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Saliva as a Diagnostic Tool in Oral Diseases

Ağız Hastalıklarında Tanı Aracı Olarak Tükürük

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ABSTRACT

Saliva is a body fluid, which is secreted from 3 major salivary glands (parotid, submandibular and sublingual) and many minor salivary glands. It contains organic and inorganic substances with 99% water, and has several functions such as contribution to articulation, digestion, cleansing and protection of the oral mucosa, and antimicrobial effects. The concentration of saliva's substances vary according to the responses to physiological processes in the human body. Containing genetic materials such as DNA and RNA also highlights saliva as a potential diagnostic tool. Saliva analysis has advantages such as being cheaper, non-invasive, easier patient cooperation, and low technical sensitivity compared to blood tests; it can be used in the diagnosis of many diseases or routine risk assessments. It is also promising for its advantages in collection and storage of the samples. Advances in molecular biology, genomics, and proteomics have revealed the importance of saliva in the detection of many diseases, coining the term salivaomics. The early diagnosis of the diseases in which symptoms can be seen in late stages, may provide an easier treatment and improve the prognosis. In this review, the biomarkers of saliva in the presence of different diseases and the advantages of their use in diagnosis were examined.

Keywords: Saliva, oral diseases, diagnosis

ÖZ

Tükürük; başlıca üç majör tükürük bezi (parotid, submandibular ve sublingual) ve birçok minör tükürük bezinden salgılanan bir vücut sıvısıdır. İçerisinde %99 suyla birlikte organik ve inorganik maddeler bulunduran tükürüğün; artikülasyon, sindirim, ağız mukozasının temizlenmesi ve korunması ile antimikrobiyal etkiler gibi birçok işlevi vardır. Tükürüğün içerisindeki maddelerin konsantrasyonları vücuttaki fizyolojik süreçlere verilen yanıtlara göre değişiklik gösterir. DNA ve RNA gibi genetik materyalleri barındırması da tükürüğü potansiyel bir teşhis aracı olarak öne çıkarmaktadır. Kan tahlillerine göre hasta kooperasyonunun daha kolay olması, daha ucuz, non-invaziv ve teknik hassasiyetin az olması gibi avantajları olan tükürük testleri; birçok hastalığın teşhisinde kullanılabileceği gibi rutin risk değerlendirmelerinde de kullanılabilir. Örnek toplanması ve saklanmasındaki avantajlarından dolayı da gelecek vaad etmektedir. Moleküler biyoloji, genomik ve proteomik alanlarındaki gelişmeler sayesinde salivaomik terimi ortaya çıkmış ve birçok hastalığın saptanmasında tükürüğün önemi belirtilmiştir. Özellikle semptomların geç görülmeye başladığı hastalıkların tükürük testleri sayesinde erken teşhis edilmesi, tedaviyi büyük oranda kolaylaştırabilir ve prognozu iyileştirebilir. Bu derlemede, farklı hastalıkların varlığında tükürükte bulunan biyobelirteçler ve teşhiste kullanımının avantajları incelenmiştir.

Anahtar Kelimeler: Tükürük, ağız hastalıkları, teşhis

INTRODUCTION

Saliva is a body fluid, which is secreted from 3 major salivary glands, which are parotid, submandibular and sublingual, and nearly 1000 minor salivary glands. It helps to maintain the health and hygiene of the oral cavity and has many functions such as contribution to articulation, swallowing, and maturation of erupted teeth (1). Thanks to its antimicrobial properties, it is beneficial for the protection of microbial balance and the prevention of infections (2).

Saliva, secreted between 0.75 and 1.5 liters per day, is odorless, colorless and has a pH range of 6.5-7.5. It contains 99% water, organic and inorganic substances, and many microorganisms that play roles in different diseases (3). Organic substances are composed of urea, uric acid, glucose, fatty acids, glycerides, creatinine, peroxidase, amylase, and hormones. As for the inorganic molecules; Na^+, K^+, Ca^{2+}, Cl^-, Mg^{2+}, F^-, I^-, HCO_3- and $H_2PO_4^-$ are some of the ions found in saliva (4,5). These substances in the structure of saliva have different functions (6). For instance, amylase and lipase

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catalyze the digestion of carbohydrates and fats, while thiocyanate ions play a bactericidal role. Calcium in saliva contributes to the process of remineralization of tissues (7). Also, antioxidant enzymes in saliva protect the oral cavity from the negative effects of free radicals, reactive oxygen, and different forms of nitrogen (8,9). Some of the agents in saliva pass through transcellular and paracellular pathways from blood and their concentrations vary according to physiological processes, which makes saliva a potentially good diagnostic tool (10). Developments in molecular biology, genomics, and proteomics led to coining the term "salivaomics", which reveals the importance of salivary biomarkers in diagnosis of oral and systemic diseases and current stages of them (10).

