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ORIGINAL ARTICLE

# Salivary and Serum Biochemical Analysis from Patients with Chronic Renal Failure in Hemodialysis: A Cross-Sectional Study

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**ABSTRACT**

**Objective:** To compare salivary and serum biochemical levels in patients with chronic renal failure undergoing hemodialysis. **Material and Methods:** The sample was composed of 57 patients treated in Hemodialysis Reference Centers, from a state of Northeastern Brazilian, with age ≥21 years old with at least 3 months of hemodialysis treatment time. Serum data were obtained from records. Unstimulated and stimulated saliva were collected. Flow rate (mL/min) was measured. Spectrophotometry was performed for the measurement of salivary levels of calcium (570 nm), urea (340 nm), and creatinine (510 nm). Statistical analysis used Mann Whitney and Kruskal-Wallis tests ($p<0.05$). **Results:** Unstimulated and stimulated salivary flow rates were 0.43 mL/min and 1.69 mL/min, respectively. There was significant difference ($p<0.001$) of levels of calcium (5.41 mg/dL and 9.70 mg/dL), urea (118.03 mg/dL and 183.22 mg/dL) and creatinine (0.59 mg/dL and 9.20 mg/dL) between saliva and serum, respectively. Concerning the time of hemodialysis, salivary and serum calcium not exhibited significant association; however, serum urea ($p=0.012$) and serum creatinine ($p=0.025$) showed significant association to the time of hemodialysis. **Conclusion:** Salivary biochemical levels of urea, creatinine and calcium can indicate the presence of a possible chronic renal failure and the saliva demonstrated to be a potential auxiliary biofluid for clinical monitoring renal alterations.

**Keywords:** Kidney Failure, Chronic; Renal Insufficiency, Chronic; Calcium; Creatinine; Saliva.

## Introduction

According to The Global Burden of Disease study is estimated that 1.2 million people have died of kidney failure, with an increase of 32.0% since 2005. It has been observed that 5 to 10 million people die each year from kidney disease [1-4]. Chronic renal failure (CRF) is a progressive disease characterized by the gradual destruction of nephrons and a consequent reduction of kidney function occurring over a few months or years [5-7]. With the development of that process, the glomerular filtration rate reduces below 15 mL/min, leading to accumulation of metabolic such as urea and creatinine in serum [4,8-13]. CRF can be diagnosed by measurement creatinine serum levels, which are a degradative product of muscle protein. High creatinine levels indicate CRF; its activities are raised, indicating a lowered glomerular filtration rate [11,13,14].

Dialysis treatment leads to systemic changes, oral complications, and salivary flow rate changes and saliva composition [9,15]. Analyze the flow rate, pH and biochemical composition (urea, creatinine, and calcium) that demonstrate identifiable and regular changes from pre-dialysis to post-dialysis states can enable necessary monitoring of dialysis efficacy and the level of renal function in patients with CRF [9,14]. Ninety percent of patients with CRF have oral complications caused by changes in bones and soft tissues of mouth [7,16]. Such oral complications alter salivary composition reflecting at systemic levels. In such a way, saliva has been increasingly appreciated as a biofluid readily available in laboratory tests for bacteria, genomics, drugs of abuse, hormones, an increasing number of other indicators of health, cancer and CRF [14,17]. Saliva is considered a filtrate of the blood where various molecules pass through transcellular or paracellular routes into saliva [8,16-18]. The use of saliva as a substitute for other body fluids, such as blood, would have advantages for the diagnosis, such as the non-invasive characteristic of the test, ease in the saliva collection procedure, the quantity required to perform the test, reduced costs in collecting, transporting, and storing the samples to be examined and greater safety for health professionals regarding the risk of contamination [8,9,11,17-19].

Studies have shown variations in salivary levels of urea, creatinine, sodium, and potassium in renal failure patients [1,5,11,14,18,20-23]. Based on the availability of improved salivary diagnostic systems, this study analyzed salivary levels of creatinine, urea, and calcium of patients with CRF, considering the time of hemodialysis treatment, and comparing with serum levels, thus suggesting a possible use of saliva as a biomarker of chronic renal failure.

## Material and Methods

### Study Design and Ethical Approval

This cross-sectional study included 57 patients. Patients were diagnosed and treated at four services reference for CRF treatment, from a state of Northeastern Brazilian, and evaluated by experient stomatologist. Inclusion criteria were patients who had above 21 years old, ≥ with at least 3 months of hemodialysis treatment time and free from any infectious condition related to CRF. Exclusion criteria were records without necessary information for research and with hemodialysis treatment time lower than 3 months. The study was approved by the Research Ethics Committee (Approval No. 0336.0.133.000-11). Patient anonymity was guaranteed according to the Helsinki Declaration.

