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Salivary markers of kidney function — Potentials and limitations

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ABSTRACT

Saliva can be collected non-invasively, repeatedly and without trained personnel. It is a promising diagnostic body fluid with clinical use in endocrinology and dentistry. For decades, it is known that saliva contains also urea, creatinine and other markers of renal function. Clinical studies have shown that the salivary concentrations of these markers could be useful for the assessment of kidney function without the need of blood collection. This article summarizes the clinical and experimental data on the use of saliva as a diagnostic fluid in nephrology and points out the advantages, pitfalls, technical requirements and future perspective for the use of saliva as a novel potential diagnostic biofluid.

Contents

1. Introduction

Saliva is a body fluid with a broad diagnostic potential. It is used as a source of DNA, either for genotyping of human DNA or for the analysis of oral microbiome [1]. Salivary RNA is studied as a potential marker of oral

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malignancies [2]. Nucleic acids present in saliva are of local origin, although the cells from which they are derived might have originated from elsewhere such as blood or bone marrow [3]. Low molecular weight compounds present in saliva often originate from the systemic circulation [4]. The salivary concentration of such solutes partially correlates with their plasma concentrations. The most commonly clinically used salivary biomarkers are salivary steroids, such as cortisol, testosterone and estradiol. Numerous other molecules present in saliva are under investigation such as melatonin, oxytocin, interferon and interleukins [5].

Urea was found in saliva already in 1951 and a number of studies analyzed its changes as a potential marker of kidney diseases [6–9]. This review summarizes the available literature on the use of saliva for the measurement of renal function, outlines the obstacles that hindered the clinical use of saliva in nephrology and points out the main advantages of saliva that could spark future research and potential clinical applications.

2. Saliva secretion and composition

Daily salivary secretion is approximately 1000 ml, ranging from 800 ml to 1500 ml. Saliva is an aqueous solution with a pH of 6.0–7.0, which is the most suitable range for the digestive action of enzymes such as ptyalin [10]. Initial saliva has the same ion composition as plasma, i.e. it is isotonic. The final saliva is hypotonic with high potassium and bicarbonate and low natrium and chloride concentrations. Within the salivary glands, the acinar cells secrete initial saliva with proteins/peptides such as amylase, lipase, mucin glycoproteins, immunoglobulin A and kallikrein and the ductal cells modify the initial saliva to hypotonic final saliva via ion transporters, ion channels and a relative water impermeability [11].

The final saliva has a complex composition. In addition to solutes mentioned above, it includes magnesium, calcium, zinc, phosphates, urea, and ammonium [12]. Antibacterial substances like lysozymes, agglutinins, secretory immunoglobulin A, lactoferrin, peroxidase or cystatins and statherins are secreted into saliva. A fungal growth is inhibited by histidine-rich proteins, or histatins [13]. Saliva also contains mucin that coats food and thereby protects mucous epithelium against mechanical, thermal or chemical irritation [11] and proline-rich proteins [14]. To date, more than 2400 proteins were identified in saliva, and each of them might be potentially interesting as a biomarker [15].

Besides substances that are produced and/or secreted by the salivary glands, saliva contains also compounds originating from other body compartments. Desquamated or death epithelial cells of the oral cavity and buccal-pharyngeal mucosa are found in the saliva, including released organelles or microvesicles such as exosomes [16]. Blood or serum components can get into saliva by either passive diffusion, active transport or by ultrafiltration of extracellular fluids induced by hydrostatic pressure through tight junctions between acinar cells. The gingival crevicular fluid, i.e. the exudate from the gingival margin termed crevice, along with the bronchial or nasal fluids are further components of whole saliva [17]. Depending on the status of the gingiva and microbial colonization, the crevicular fluid can be either a serum transudate with low protein content or exudate with higher protein content due to local inflammation, both containing serum constituents, e.g. microRNAs [18], cytokines or steroid hormones such as cortisol or sex hormones [19].

