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Recent trends in the development of diagnostic tools for diabetes mellitus using patient saliva

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ABSTRACT

Diabetes mellitus is a worldwide health concern due to its high prevalence; almost 8.3% of the global population suffers from diabetes. It is a group of metabolic diseases classified by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Owing to the lack of simple diagnosis and treatment strategies, diabetes is a major cause of death worldwide, and more than 50% of cases remain undiagnosed. In addition, without timely diagnosis, diabetes-related complications and morbidity increase exponentially. Therefore, early diagnosis of diabetes is essential to prevent devastating complications. The current method of investigation requires a painful needle-prick to take blood, which could discourage individuals from seeking diagnosis. Recently, researchers have attempted to use patient saliva as a non-invasive method for identifying cases of diabetes. In this feature article, we discuss recent trends in the development of diagnostic tools for diabetes mellitus using patient saliva.

1. Introduction

Diabetes mellitus is a multifarious metabolic disorder in which the concentration of fasting plasma glucose (FPG) is higher than 126 mg/dL, or in which blood glucose is above 200 mg/dL at any time of day [1,2]. This hyperglycemic condition results from defects in insulin secretion, insulin action, or both. Based on the current statistics from the International Diabetes Federation (IDF, Belgium), more than 415 million adults worldwide were living with diabetes in 2015, and this is expected to increase to 642 million people by 2040 [3]. There are three major types of diabetes in addition to a stage immediately preceding diabetes called pre-diabetes. In all three major types of diabetes mellitus, the common feature is glucose homeostasis disorder, which represents a leading cause of morbidity and mortality worldwide [4,5]. Pre-diabetes is a metabolic condition wherein blood sugar rises to a level higher than that of the normal range but lower than that of diabetes [6]. Patients with pre-diabetes have an increased risk for type 2 diabetes and other complications [7–9]. In addition, specific types of diabetes are caused by other conditions, including monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes in young individuals), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with treatment for HIV/AIDS or after organ transplantation) [10].

Almost all types of diabetes result in an increased risk for developing a number of serious health complications; particularly, high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys, nerves, and teeth (Fig. 1). In addition, people with diabetes are at a higher risk of developing infections, which significantly shortens life expectancy [11–14]. Early diagnosis can prevent or delay long-term health complications in people with diabetes; thus, a person living with undiagnosed and/or untreated diabetes is likely to experience a worse health outcome. However, the early stages of diabetes might not cause any signs and symptoms. Quickly recognizing elevated blood glucose levels can reduce the complications associated with diabetes. Currently, a diagnosis is achieved by evaluating blood glucose levels, and a blood glucose level above 126 mg/dL is diagnosed as diabetes [5]. However, monitoring blood glucose at frequent intervals causes unnecessary discomfort and mental trauma to patients, and hence a much simpler and non-invasive technique for the diagnosis and monitoring of diabetes is desirable. To overcome

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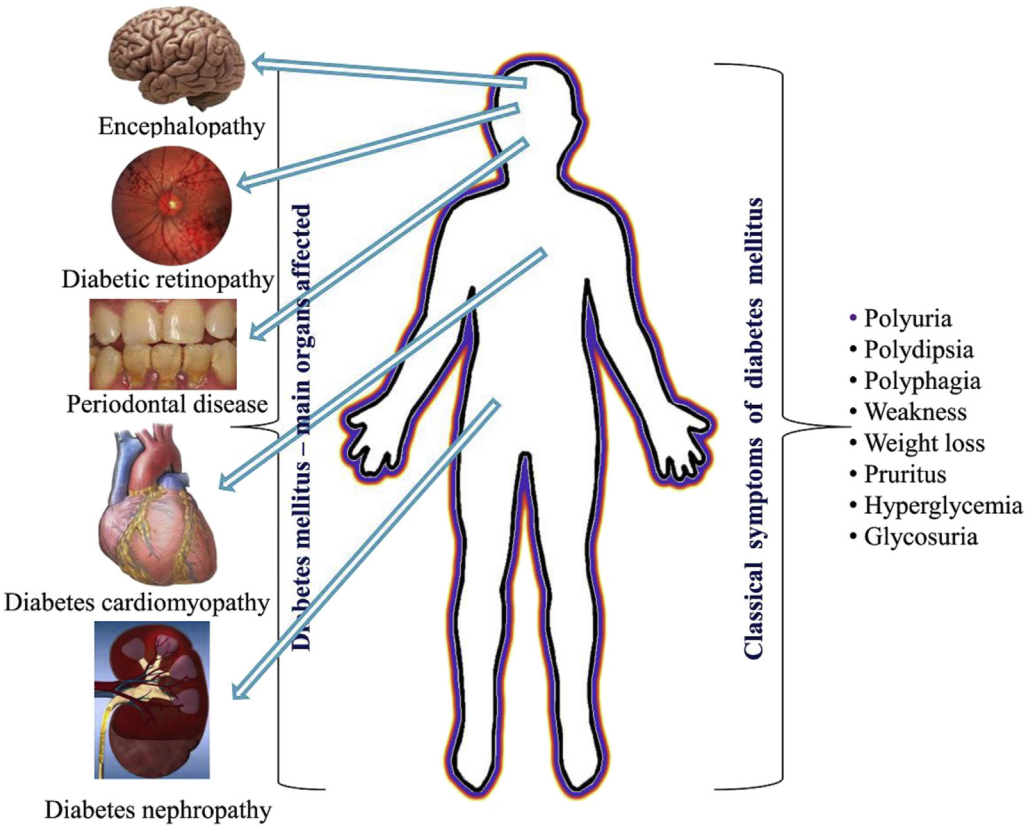

