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Saliva Is a Diagnostic Tool- A Review

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ABSTRACT:
Early diagnosis of diseases is key to preventing problems that could harm a patient's quality of life. To get the better of these challenges, researchers are resolving biomarkers. These biomarkers include genetic material like DNA, RNA and protein molecules that consider the current physiological state of an individual and hence reinforce scientists to better understand the main cause of a disease. Due to its ease and non-invasive accessibility along with its plenty of biomarkers such as genetic material and proteins, saliva has been studied considerably as a potential diagnostic tool over the last decade.

Keywords: Saliva, diagnostic tool, biomarkers, body fluids.

I. INTRODUCTION:

Early diagnosis of diseases is key to preventing problems that could harm a patient's quality of life. For example, ovarian cancer, the fifth most frequent cancer and cause of death in females has a 5-year survival rate of 10% when identified at stage 4 in comparison to 93% if diagnosed at stage 1.[1] Similarly, type 2 diabetes, which affects 7% of the adult population, can be primarily controlled by diet and change in lifestyle if the diagnosis is made untimely. [2] Moreover, despite regular screenings and check-ups, many diseases are obscure until a late phase where pathological symptoms become apparent. To get the better of these challenges, researchers are resolving biomarkers. These biomarkers include genetic material like DNA, RNA and protein molecules that consider the current physiological state of an individual and hence reinforce scientists to better understand the main cause of a disease.[3] Over the years, studies have shown that changes in human genetics can be identified by molecular diagnostics, and abnormality in nucleic acids and proteins present in the patient's body fluids such as blood, cerebrospinal fluid (CSF) and urine can be used as biomarkers for disease diagnosis[.4–6]However, many obstacles remain such as lack of biomarkers for certain diseases, absence of economical sample collection methods sustaining minimal discomfort, and sparsity of accurate and portable detection systems.[3] Fortunately, some of these restrictions can be overcome by analyzing one's saliva. Due to its ease and non-invasive accessibility along with its plenty of biomarkers such as genetic material and proteins,3 saliva has been studied considerably as a potential diagnostic tool over the last decade.[7]

Brain diseases:

The use of alternative biomarkers has become common when identifying methylation changes associated with mental diseases[8]. The extent to which surrounding tissues can be used as a substitute for brain DNA methylation was determined by Braun et al[9]. Saliva-brain correlation (r ¼ 0.90) was higher when compared with blood-brain (r ¼ 0.86) and buccal-brain correlation (r ¼ 0.85). Hence Proved that the biomarkers in saliva can be used for the detection of diseases[9] related to the brain in which, AD is a long neurodegenerative disease, which mainly occurs in the brain[10] .In the saliva sample of AD patients, various amino acids and derivatives were determined based on chromatography-tandem mass spectrometry. In agreeing with diagnostic model results got the specificity, accuracy, and sensitivity with 92% ,80.6%, 61%, respectively. It shows that certain amino acids and derivatives are potential biomarkers for early and non-invasive AD detection. A small but statistically significant increase in salivary Aβ42 levels in patients with mild AD was found by McGeer et al.[11].It shows that the level of Aβ42 in saliva can be regarded as a potential biomarker of AD. It also helps to differentiate it from other types of neurodegenerative diseases. It proves that

biomarkers in saliva are important for detecting brain-related diseases.

Oral disease:

Oral diseases are one of the most prevalent diseases globally and have serious health and economic burdens, greatly reducing the quality of life of the affected people. Saliva can be used as a diagnostic tool for various oral diseases. Two biomarkers significantly upregulated in oral squamous cell carcinoma (OSCC)saliva and were not affected by risk factors (smoking, alcohol, betel nut chewing, human papillomavirus and Epstein Barr Virus) impact. Detection of early OSCC, PRDX-2 got the accuracy, sensitivity and specificity with 95.9%, 95%, and 93.83%, respectively ZAG got the accuracy, sensitivity and specificity with 90.4%, 85%, and 100%, respectively, the two biomarkers combined got the accuracy, sensitivity and specificity with 99.9%, 100% salivary biomarkers to diagnose autoimmune diseases (Sjogren's syndrome)have been found.