3. Factors influencing saliva secretion

Saliva secretion, especially its flow, is mostly increased because of chewing or taste [20]. Apart from these, another major factor influencing the speed of saliva secretion is autonomic nervous system, where sympathetic stimulation generally down-regulates and parasympathetic stimulation on the contrary up-regulates the salivary flow [11]. Indeed, the autonomic nervous system with brainstem solitary tract nuclei is linked with other — higher brain centers as is amygdala, or orbitofrontal cortex. Such salivary flow is a constant process and when not further increased by chewing, it is referred to resting salivary flow. On contrary, the chewing stimulation of salivary secretion, it is important for food to stimulate the receptors in periodontal ligament. Additionally, the taste salivary secretion is dependent on diet composition [21]. In studies, acids, i.e. citric acid are the most potent salivary flow stimulants. However, since such stimulants do not commonly occur in the diet in its acidic form, the chewing and taste can be equally efficient. Smell is another factor that through orbitofrontal cortex can trigger salivation, although to smaller extent then aforementioned factors [11]. Although the Pavlovian type response can influence the salivary flow, this is true in animals, e.g. dogs. In humans, it seems that mouthwatering during the sight or thought of food is induced by smell sense [22]. Additionally, the mouthwatering when smell stimulus is missing, is not considered as increased salivary flow, rather it is due to the contraction of skeletal facial muscles that squeeze the salivary ducts resulting in increased saliva in mouth. From other physiologic properties of human body, the circadian cycle also contributes to the speed of resting salivary flow [23]. While salivary flow is highest in the afternoon hours, it diminishes to very low speed during sleep thus copying the activation of autonomous nervous system during daytime. Gender also influences the salivary flow, with females having smaller salivary flow when compared to males, however, this is simply explained by smaller salivary glands in females [21]. The effect of age on salivary flow currently remains obscure. Several studies found that elderly people have decreased salivary flow when compared to young controls. Nevertheless, this contributed to higher and continuous medication such as hypertensive, antipsychotic, and anxiolytic use in the elderly rather than the direct effect of age [24]. Indeed, overall status and systemic diseases may as well contribute to the variability in salivary flow. Of these, dehydration is one of the most important factors, where decrease in body fluids by approximately 8% leads to dramatic reduction in salivary flow [21].

The relatively high number of components renders saliva a promising diagnostic biological fluid. The various factors influencing salivary composition might be, however a source of biased results. As exemplified for urea, its salivary concentration can be decreased by bacteria of oral cavity possessing urease activity [25]. Some substances, considered as uremic toxins such as malondialdehyde or advanced oxidation protein products [26], can also be directly or indirectly influenced by the oral microbiome. Although the long-term dietary habits seem not to influence the oral microbiome [27], short-term changes in diet, in particular of those containing microbiota, may influence the oral microbiome resulting in change of malondialdehyde and advanced oxidation protein products [28]. Thus, the major salivary source of markers of renal function is derived from circulation, however, other factors have to be taken into account when interpreting these parameters. Under normal circumstances, metabolic degradation products such as urea, creatinine, and nitritesis excreted by the kidneys into the urine. In diseased kidneys, these compounds accumulate in the systemic circulation and get into saliva, either directly or are excreted by salivary glands. Exogenous sources or sources of potential bias are food contamination or salivary microbiome composition.

For further details, there are several comprehensive high quality review articles regarding saliva physiology, composition and functions [11,17,21,29–31].

4. Kidney disease classification

Currently, the use of serum creatinine as a marker of kidney function is inadequate. Since the serum creatinine is influenced by creatinine secretion or extrarenal secretion, the real glomerular filtration rate must decline by half to detect elevated creatinine serum concentrations [32]. Therefore, the glomerular filtration rate (GFR) is the measure of choice to determine overall kidney status. In clinical practice, Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommended the use of serum creatinine based estimates of GFR, which is referred to