The most important step for the treatment is to make an accurate diagnosis. When the clinical, radiological, and histological features of the disease are known, it will be easier to eliminate the disease factors (11). Caries, periodontal diseases, and oral malignant lesions are some of the examples of oral diseases that can be diagnosed with saliva tests (12). In addition to oral diseases, saliva can be used for the diagnosis of systemic diseases such as diabetes mellitus, cardiovascular diseases, and other infections. Also, it can be used for detection of drugs, and identification in forensics (13,14).

DENTAL CARIES

Dental caries is a common multifactorial oral disease that can progress to the loss of teeth with symptoms of pain by demineralization of mineralized tissues in enamel, dentin and cement (6). Dental caries are not reversible especially in the later stages, therefore it's essential to prevent it with good oral hygiene or to diagnose in early stages. Saliva can be easily used to detect risk factors because it contains structures such as molecules that cause remineralization and bacteria. There are many studies analyzing biomarkers by taking different saliva samples. Among the most important caries markers in saliva are microorganisms. *Lactobacilli* and *Streptococcus mutans* are the primary bacteria that cause caries. Other bacteria such as *Streptococcus sobrinus, Streptococcus cricetus, Streptococcus rattus, Streptococcus macacae, Streptococcus downei, and Prevotella genus* differ between healthy individuals and patients (8,15). Proteins like statherin, cystatin, histatins, and proline-rich proteins (PRP) contribute to maintenance of enamel's structural integrity, so they are important biomarkers in caries diagnosis. It has been shown that these proteins are found in larger amounts in individuals without previous caries history (16). It is thought that there is a difference in immunoglobulin (Ig) levels in the presence of caries. Although studies on this subject are limited, it has been revealed that IgA levels are higher in individuals with caries (17). Oxidative stress in saliva also causes the carious lesions, restricting the movement of dentin fluids, so the inflammatory response of dentin is affected. As a result, dentin becomes more sensitive to bacterial acids and the destruction of hard dentin tissues is observed. A study that examines the relation of salivary glutathione and dental health also showed that there may be a relation between caries and antioxidants found in saliva (18). Matrix metalloproteinases (MMP) such as collagenase in extracellular fluids, are enzymes that show cell death. Dentin contains collagen Type I and a small amount of collagen Type V, so the presence of collagenase in saliva causes destruction of dentin and indicates pulp or periodontal tissue destruction due to severe dental caries (19). Studies have shown that mucins may be another potential biomarker of caries. Mucins help to enhance the agglutination of bacteria, therefore they contribute to the protection of teeth from caries. So the decrease in mucins may accelerate demineralization (20). The amount, flow rate, and viscosity of saliva are important as well as the content for the prevention of dental caries (21). In the patients whose salivary flow rate is insufficient, saliva may not be able to clear the acids of the food consumed and eventually, the pH balance will deteriorate thorough acidic direction, which will increase the risk of caries (20). In a study in which erosion was examined by taking unstimulated saliva in children, the rate of saliva flow in children with erosion was noticeably lower than the control group. In the same study, the amount of chloride was higher in children with erosion (22).

