pediatric cardiologists and pediatric dentists in parents education and the improvement of oral care for children with chronic diseases such as congenital heart defects [47].

The oral health program for children with congenital heart improved their oral hygiene, decreased the number of untreated caries lesions and reduced gingival bleeding. However, the this program did not decrease the prevalence of caries and dental erosion [48].

Hughes *et al.* noted that children with congenital heart disease have an increased risk of infective endocarditis, poor oral health, a high level of dental fear and anxiety. Most children with heart disease have reduced access to dental care. New Paediatric Congenital Heart Disease Standards and Specifications (PCHDSS) in England include an oral health section. These standards highlight the need of paediatric patients with cardiac disease for complex management and cooperation between cardiologists, dental healthcare professionals of primary care and paediatric dentists [49].

Patients of all ages with problems in the cardiovascular system show high intensity of caries and a high level of teeth loss [50]. Endothelium thinning characteristic of atherosclerosis is revealed in patients with inflammatory parodontopathy [51]. Microcirculatory impairments which are essential for pathogenesis of cardiovascular diseases also predispose the development of inflammatory-destructive periodontal disease [52].

Pathogenic oral microflora presents special significance for the development of cardiovascular diseases and periodontal disease [53]. Bacteremia and toxemia favor the mechanisms of chronic systemic inflammation development and endothelial dysfunction that cause similar pathologic changes in periodontal cerebral and coronary vessels [54]. Mazur et al. studied microbiotas of gingival pockets and biologic material of the heart valves that were removed during surgical intervention in patients with periodontitis and cardiac valve pathology. It was determined that bacterial load of the cardiac valves depends on the course of generalized periodontitis. The results of clinical-microbiological research confirm the presence of DNA of the pathogenic flora of periodontium in the cardiac valves tissues [55].

Analyzing the interconnection between dental diseases and atherosclerotic stenosis of the carotid arteries, it was determined that dystrophic diseases of periodontitis with gum recession and tooth roots exposure prevail in patients with atherosclerosis [50]. The impairment of the central and regional hemodynamic in patients with arterial hypertension promotes development of oral pathology. For this reason a dentist should conduct purposeful preventive manipulations in patients with arterial hypertension in order not to aggravate their dental status.

Chronic inflammatory oral diseases were reported to have the interconnection with acute myocardial infarction [56]. The analysis of the oral health of patients with postinfarction cardiosclerosis demonstrated high prevalence and the intensity of dental caries and periodontal disease. In periodontal diseases an extensive foci of necrosis are formed in the osseous tissues which negatively affect the patient's health in general and the cardiovascular system in particular.

Pussinen et al. conducted a longitudinal study to assess the interconnection between oral infection in childhood and subclinical carotid atherosclerosis in adulthood. Dental examination of 755 children aged 6, 9 and 12 years included the registration of caries and periodontal disease signs, and cardiovascular risk factors assessment. Follow-ups were conducted after 21 and 27 years. It was revealed that the presence of bleeding on probing, periodontal pockets, caries and dental fillings in childhood increased the frequency of the cases of carotid artery intima-media thickness (a well known sign of subclinical atherosclerosis) in adulthood. The presence of any sign of caries or periodontal disease in childhood, independently of cardiovascular risk factors, significantly increased relative risk of atherosclerosis in adults with the obvious association:

the more signs of oral infection, the more risk of atherosclerosis [57].

Epidemiological characteristics and clinical laboratory manifestations of oral diseases in patients with chronic heart diseases (chronic stress angina pectoris, stable angina pectoris, and cardiosclerosis), the pathogenic aspects of periodontal disease formation were studied by Van Dyke and Starr. The level of caries in patients with chronic heart disease or without it had no statistically significant difference in the authors' opinion, though periodontal and oral mucosa diseases prevail in patients with the pathologies of the cardiovascular system [58].

The interconnection between chronic pathology of dentition and chronic heart disease and its complications were studied by Ivashenko et al. It was determined that severe chronic generalized periodontitis, dentition abnormalities and multiple dental caries occurred more often in the patients who had myocardial infarction than in those who did not have it in their history. However, according to the research, only severe periodontitis was an independent factor associated with the previous and acute myocardial infarction [59].