Fig. 1. Classical symptoms and organs affected in diabetes mellitus.

these challenges, researchers have attempted to use saliva as a diagnostic tool for diabetes, as it can be obtained easily, using non-invasive methods [15–22]. In addition, as in serum, saliva contains antibodies, enzymes, growth factors, hormones, and microbes and their products; thus, in many cases, it can be seen as a reflection of the physiological state of the body, and as such, researchers have shown variable correlation rates between serological and saliva parameters [15,22–24]. This review will summarize emerging trends in the development of diagnostic tools for diabetes mellitus using patient saliva.

2. Physiological considerations in the use of saliva as a diagnostic tool

Human saliva, a biological fluid of great importance produced by the salivary glands, has high potential for the surveillance of general health and diseases [25–27]. In addition, its collection is easy and non-invasive. Saliva, the properties of which are mainly determined by secretions from the major and minor salivary glands [28], performs a large number of functions that are indispensable for both oral and general health (Fig. 2). Saliva is principally composed of water (>99%), but has several minor components including cytokines, digestive enzymes, growth factors, immunoglobulins, mucus, antibacterial peptides, bacterial cells, salts, and low molecular weight metabolites [28]. In addition, saliva contains several biomarkers, which makes it useful for multiplexed assays that are being developed for point-of-care devices, rapid tests, or for more consistent formats for centralized clinical laboratory operations. Salivary diagnostics is a dynamic field that is being integrated for disease diagnosis and clinical monitoring, and for making significant clinical decisions regarding patient care [29,30]. A list of salivary components having potential for diagnostics is presented in Table 1. The most important observation is that proteins present in blood are similarly present in saliva from fluid leakage at the gum line [28]. Therefore, it is significantly easier, safer, and more economical to collect saliva than to draw blood. In addition, unlike blood testing, the analysis of saliva occurs at the cellular level, and consequently saliva is representative of clinically relevant parameters [31]. In contrast, in the blood, compounds travel throughout the blood serum, most of which are protein bound. As a result, saliva has played a significant role in the early detection, treatment planning, and prognosis. It also offers an advantage over serum and other biological fluids through its economical and non-invasive collection. There are many health issues and disease parameters that can be successfully assayed using saliva, including acne [32], cholesterol [33], cancer [34,35], stress [36], periodontal diseases [37], acute coronary syndrome [38], allergies [39], gingival overgrowth [40], heart problems [15,41], chronic renal failure [42], diabetes mellitus [17,43], cold body temperature [44], pathogenic diseases [15,45], sleep problems [44], difficulties in conceiving [46], and oral hygiene [47]. Saliva-based diagnostics can also help in devising early treatment strategies. Thus, based on the enhanced efficiency of genomic and proteomic technologies, the use of salivary diagnostics in a clinical setting is becoming a reality. In addition, a recent improvement in salivary diagnostics, specifically through 'salivary metabolomics', which investigates a large array of low molecular weight endogenous metabolites in the saliva, has become an important tool for the detection of many diseases including diabetes. Moreover, there have been several reports demonstrating changes in salivary composition during diabetes mellitus [17,43,48].