PERIODONTAL DISEASES AND PERI-IMPLANTITIS

Periodontal diseases develop with inflammation of the gingiva, the periodontal ligament and alveolar bone around teeth and it is one of the reasons for tooth loss (23). Peri-implantitis, on the other hand, is a disease that develops in tissues around the implant and includes bone loss (24). Although their etiologies are similar, resorption in peri-implantitis progresses much faster. Many studies were carried out to provide early diagnosis of these diseases by detecting biomarkers in gingival fluid and saliva. The most important biomarkers are gram (-) bacteria such as *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, Prevotella intermedia, Campylobacter rectus, Fusobacterium nucleatum* and *Eikinella corrodens* (4,16). Studies revealed that an increase in the amount of salivary IgA, IgG, and IgM could contribute to the immunological response against these bacteria. The most commonly used methods for the detection of Igs in saliva are radial immunodiffusion and nephelometer. Also, an enzyme-linked immunosorbent assay (ELISA) can be used in detection of many biomarkers found in saliva in addition to Igs. Likewise, it has been observed that these glycoproteins decrease after treatment (25). Interleukins (IL) such as IL-1 and IL-6 are also involved in the inflammatory process in periodontitis and they have been proved to trigger osteoclastic activity and cause bone and tissue destruction. Interleukins may be products of epithelial cells, fibroblasts, osteoblasts, polymorphonuclear neutrophils, and endothelial cells and play a role in the activity of MMPs and their inhibitors (26). MMP-8 and MMP-9 are very important biomarkers in periodontal and implant-related diseases. PerioSafe and ImplantSafe, which are developed as applicable chair-side, are used in detecting active MMP-8, especially in oral fluids. While active MMP-8 was positive in patients with periodontitis or peri-implantitis, the response turned negative after the treatments (27). Other important factors determining periodontal health are oxidative stress markers. Studies that evaluated the total antioxidant capacity levels showed a decrease in antioxidants in non-smoking individuals with periodontal disease. The level of antioxidants rises again after the treatment (28,29). In another study, it was observed that the level of nitric oxide in saliva increased in patients with gingivitis, chronic and aggressive periodontitis as compared to healthy individuals, while adrenomedullin may be an important marker only in patients with aggressive periodontitis (8).

SJÖGREN'S SYNDROME

Sjogren's syndrome (SS) is an autoimmune disease that affects the secretory glands. Although the cause of this disease is not yet fully known, it may be accompanied by some inflammatory rheumatic diseases (30). Today, the diagnosis of SS is made by evaluation of the symptoms and the biopsy of the salivary glands. But it is possible to distinguish primary and secondary SS from each other or other autoimmune diseases such as systematic lupus erythematosus by conducting proteomic and transcriptomic examinations of saliva. Rheumatoid factor, Anti-Ro/SS-A and Anti-La/SS-B are conventional biomarkers used in the diagnosis of SS (31). Other than that, studies showed a relation between SS and 19 different genes, which were involved in the presentation of antigens and osmosis of lymphocytes (32). When patients and healthy individuals are compared; higher levels of IL-2, IL-4, IL-5, IL-6, clusterin, cathepsin-d, α-enolase, and β2-microglobulin are observed (10,26). It is also mentioned that there is oxidative stress in the presence of a disease. Markers such as increased oxidative DNA damage can play an important role in controlling the disease (4). A recent study evaluating lymphocytes in patients with SS concluded that lymphocytes are found in parotid saliva in both primary and secondary SS while there are no findings in healthy individuals (33).

ORAL PREMALIGNANT LESIONS AND ORAL CANCERS

Oral premalignant lesions are among the abnormalities that dentists frequently encounter after caries and periodontal diseases in their clinical applications. These lesions can turn into cancer if they are not treated or controlled with follow-up examinations. Lichen planus (LP) especially when it shows an erosive-atrophic pattern, leukoplakia, erythroplakia, precancerous melanosis and oral submucous fibrosis are some of the premalignant lesions that could be seen in the oral cavity (34).

Lichen planus: Chronic inflammation in epithelial cells can be seen as a white lesion with reticular structure and erythematous borders. Amalgam, non-steroidal anti-inflammatory drugs, and hepatitis C virus are thought to cause antigenic change as etiological factors (35). Currently, the most studied biomarkers in the diagnosis of lichen planus are cortisol, Igs, cytokines, and oxidative stress-related molecules. In a study, an increase was observed in salivary cortisol levels due to anxiety in patients with lichen planus when compared to healthy individuals (36). An analysis of Ig by ELISA showed an increase in IgA and IgG levels (25).

Leukoplakia: It is one of the frequently encountered precancerous lesions. There is a 10% risk of developing cancer in leukoplakia (37). Studies are carried out on cytokines as biomarkers. There are studies showing the increase in IL-1β, IL-6, cystatin, and apolipoprotein A-1 on unstimulated whole saliva in patients with leukoplakia (38,39).