It was proved that periodontitis increases atherosclerotic disorders of blood circulation [53,60,61], and its active course enhances the risk of the development of acute cardiovascular diseases (myocardial infarction and stroke) [62,63]. A number of cardio-vascular diseases biomarkers increases in the patients with chronic periodontal diseases followed by non-treated odontogenic infection foci including apical periodontitis [64,65,66].

The topicality of somatic and dental mutual aggravation problem is reflected in the reports of the American Heart Association (AHA), 2008-2014 [44,67]. A large part of it deals with the aspects of aggravating interaction between inflammatory oral diseases and atherosclerotic damage to the vessels. The final conclusion was the substantiation of the appropriateness of purposeful oral treatment to prevent atherosclerosis progress. The role of oral hygiene in lowering the risk of ischemic heart disease complications was stressed by Reichert S. et al., 2015 [68].

According to a number of researches, practically all general diseases affect oral health to some degree. Stephens et al. confirmed that patients with poor oral health more often have respiratory and cardiovascular diseases, adverse pregnancy outcomes, and diabetes mellitus than patients with good oral health. Moreover, constantly taken medications can contribute to the development of caries, erosion and other oral diseases [69].

Consequently, bacteremia and toxemia are the interaction mechanisms of both inflammatory periodontal and cardiovascular diseases, which are provided by the vital activity of oral periodontal pathogenic microflora and endothelial dysfunction. General pathologic changes are formed in periodontal vessels, coronary and cerebral vascular systems. The factors of chronic systemic inflammation arising both in periodontal and cardiovascular pathology act jointly and aggravate the clinical picture of the

diseases [61,70,71,72,73].

The number of adverse systemic conditions, including diabetes mellitus and cardiovascular diseases, affecting dental health, is high. Consequently, an urgent healthcare problem is the interdisciplinary interaction of general practitioners and dentists in order to develop a holistic approach to the diagnosis, treatment and management of patients with comorbid pathologies.

4. Conclusions

The number of adverse systemic conditions, including diabetes mellitus and cardiovascular diseases, affecting dental health, is high. Consequently, an urgent healthcare problem is the interdisciplinary interaction of general practitioners and dentists in order to develop a holistic approach to the diagnosis, treatment and management of patients with comorbid pathologies.