Diseases of the esophagus:

Gastroesophageal reflux disease (GERD) develops when gastric reflux causes uncomfortable symptoms and complications [12].GERD is a common disease of the esophagus. the enzyme which plays an important role in the pathophysiology of GERD is pepsin. The detection of salivary pepsin may help the diagnosis of GERD found by Samuels et al[13]. The study suggests that salivary pepsin may reduce the use of unnecessary antireflux therapy. It has been proposed that salivary pepsin can be used as a non-invasive diagnostic method for reflux disease [14]. The study by Yu et al. [15] found that IS (intercellular space) was an important saliva biomarker for detecting esophagus-related diseases. Wang et al. [16]conducted a study to investigate the oral microflora of patients with esophageal squamous cell carcinoma (ESCC). His study includes 20 patients with ESCC and 21 healthy controls. He collects saliva samples from both control and patients with ESCC. The amplification of the V3–V4 region of 16S rDNA was done and sequenced by the IlluminaMiSeq high-throughput sequencing platform. The study shows that the bacterial diversity and richness of the ESCC group were lower than that of the control group. it was also found that the variability of the ESCC group was higher than the control group. They also specify that the high risk of ESCC is related to actinomycetes. Hence this saliva biomarker can be used to detect esophageal cancer.

Large intestine diseases:

Ulcerative colitis (UC) is one of the familiar diseases of the digestive system. It is difficult to determine the development, outcome, and prognosis of the disease as there are no specific indicators for determining the degree of UC[17]. Recently, it was found by Althaus et al.[18] that the disease degree of patients with active ulcerative colitis can be reflected by serum C reactive protein (CRP) in saliva. Colorectal cancer (CRC) is another familiar disease of the digestive system and also the third most common cancer in humans. Using real-time qRT-PCR, the expression of miR-21 in peripheral blood and saliva samples obtained from healthy controls and patients diagnosed with different degrees of malignant CRC was quantified. Significant differences were found between the CRC patients in the control group and the entire experimental group. The diagnostic sensitivity and specificity of miR-21 expression in plasma were 65% and 85%. The diagnostic sensitivity and specificity of miR-21 expression obtained were 97% and 91% in saliva. The data of this study shows that miR-21 in both the saliva and plasma could be a proper biomarker for CRC screening. the study also proves that the saliva miR-21 expression test is the best due to its higher sensitivity, specificity, and technical simplicity. Besides, esophageal cancer (EC) study on miR-10b*, miR-144, miR-21, and miR-451 shows that their specificities were 57.9, 89.5, 47.4, and 84.2%, and sensitivities were 79.5, 43.6, 89.7, and 51.3% respectively [19]. Alexandre et al.[20] also highlighted that saliva is the most ideal biomarker for the detection of colorectal diseases, and also disease can be detected earlier even before clinical symptoms appear.

Kidney symptoms related to diseases

The diagnostic value and significance of saliva diagnosis for kidney diseases have been seen by more researchers in recent years[21]. It was found that the amount of saliva secretion, saliva flow rate, and its contents are closely related to the rise and fall of kidney yin and kidney yang and their regulatory functions by Idkaidek et al.[22]. Alexandra et al. [23]have also found that the detection of saliva creatinine content and the detection of serum creatinine content has similar clinical significance. To determine the disease status of patients with chronic renal insufficiency saliva diagnosis can be used. By detecting the content of salivary urea nitrogen in saliva[24], the effect of dialysis has been determined in patients with kidney disease. Pallas et al.[25] also found that in chronic renal failure, patient the level of

nitric oxide is significantly increased.in addition to that saliva showed higher levels of immunoglobulin, after hemodialysis treatment. Finally, this study highlighted that the levels of immunoglobulin and nitric oxide in saliva play an important role in monitoring kidney disease.

Ovary cancer

The deadliest of all reproductive tract cancers in females is Ovarian cancer. Its survival rate is only 30%[26] as it is usually detected in the advanced stage. CA-125 and MUC16 proteins are the saliva biomarkers that are most commonly used for the diagnosis of ovarian cancer. It is impossible to differentiate ovarian cancer from benign diseases (e. g. pregnancy, endometriosis, menstrual abnormalities, and pelvic inflammatory disease) as CA-125 is also elevated in these benign diseases. To enhance its ability to distinguish ovarian cancer from benign diseases[27], it is important to find CA-125 auxiliary biomarkers .for malignancy of ovarian cancers, it was proposed by Berbec et al.[26] that the salivary TSA level can be used as an auxiliary indicator. To diagnose ovarian cancer, identify benign diseases and tumors, and evaluate the prognosis of treatment, the level of SA in saliva can be used as an auxiliary means which was proved by Zermeo et al.[28]. To distinguish stage III ovarian cancer from benign diseases, the level of TSA in the saliva is used as the level of TSA in the saliva of stage III ovarian cancer was significantly lower than that of benign diseases and healthy controls which were shown by Wu et al.[29].the level of TSA in the saliva is reduced in early-stage (stage I/II) ovarian cancer. These findings are helpful for the early detection of ovarian cancer. As a potential auxiliary biomarker, TSA can compromise the lack of sensitivity and specificity of CA-125.