*Oral cancer*s: Carcinomas seen in the oral cavity are among the most common cancers in the head and neck region (34). The most common is oral squamous cell carcinoma (OSCC). It has a high mortality rate in many countries. The initial diagnostic tool of carcinomas today is biopsies which are mostly invasive procedures (3). So the need for non-invasive diagnostic tools is increasing. More than 100 biomarkers are known for the diagnosis of oral cancers, primarily salivary proteins, RNA and DNA (4). While unstimulated whole saliva is generally used in detecting these biomarkers, there are studies showing that stimulated saliva gives the same valuable results. MicroRNAs (miRNA) obtained from saliva may have an important role in the diagnosis of head and neck cancers (10). It has been observed that miRNA-9 and miRNA-191 obtained from small amounts of saliva using the miRNA isolation kit and QIAzol methods together can be important biomarkers while there was a decrease in miRNA-125a and miRNA-200a levels in samples taken from patients with OSCC (16,40). In addition to miRNA, the tumor suppressor p53 gene and anti-p53 proteins that are produced in the presence of multiple DNA damages, CA15-3 and CA125 can be used as biomarkers for cancers in other regions (breast, ovarian, and lung cancers, etc.) as well as head and neck cancers (41). Moreover, MMPs are thought to play a role in different stages of the progression of tumors. In the cell proliferation phase, proteolytic MMPs may cause the activation of growth factors or intercellular destruction (19). In angiogenesis, they can change the activities of the endothelial and epithelial growth factor, control the inflammatory response, and affect invasion in the pathological process of new blood vessels. At the stage of invasion and metastasis, tumors need MMPs to interact with the membrane and extracellular matrix. Therefore, some MMPs can be produced by tumors or growth factors, chemokines, and cytokines. This way, tumors may grow locally and metastasize. Studies evaluating MMPs found in higher levels of MMP-1, MMP-2, MMP-9, MMP-10, and MMP-12 in patients as compared to healthy people (12,19).

SYSTEMIC DISEASES

Cardiovascular Diseases

They are among the leading causes of death in the world, include diseases such as hypertension, atherosclerosis, and myocardial infarction. In the presence of these diseases, changes in the levels of some biomarkers can be detected in saliva (42). In addition to the classical diagnostic methods (clinical findings and electrocardiogram, etc.) used today, studies on saliva analysis as a supportive tool are continuing. The level of C-reactive protein (CRP) in saliva can be determined by using a system based on nano-biochips, that can be applied chair-side (5). In a study of acute myocardial infarction patients who experienced chest pain in the previous 48 hours, CRP, MMP-9, IL-1β, adiponectin, gro-α, E-selectin, and IL-18 increased in saliva more than serum (42). In addition, there are studies showing that the amount of MMP-8 and lysozyme in saliva increases in the presence of hypertension (42). The level of vitamin C and antioxidants in serum and saliva can also affect the nitric oxide level, indicating carotid endothelial damage in atherosclerosis patients (43). In a study in individuals with ischemic heart disease and periodontitis, it was found that patients with ischemic heart disease have lower levels of lutein, lycopene, α-tocopherol and β-carotene levels in saliva (43).

Diabetes Mellitus

Today, the control of diabetes is done with blood tests, which is an invasive method. In saliva, glucose and urea levels are found to be in direct relation with blood levels (44). In diabetic patients, there was also an increase found in the levels of amylase, total protein, and electrolytes such as potassium, calcium and chloride (44,45).

Infections

It is common to use viral DNA and RNA biomarkers in saliva for the diagnosis of infections. Saliva is used in the diagnosis of many viruses such as Human Immunodeficiency Virus, Hepatitis A, B and C viruses, and rubella (8). Many studies are conducted on the use of saliva as a non-invasive tool to detect the COVID-19, which appeared in 2019 and the number of cases is increasing rapidly. The results of studies comparing the saliva and nasopharyngeal samples are promising (46). In a study conducted with 200 patients, who have symptoms of COVID-19, with an average age of 36, viral DNA was obtained from the samples taken and 19 patients were found to carry the virus according to the nasopharyngeal samples. When the saliva samples of these patients are examined, it has been shown that saliva can be used in virus detection by determining the compatibility of two samples with 84.2% sensitivity and 98.9% specificity (47).