REFERENCES

- [1] Dedov II. Diabetes mellitus - the most dangerous challenge to the world community. *Bulletin of RAMS*. 2012. 1:7–13 [In Russ].
- [2] Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. World Health Organization, Geneva, 1999. Report Number: WHO/NCD/NCS/99.2. [https://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf].
- [3] NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants // *Lancet* (London, England). 2016. 387(10027): 1513–30. doi:10.1016/S0140-6736(16)00618-8.
- [4] World Health Organization. Diabetes. [http://www.who.int/diabetes/en]. Accessed October 1, 2015.
- [5] Diabetes mellitus: diagnosis, treatment, prevention / ed. II Dedov, MV Shestakova. Moscow: MIA, 2011:808 [in Russ].
- [6] Ivchenko LG, Domenyuk DA The structure and prevalence of major dental diseases in children with autoimmune diabetes mellitus at various stages of endocrinopathy compensation. *Actual issues of clinical dentistry*. Stavropol, 2017: 388–91 [In Russ].
- [7] Twetman S, Petersson GH, Bratthall D. Caries risk assessment as a predictor of metabolic control in young Type 1 diabetics. *Diabet Med*. 2005. 22(3): 312–15.
- [8] Orekhova LYu, et al. Features of dental status in patients with diabetes mellitus and pregnant women. Dental disease prevention measures in these patient groups (literature review). *Periodontology*. 2014.19, 4(73): 18–25.
- [9] Lal S, et al. Accelerated tooth eruption in children with diabetes mellitus. *Pediatrics*. 2008. 121(5): e1139–43.
- [10] Costella AMU, Saber M. Influence of diabetes mellitus on orthodontic treatment: a literature review. *Orthodont CYBER J*. 2013. [http://orthocj.com/2013/05/influence-of-diabetes-mellitus-on-orthodontic-treatment-a-literature-review].
- [11] Akpata ES, et al. Caries experience among children with type 1 diabetes in Kuwait. *Pediatric Dentistry*. 2012. 34(7): 468–72.
- [12] Malvania EA, et al. Dental caries prevalence among type II diabetic and nondiabetic adults attending a hospital. *J Int Soc Prev Community Dent*. 2016. 6(Suppl 3): S.232–6.
- [13] Garton BJ, Ford PJ. Root caries and diabetes: risk assessing to improve oral and systemic health outcomes. *Australian Dent J*. 2012. 57(2):114–22.
- [14] Kaur G, et al. Association between type 1 and type 2 diabetes with periodontal disease and tooth loss. *J Clin Periodontol*. 2009. 36(9):765–74.
- [15] Serrano C, Perez C, Rodriguez M. Periodontal conditions in a group of Colombian type 2 diabetic patients with different degrees of metabolic control. *Acta Odontol. Latinoam*. 2012. 25(1): 130–7.
- [16] Bender IB, Bender AB. Diabetes mellitus and the dental pulp. *J Endod*. 2003. 29:383–9.
- [17] Lopez-Lopez J, et al. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. *J Endodont*. 2011. 37(5): 598–601.
- [18] Taylor GW, Manz MC, Borgnakke WS. Diabetes, periodontal diseases, dental caries, and tooth loss: a review of the literature. *Compend Contin Educ Dent*. 2004. 25(3): 179–190.
- [19] Jawed M, et al. Protective effects of salivary factors in dental caries in diabetic patients of Pakistan. *Exp Diabetes Res*. 2012: 947304. doi: 10.1155/2012/947304.
- [20] Carda C, et al. Structural and functional salivary disorders in type 2 diabetic patients. *Med Oral Patol Oral Cir Bucal*. 2006. 11(4): 309–14.
- [21] Alves C, et al. Oral health knowledge and habits in children with type 1 diabetes mellitus. *Braz Dent J*. 2009. 20(41): 70–3.
- [22] Merchant AT, Oranbandid S, Mayer-Davis EJ. Oral care practices and A1c among youth with type 1 type 2 diabetes. *J Periodontol*. 2012. 83(7): 856–63.
- [23] Orlando VA, et al. Oral Health Knowledge and Behaviors among Adolescents with Type 1 Diabetes. *Int J Dent*. 2010. 2010: 942124. doi: 10.1155/2010/942124.
- [24] Aggarwal A, Panat SR. Oral health behavior and HbA1c in Indian adults with type 2 diabetes. *J Oral Sci*. 2012. 54(4): 293–301.
- [25] Karikoski A, Ilanne-Parikka P, Murtomaa H. Oral self-care among adults with diabetes in Finland. *Community Dent Oral Epidemiol*. 2002. 30: 216–23.
- [26] Strauss S, Stefanou L. Interdental cleaning among persons with diabetes: relationships with individual characteristics. *Int J Dent Hyg*. 2014. 12(2): 127–32.
- [27] Cinar AB, Oktay I, Schou L. Self-efficacy perspective on oral health behaviour and diabetes management. *Oral Health Prev Dent*. 2012. 10(4): 379–87.