Prostate cancer

Prostate cancer is a malignant tumor of the male reproductive system and has the highest mortality[30]. The biomarkers in saliva that are used for prostate cancer detection are MiR-141 and miR-21.in advanced prostate cancer patients, MiR-141 is significantly elevated. in early prostate cancer patients, miR-21 is overexpressed. nanographene oxide is proven to be helpful in the detection of the expression of miR-21 and miR-141 in saliva. It will be used as a minimally invasive or a non-invasive method for diagnosing early prostate cancer[31].

Liver diseases

Viral infection can be detected by antiviral antibodies and viral antigens in saliva[32] By detecting antiviral antibodies in saliva, viral infections can be determined such as hepatitis A virus, hepatitis B virus, and hepatitis C virus .also there is a significant correlation between liver disease and saliva caffeine clearance. Hence for the diagnosis and assessment of chronic liver disease, saliva can be used as an effective biochemical parameter[33].

II. CONCLUSION

The significance of saliva in the early detection of tissue and organ-related diseases, that's expected to develop into customized medicine. The effectiveness of saliva diagnosis in identifying diseases including cancer can successfully correspond with clinical diagnosis, and further research can be used as a biomarker for the histological grading and clinical stage of the disease. Despite this, the clinical effectiveness of saliva in the assessment of systemic diseases has been established in this review. This review suggested that it is obligatory to design experiments to reduce the effect of factors influencing saliva diagnosis on the final forecast results. The union of saliva biomarkers obtained by chip devices and artificial intelligence can greatly refine the accuracy of diagnosis.

REFERENCE:

[1]. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. SeminSurgOncol. 2000;19 (1):3–10.
[2]. Crandall JP, Knowler WC, Kahn SE, et al. The prevention of type 2 diabetes. Nat ClinPractEndocrinolMetab. 2008;4 (7):382–393.
[3]. Lee YH, Wong DT. Saliva: an emerging biofluid for early detection of diseases. Am J Dent. 2009;22(4):241–248.
[4]. Anker P, Mulcahy H, Chen XQ, Stroun M. Detection of circulating tumor DNA in the blood (plasma/serum) of cancer patients. Cancer Metastasis Rev. 1999;18(1):65–73.
[5]. Rieger-Christ KM, Mourtzinos A, Lee PJ, et al. Identification of fibroblast growth factor receptor 3 mutations in urine sediment DNA samples complements cytology in bladder tumor detection. Cancer. 2003;98(4):737–744.
[6]. Wong LJ, Lueth M, Li XN, Lau CC, Vogel H. Detection of mitochondrial DNA mutations in the tumor and cerebrospinal