Renal Diseases

Saliva can also be used in the diagnosis of renal diseases. Salivary creatinine levels show an increase in patients with renal diseases (48). Studies also have shown that selenium in saliva decreases in the presence of renal stones so it can be used as a biomarker (49). In addition, dialysis patients' salivary pH increases because of high urea concentrations (48).

CONCLUSION

Saliva is an important tool that contains biomarkers that are used in the diagnosis and treatment of many oral and systemic diseases. Saliva analysis has advantages such as being non-invasive, cheaper compared to blood tests, having good patient cooperation and low technical sensitivity. It is also promising for its advantages in collecting and storing samples. Saliva is actively used for some diseases today and with the advances in salivaomics, it can help as an alternative to serum or can be used in addition to some conventional diagnostic methods. However, studies need to be more comprehensive and standardized so that saliva tests will become more widespread and gain more importance in early diagnosis by using routine controls in the coming years.

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REFERENCES

1. Emekli N, Yarat A. Tükürük. Nobel Tıp Kitapevleri, İstanbul, 2008.
2. Sharma S, Gaur P, Gupta S. Impact of saliva on health: An overview. EJBPS 2018; 5(6): 202-4.
3. Martina E, Campanati A, Diotallevi F, Offidani A. Saliva and oral diseases. J Clin Med 2020; 9: 466. [CrossRef]
4. Wu DT, Tao O, Trinh N, Javaid MA, Ahmed AS, Durand R, et al. Saliva - A promising tool for diagnosing oral diseases. Curr Oral Health Rep 2018; 5: 242-9. [CrossRef]
5. Yordanova M, Gerova D, Galunska B. Saliva application in oral and systemic diseases. Scr Sci Med 2018; 50(2): 13-8. [CrossRef]
6. Akyüz S, Yarat A, Emekli Alturfan E, Kaya S. Flouride in saliva and its impact on health. In: Preedy VR, editor. Fluorine: Chemistry, Analysis, Function and Effects (Food and Nutritional Components in Focus). London: Royal Society of Chemistry 2015.p.173-85. [CrossRef]
7. Yarat A, Emekli Alturfan E, Akyüz S. Calcium in saliva and impact on health. In: Preedy VR, editor. Calcium: Chemistry, Analysis, Function and Effects (Food and Nutritional Components in Focus). London: Royal Society of Chemistry 2015.p.364-83. [CrossRef]
8. Zhang CZ, Cheng XQ, Li JY, Zhang P, Yi P, Xu X, et al. Saliva in the diagnosis of diseases. Int. J. Oral Sci. 2016 Sep 2. [CrossRef]
9. Tóthová L, Kamodyová N, Cervenka T, Celec P. Salivary markers of oxidative stress in oral diseases. Front Cell Infect Microbiol 2015; 5: 73. [CrossRef]
10. Tasoulas J, Patsouris E, Giaginis C, Theocharis S. Salivaomics for oral diseases biomarkers detection. Expert Rev Mol Diagn 2015; 17.
11. Bhat M, Bhat D. Salivary diagnostics in oral diseases. In: Gokul S, editor. Saliva and Salivary Diagnostics (book online) 2019 May (cited 2020 Mar 2): (19 pages). Available from: URL: https://www.intechopen.com/books/saliva-and-salivary-diagnostics/salivary-diagnostics-in-oral-diseases [CrossRef]
12. Buzalaf MAR, Ortiz AC, Carvalho TS, Fideles SOM, Araújo TT, Moraes SM, et al. Saliva as a diagnostic tool for dental caries, periodontal disease and cancer: is there a need for more biomarkers?. Expert Rev Mol Diagn 2020; 20(3): 543-55. [CrossRef]