- [28] Kuryakina NV, Alekseeva OA. Change in indicators of general immunity at different times after a course of complex treatment in patients with periodontitis against diabetes mellitus. *Periodontology*. 2000. 1:22–5. [In Russ].
- [29] Bastos AS, et al. Diabetes mellitus and oral mucosa alterations: prevalence and risk factors. *Diabetes Res Clin Pract*. 2011. 92(1): 100–05.
- [30] González-Serrano J, et al. Prevalence of oral mucosal disorders in diabetes mellitus patients compared with a control group. *J Diabetes Res*. 2016. 2016: ID 5048967.11 p. doi:10.1155/2016/5048967.
- [31] Ship JA. Diabetes and oral health: an overview. *JADA*. 2003. 134(4): 1–10.
- [32] Mealey BL. Periodontal disease and diabetes: A two-way street. *J Am Dent Assoc*. 2006. 137(Suppl.): 26S–31.
- [33] Casarin RS, et al. Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis. *J Periodontal Res*. 2013. 48(1):30–6.
- [34] Alexandrov EI. Microflora and immunological resistance in case of dental caries and periodontal diseases against the background of diabetes mellitus. Medical and social problems of the family. 2014. 19(1):109–14. [In Russ].
- [35] Lalla E, et al. Periodontal changes in children and adolescents with diabetes: a case-control study. *Diabetes Care*. 2006. 29(2): 295–9.
- [36] Lopez R, Frydenberg M, Baelum V. Contextual effects in the occurrence of periodontal attachment loss and necrotizing gingival lesions among adolescents. *Eur J Oral Sci*. 2009. 117(5): 547–54.
- [37] Zharkova IV, Kabirova MF, Gerasimova LP. Dental status of persons with insulin-dependent diabetes mellitus. *Periodontology*. 2017. 22(4): 14–6. [In Russ].
- [38] Allen EM, Chaplle IL. The relationship between periodontitis and glycaemic control in type 2 diabetes. *Eur Endocrinol*. 2012. 8(2): 89–93.
- [39] Costa FO, et al. Progression of periodontitis and tooth loss associated with glycemic control in individuals undergoing periodontal maintenance therapy: a 5-year follow-up study. *J Periodontol*. 2013. 84(5): 595–605.
- [40] Schmidt AM, et al. Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: a potential mechanism underlying accelerated periodontal disease associated with diabetes. *J Periodontal Res*. 1996. 31(7): 508–15.
- [41] Albrecht M, et al. Occurrence of oral leukoplakia and lichen planus in diabetes mellitus. *J Oral Pathol Med*. 1992. 21: 364–6. <https://doi.org/10.1111/j.1600-0714.1992.tb01366.x>.
- [42] Saini R, et al. Oral mucosal lesions in non-oral habit diabetic patients and association of diabetes mellitus with oral precancerous lesions. *Diabetes Res Clin Pract*. 2010. 89: 320–6.
- [43] Oganov RG. Cardiovascular diseases at the beginning of the XXI century: medical, social, demographic aspects and ways of prevention. *Occupational medicine, restorative and preventive medicine*. 2013. 1: 257–64.
- [44] ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008. 52(8): 676–85.
- [45] Sivertsen TB, et al. Oral health among children with congenital heart defects in Western Norway. *Eur Arch Paediatr Dent*. 2016. Oct; 17(5): 397–406. doi: 10.1007/s40368-016-0243-y.
- [46] Pourmoghaddas Z, et al. Dental caries and gingival evaluation in children with congenital heart disease. *Int J Prev Med*. 2018. Jun 19; 9:52. doi: 10.4103/ijpvm.IJPVM_401_15. eCollection 2018.
- [47] Koerdt S, et al. Dental prevention and disease awareness in children with congenital heart disease. *Clin Oral Investig*. 2018 Apr; 22(3): 1487–1493. doi: 10.1007/s00784-017-2256-2.
- [48] Sivertsen TB, et al. Effectiveness of an oral health intervention program for children with congenital heart defects. *BMC Oral Health*. 2018. Mar 23; 18(1): 50. doi: 10.1186/s12903-018-0495-5.
- [49] Hughes S. The dental management of children with congenital heart disease following the publication of paediatric congenital heart disease standards and specifications. *Br Dent J*. 2019. Mar; 226(6): 447–452. doi: 10.1038/s41415-019-0094-0.
- [50] Makusheva NV. Clinical and diagnostic significance of the assessment of dental status in patients with atherosclerotic stenosis of the carotid arteries: dis. ... cand. honey. Sciences. Ufa, 2011:101 [In Russ].
- [51] Orlandi M, et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. *Atherosclerosis*. 2014. 236(1): 39–46. doi: 10.1016/j.atherosclerosis.2014.06.002.
- [52] Babenya AA. Features of the course of dental pathology in people with diseases of the cardiovascular system (literature review). *Bulletin of dentistry*. 2015. 1(90):97–100 [In Russ].
- [53] Reyes L, et al. Periodontal bacterial invasion and infection: contribution to atherosclerotic pathology. *J Clin Periodontol*. 2013. 40 (Suppl 14):30–50. doi: 10.1111/jcpe.12079.
- [54] Glascoe AL, et al. Oral-periodontal and systemic relationships: Part I. Cardiovascular and diabetes. *Austin J Dent*. 2015. 2(3): 1022. [<https://www.austinpublishinggroup.com/dentistry/fulltext/jd-v2-id1022.php>].
- [55] Mazur IP, Vitovsky RM, Slobodyanik MV. Microbiomes of periodontal pockets and biological material in patients with generalized periodontitis and valvular heart disease. *Dentistry. Aesthetics. Innovation*. 2018. 2:191–207. [In Russ].
- [56] Emingil G, et al. Association between periodontal disease and acute myocardial infarction. *J Periodontol*. 2000. 71(12): 1882–6.
- [57] Pussinen PJ, et al. Association of childhood oral infections with cardiovascular risk factors and subclinical atherosclerosis in adulthood. *JAMA Netw Open*. 2019. Apr 5; 2(4): e192523. doi: 10.1001/jamanetworkopen.2019.2523.