fluid of medulloblastoma patients. Cancer Res. 2003;63(14):3866–3871.
[7]. Pfaffe T, Cooper-White J, Beyerlein P, Kostner K, Punyadeera C. Diagnostic potential of saliva: current state and future applications. Clin Chem. 2011;57(5):675–687.
[8]. Wong CCY, Smith RG, Hannon E, et al. Genome-wide DNA methylation profiling identifies convergent molecular signatures associated with idiopathic and syndromic autism in post-mortem human brain tissue. Hum Mol Genet 2019;28(13):2201–11. https://doi.org/10.1093/hmg/ddz052.
[9]. Braun P, Hafner M, Nagahama Y. Genome-wide dna methylation comparison between live human brain and peripheral tissues within individuals. EurNeuropsychopharmacol 2017;27:506–16. https://doi.org/10.1038/s41398-019-0376-y.
[10]. Sylwia W, Strosznajder AK, Jeyna M. The novel role of PPAR alpha in the brain: promising target in therapy of Alzheimer's disease and other neurodegenerative disorders. Neurochem Res 2020;45(2):1–17. https://doi.org/10.1007/s11064-020-02993-5.
[11]. Bautista C, Torres CI, Baquero M. Early neurotransmission impairment in non-invasive Alzheimer Disease detection.Sci Rep 2020;10:16396.https://doi.org/10.1038/s41598-02073362-z.
[12]. Bognar L, Vereczkei A, Papp A. Gastroesophageal reflux disease might induce certain—supposedly adaptive—changes in the esophagus: a hypothesis. Dig Dis Sci 2018;63(10):2529–35. https://doi.org/10.1007/s10620-018-5184-3.
[13]. Samuels TL, Johnston N. Pepsin in gastroesophageal and extraesophageal reflux: molecular pathophysiology and diagnostic utility. CurrOpinOtolaryngol Head Neck Surg 2020;28(6):1–9. https://doi.org/10.1097/MOO.0000000000000664.
[14]. Mohamed H, Khodeer S, Shaheen W. Study of pepsin level in saliva as a noninvasive marker for diagnosis of gastroesophageal reflux disease. Menoufia Med J 2020;33(1):94–103. https://doi.org/10.4103/mmj.mmj_371_16.
[15]. Yu WL, Daniel S, Chenxi. Relationship between salivary pepsin concentration and esophageal mucosal integrity in patients with gastroesophageal reflux disease. J NeuroGastroenterolMotil 2017;23(4):517–25. https://doi.org/10.5056/jnm16178.
[16]. Wang Q, Rao Y, Guo X. Oral microbiome in patients with oesophageal squamous cell carcinoma. Sci Rep 2019;9:19055. https://doi.org/10.1038/s41598-019-55667-w
[17]. Matsuoka K, Kobayashi T, Ueno F. Evidence-based clinical practice guidelines for inflammatory bowel disease. J Gastroenterol 2018;53(3):305–53. https://doi.org/10.1007/s00535-018-1439-1.
[18]. 18.Althaus T, Lubell Y, Maro VP. Sensitivity of C-reactive protein for the identification of patients with laboratory-confirmed bacterial infections in northern Tanzania. Trop Med Int Health 2019;25(3):1–9. https://doi.org/10.1111/tmi.13358.
[19]. Xie Z, Chen G, Zhang X. Salivary microRNAs as promising biomarkers for detection of esophageal cancer. PLoS One 2013;8(4):57502. https://doi.org/10.1371/journal.pone.0057502.
[20]. AlexandreLoktionov. Biomarkers for detecting colorectal cancer non-invasively: DNA, RNA or proteins. World J GastrointestOncol 2020;12(2):4–28. https://doi.org/10.4251/wjgo.v12.i2.124
[21]. Marinoski J, Bokor BM, Mitic I. Oral mucosa and salivary findings in non-diabetic patients with chronic kidney disease. Arch Oral Biol 2019;102:205–11. https://doi.org/10.1016/j.archoralbio.2019.04.021.
[22]. Idkaidek N, Hamadi SA, Qatouseh LF. Applicability of saliva for evaluation of some biochemical parameters of kidney and liver function in healthy individuals.Med Lab J 2020;14(4):135–47. https://doi.org/10.29252/mlj.14.4.1.
[23]. Alexandra GK, Kristína P, Robert L. Dynamics of salivary markers of kidney functions in acute and chronic kidney diseases. Sci Rep 2020;10(1):21260.https://doi.org/10.1038/s41598-020-78209-1.
[24]. Calice SV, Vieira MA, Raimann JG. Saliva urea nitrogen dipstick-a novel bedside diagnostic tool for acute kidney injury.ClinNephrol 2014;82(6):358–66. https://doi.org/10.5414/CN108370.

[25]. Pallos D, Le~ao MV, Togeiro FC. Salivary markers in patients with chronic renal failure. Arch Oral Biol 2015;60(12):1784–8. https://doi.org/10.1016/j.archoralbio.2015.09.008.

[26]. Berbec H, Paszkowska A, Siwek B. Total serum sialic acid concentration as a supporting marker of malignancy in ovarian neoplasia. Eur J Gynaecol Oncol1999;20(5–6):389. https://doi.org/10.1016/S0009-9120(01)00265-X.

[27]. Alan K, Marta U, Dwyer ME. Glycosylation-based serum biomarkers for cancer diagnostics and prognostics.BioMed Res Int 2015;2015:490531. https://doi.org/10.1155/2015/490531.

[28]. Zermeo NJ, Martínez MM, Ramirez AL. Determination of sialic acid in saliva by means of surface-enhanced Raman spectroscopy as a marker in adnexal mass patients: ovarian cancer vs benign cases. J Ovarian Res 2018;11(1):61–9. https://doi.org/10.1186/s13048-018-0433-9.

[29]. Jing W, Xiao L. Altered expression of sialylated glycoproteins in ovarian cancer sera using lectin-based ELISA assay and quantitative glycoproteomics analysis. J Proteome Res 2017;12(7):3342–52. https://doi.org/10.1021/pr400169n.

[30]. Bray F, Kiemeney LA. Epidemiology of prostate cancer in Europe: patterns, trends and determinants[M]//Management of Prostate Cancer. Cham: Springer; 2017.p. 1–27. https://doi.org/10.1007/978-3-319-42769-0_1.

[31]. Hizir MS, Balcioglu M, Rana M. Simultaneous detection of circulating oncomiRs from body fluids for prostate cancer staging using nanographene oxide. ACS Appl Mater Interfaces 2014;6(17):14772–8. https://doi.org/10.1021/am504190a.

[32]. Corstjens PLAM, Abrams WR, Malamud D. Saliva and viral infections.Periodontology 2000;70(1):93–110. https://doi.org/10.1111/prd.12112.2016.

[33]. Tripathi A, Tiwari B, Patil R, et al. The role of salivary caffeine clearance in the diagnosis of chronic liver disease. J Oral BiolCraniofac Res 2015;5(1):28–33.https://doi.org/10.1016/j.jobcr.2014.12.003.