13. Jessica, Auerkari EI. Saliva as a diagnostic tool in forensic odontology. J Dentomaxillofac Sci 2019; 4(3): 124-7. [CrossRef]
14. Pillai G, Krishnan AR, Subodh A, Rajan NS. Saliva: A diagnostic tool. World J Pharm Pharm Sci 2020; 9(5): 426-35.
15. Guo L, Shi W. Salivary biomarkers for caries risk assessment. J Calif Dent Assoc 2013; 41(2) :107-18.
16. Zhang X, Kulasinghe A, Karim R, Punyadeera C. Saliva diagnostics for oral diseases. In: Streckfus C, editor. Advances in Salivary Diagnostics. Springer, Berlin, Heidelberg 2015; 131-56. [CrossRef]
17. Silva Fidalgo TK, Freitas-Fernandes LB, Ammari M, Mattos CT, de Souza IPR, Maia LC. The relationship between unspecific s-IgA and dental caries: a systematic review and meta-analysis. J Dent 2014; 42(11): 1372-81. [CrossRef]
18. Öztürk LK, Furuncuoglu H, Atala MH, Uluköylü O, Akyüz S, Yarat A. Association between dental-oral health in young adults and salivary glutathione, lipid peroxidation and sialic acid levels and carbonic anhydrase activity. Braz J Med Biol Res 2008; 41: 956-9. [CrossRef]
19. Maciejczyk M, Pietrzykowska A, Zalewska A, Knaś M, Daniszewska I. The significance of matrix metalloproteinases in oral diseases. Adv Clin Exp Med 2016; 25: 383-90. [CrossRef]
20. Gao X, Jiang S, Koh D, Hsu CYS. Salivary biomarkers for dental caries. Periodontol 2000. 2016; 70: 128-41. [CrossRef]
21. Ezhil I, Savitha G, Kumar MPS. Saliva as a diagnostic tool: A review. Drug Invent. Today 2018; 10(11): 2188-93.
22. Zwier N, Huysmans MCDNJM, Jager DHJ, Ruben J, Bronkhorst EM, Truin GJ. Saliva parameters and erosive wear in adolescents. Caries Res 2013; 47(6): 548-52. [CrossRef]
23. Irani S, Barati I, Badiei M. Periodontitis and oral cancer - current concepts of the etiopathogenesis. Oncol Rev 2020; 14(1): 465: 23-34. [CrossRef]
24. Garcés MÁS, Escoda CG. Periimplantitis. Med Oral Patol Oral Cir Bucal 2004; 9: 63-74.
25. Lorenzo-Pouso A, Pérez-Sayáns M, Bravo SB, López-Jornet P, García-Vence M, Alonso-Sampedro M, et al. Protein-based salivary profiles as novel biomarkers for oral diseases. Dis Markers (journal online) 2018 Nov 7 (cited 2020 Mar 2): 6141845: (22 pages). Available from: URL: https://www.hindawi.com/journals/dm/2018/6141845/ [CrossRef]
26. Roi A, Rusu LC, Roi CI, Luca RE, Boia S, Munteanu RI. A new approach for the diagnosis of systemic and oral diseases based on salivary biomolecules. Dis Markers (journal online) 2019 Feb 17 (cited 2020 Mar 2): 8761860: (11 pages). Available from: URL: https://www.hindawi.com/journals/dm/2019/8761860/ [CrossRef]
27. Alassiri S, Parnanen P, Rathnayake N, Johannsen G, Heikkinen AM, Lazzara R et al. The ability of quantitative, specific, and sensitive point-of-care/chair-side oral fluid immunotests for aMMP-8 to detect periodontal and peri-implant diseases. Dis Markers (journal online) 2018 Aug 5 (cited 2020 Mar 2): 1306396: (5 pages). Available from: URL: https://www.hindawi.com/journals/dm/2018/1306396/ [CrossRef]
28. Ateş G, Öztürk H. Detection of total antioxidant capacity of saliva in periodontal diseases. EÜ Dişhek Fak Derg 2018; 39(3): 165-74. [CrossRef]
29. Başer Ü, Işık HG, Ateş G, Işık G. The effect of initial periodontal therapy on saliva and plasma total antioxidant capacity of non-smoking periodontitis patients. EÜ Dişhek Fak Derg 2015; 36(1): 38-44. [CrossRef]
30. Ramos-Casals M, Brito-Zerón P, Sisó-Almiral A, Bosch X. Primary Sjögren Syndrome. BMJ 2012; 344: e3821. [CrossRef]
31. Aktaş A, Giray B, Aktaş G. Saliva; composition and function, importance for diagnosis. ADO Journal of Clin Sci 2009; 3(2): 361-7.