- [58] Van Dyke TE, Starr JR. Unraveling the link between periodontitis and cardiovascular disease. *J Am Heart Assoc.* 2013. 16, 2(6):657.
- [59] Ivashchenko YuYu, et al. The relationship of chronic pathology of the dentition with coronary heart disease and its complications. *Saratov Journal of Medical Scientific Research.* 2013. 9(3): 408-12 [In Russ].
- [60] Carallo C, et al. Common carotid and brachial artery hemodynamic alterations in periodontal disease. *J Clin Periodontol.* 2013. 40(5): 431–6.
- [61] Inaba H, Amano A. Roles of oral bacteria in cardiovascular diseases from molecular mechanisms to clinical cases: implication of periodontal diseases in development of systemic diseases. *J Pharmacol Sci.* 2010. 113(2): 103–9.
- [62] Accarini R, de Godoy MF. Periodontal disease as a potential risk factor for acute coronary syndromes. *Arquivos brasileiros de cardiologia.* 2006. 87(5): 592–6.
- [63] Gotsman I, et al. Periodontal destruction is associated with coronary artery disease and periodontal infection with acute coronary syndrome. *J of Periodontology.* 2007. 78(5): 849–58.
- [64] Chen YW, et al. Periodontitis may increase the risk of peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2008. 35(2): 153–8.
- [65] Kholly KE, Genco RJ, Van Dyke TE. Oral infections and cardiovascular disease. *Trends Endocrinol Metab.* 2015. 26(6): 315–21. doi: 10.1016/j.tem.2015.03.001.
- [66] Liljestrand JM, et al. Association of endodontic lesions with coronary artery disease. *J Dent Res.* 2016. 95:1358–65.
- [67] Eckel RH, et al. AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol.* 2014. 63(25 part B): 2960–984.
- [68] Reichert S, et al. Use of floss/interdental brushes is associated with lower risk for new cardiovascular events among patients with coronary heart disease. *J Periodontol Res.* 2015. 50(2): 180–8. doi: 10.1111/jre.12191.
- [69] Stephens MB, Wiedemer JP, Kushner GM. Dental problems in primary care. *Am Fam Physician.* 2018. Dec 1; 98(11): 654–660. PMID: 30485039.
- [70] Benítez-Páez A, Álvarez M, Belda-Ferre P. Detection of transient bacteraemia following dental extractions by 16S rDNA pyrosequencing: A pilot study. *PLoS One.* 2013. 8(3): e57782.
- [71] Holtfreter B, et al. Periodontitis is associated with endothelial dysfunction in a general population: a cross-sectional study. *PLoS One.* 2013. 8(12): 84603.
- [72] Mustapha IZ, et al. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. *J Periodontol.* 2007. 78(12): 2289–302.
- [73] Parahitiyawa NB, et al. Microbiology of odontogenic bacteremia: beyond endocarditis. *Clin Microbiol Rev.* 2009. 22(1): 46–4.