32. Khuder SA, Al-Hashimi I, Mutgi AB, Altorok N. Identification of potential genomic biomarkers for Sjögren's Syndrome using data pooling of gene expression microarrays. Rheumatol Int 2015; 35(5): 829-36. [CrossRef]
33. Selifanova E, Beketova T, Spagnuolo G, Leuci S, Turkina A. A novel proposal of salivary lymphocyte detection and phenotyping in patients affected by Sjogren's Syndrome. J Clin Med. 2020; 9(2): 521. [CrossRef]
34. Özbayrak S, Pekiner FN. Ağız Kanserleri: Erken Tanı Bakımından Dişhekimliği. İstanbul: Quintessence; 2016. p.37-55.
35. Par M, Tarle Z. Psychoneuroimmunology of oral diseases - a review. Stoma Edu J 2019; 6(1): 55-65. [CrossRef]
36. Koray M, Dülger O, Ak G, Horasanli S, Üçok A, Tanyeri H, et al. The evaluation of anxiety and salivary cortisol levels in patients with oral lichen planus. Oral Dis 2003; 9(6): 298-301. [CrossRef]
37. Tekin M, Çam OH. Oral Mukoza Hastalıkları ve Semptomatolojisi. Klinik Gelişim 2012; 25: 93-8.
38. Brailo V, Vucicevic-Boras V, Lukac J, Biocina-Lukenda D, Zilic-Alajbeg I, Milenovic A, et al. Salivary and serum interleukin 1 beta, interleukin 6 and tumor necrosis factor alpha in patients with leukoplakia and oral cancer. Med Oral Patol Oral Cir Bucal 2012; 17(1): e10-5. [CrossRef]
39. Camisasca DR, Gonçalves LR, Soares MR, Sandim V, Nogueira FCS, Garcia CHS, et al. A proteomic approach to compare saliva from individuals with and without oral leukoplakia. J Proteomics 2017; 151: 43-52. [CrossRef]
40. Ghizoni JS, Nichele R, Oliveira MT, Pamato S, Pereira JR. The utilization of saliva as an early diagnostic tool for oral cancer: microRNA as a biomarker. Clin Transl Oncol 2020; 22(6): 804-12. [CrossRef]
41. Kaczor-Urbanowicz KE, Carreras-Presas CM, Aro K, Tu M, Garcia-Godoy F, Wong DTW. Saliva diagnostics - Current views and directions. Exp Biol Med (Maywood) 2017; 242(5): 459-72. [CrossRef]
42. Abdul Rehman S, Khurshid Z, Hussain Niazi F, Naseem M, Al Waddani H, Sahibzada HA, et al. Role of salivary biomarkers in detection of cardiovascular diseases (CVD). Proteomes 2017; 5(3): 21. [CrossRef]
43. Isola G, Polizzi A, Muraglie S, Leonardi R, Lo Giudice A. Assessment of vitamin C and antioxidant profiles in saliva and serum in patients with periodontitis and ischemic heart disease. Nutrients 2019; 11(12): 2956. [CrossRef]
44. Mrag M, Kassab A, Omezzine A, Belkacem Chebil R, Ben Fredj Ismail F, Nabiha D, et al. Saliva diagnostic utility in patients with type 2 diabetes: Future standard method. J Med Biochem 2019; 13. [CrossRef]
45. Abd-Elraheem SE, El Saeed AM, Mansour HH. Salivary changes in type 2 diabetic patients. Diabetes Metab Syndr 2017; 11(2): 637-41. [CrossRef]
46. Takeuchi Y, Furuchi M, Kamimoto A, Honda K, Matsumura H, Kobayashi R. Saliva-based PCR tests for SARS-CoV-2 detection. J Oral Sci 2020; 62(3): 350-1. [CrossRef]
47. Pasomsub E, Watcharananan SP, Boonyawat K, Janchompoo P, Wongtabtim G, Suksuwan W, et al. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease-2019 (COVID-19): a cross-sectional study. Clin Microbiol Infect 2020; 15. [CrossRef]
48. Deepa T, Thirrunavukkarasu N. Saliva as a potential diagnostic tool. Indian J Med Sci 2010; 64(7): 293-306. [CrossRef]
49. Emekli Alturfan E, Yarat A, Akyüz S. Selenium in saliva and impact on health. In: Preedy VR, editor. Selenium: Chemistry, Analysis, Function and Effects (Food and Nutritional Components in Focus). London: Royal Society of Chemistry; 2015.p.341-53. [CrossRef]