### Patient Information and Clinical Data

Clinical parameters considered were age (mean in years), sex (male and female), race (white and black), and hemodialysis treatment time (< 2 years, 2–5 years, and > 5 years). Calcium, creatinine, and urea serum levels were also obtained from medical records.

Saliva Collection

Saliva collection occurred by morning period before hemodialysis session. The collection time always occurred at close times to 8 a.m to 9 a.m due to the circadian cycle. Unstimulated and stimulated salivary flow rates were determined by the method proposed by López-Pintor et al. [22]. All subjects were given instructions not to smoke, eat, drink or toothbrush at least 90 minutes prior to saliva collection. The patients were seated in an upright position and asked to relax during spitting.

To obtain unstimulated salivary flow, the patients were asked to swallow the saliva present in the mouth and to remain seated with a bowed head without moving the tongue and/or swallowing saliva. For stimulated saliva, the patients were asked to chew Parafilm (Sigma-Aldrich Inc., Saint Louis, USA) to stimulate salivary flow. For five minutes, saliva was collected in a graduated sterile cylinder. The obtained values were expressed in milliliters per minute (mL/min), and the reading from the sample was done one hour after collection to avoid interference from foam in the saliva. Hyposalivation was considered when salivary flow rate was <0.1 mL/min at rest or <0.7 mL/min under stimulation [23].

After collection, graduated sterile cylinders containing saliva were transported to the laboratory in an icebox, under temperature at -20º C, and sent to the laboratory within 60 minutes. In the laboratory, storage of the saliva was made in -80º C freezer until the time of biochemical analysis.

Salivary Biochemical Analysis

Before biochemical analysis, stimulated saliva samples were then centrifuged at 3.500 rpm for 5 minutes - Centrifuge Ev. 04 (Evlab – Indústria e Comércio de Produtos para Laboratórios, Londrina, PR, Brazil). After this, the supernatant was discarded. Analysis was performed in triplicate using 96 well microplates. Each well containing 32 µL of first reagent (acid) and 0,4 µL of sample, and then incubated in for 5 minutes at 37º C (Splabor - Comércio de Produtos para Laboratório, São Paulo, SP, Brazil). After this, in each well was added 8 µL of second reagent (buffer solution) (Labtest Diagnóstica, Lagoa Santa, MG, Brazil). This process was performed for all salivary components evaluated.

Salivary biochemical analysis was performed to colorimetric method by spectrophotometry - EZ Read 400 Microplate Reader (Biochrom Ltd., Cambridge, UK), with levels of absorbance suggested by the manufacturer (Labtest Diagnóstica, Lagoa Santa, MG, Brazil), at a wavelength of 570 nm for calcium, 340 nm for urea, and 510 nm for creatinine. Measurement analysis was performed in the Galapagos Software for EZ Read Microplate Readers (Biochrom Ltd., Cambridge, UK), being repeated two times to confirm the results found.

## Results

Patient Information and Clinical Data

Of 57 individuals observed that majority were men (57.9%), black race (64.9%) and with age ≥ 41 years old (87.7%) Regarding the time of hemodialysis treatment, the majority had been submitted by two to five years (42.1%) (Table 1).

Unstimulated and stimulated salivary flow rates exhibited, as median, respectively, 0.43 mL/min (range: 0.26-0.79) and 1.69 mL/min (range: 1.12-2.27). Therefore, all patients evaluated were not considered to have hyposalivation.

**Table 1. Distribution of participants according to demographic variables and time on hemodialysis.**

| Variables | N | % |
|---|---|---|
| Sex | | |
| Female | 24 | 42.1 |
| Male | 33 | 57.9 |
| Ethnicity | | |
| White | 20 | 35.1 |
| No White | 37 | 64.9 |
| Age | | |
| ≤ 40 Years | 7 | 12.3 |
| ≥41 Years | 50 | 87.7 |
| Time on Hemodialysis | | |
| <2 Years | 10 | 17.5 |
| 2 to 5 Years | 24 | 42.1 |
| >5 Years | 23 | 40.4 |

Salivary Biochemical Data

Calcium, urea, and creatinine concentrations revealed a statistically significant difference between serum and saliva (p<0.001). The median of serum calcium concentration was 9.70 mg/dL, while in saliva 5.41 mg/dL. Median of serum urea concentration (183.22 mg/dL) was higher than observed in saliva (118.03 mg/dL). However, Pearson's correlation test showed a moderately positive correlation between concentrations of urea in saliva and blood (r=0.326; p=0.013). Median of serum creatinine concentration (9.20 mg/dL) was higher than observed in saliva (0.59 mg/dL). Spearman's correlation test revealed a moderately positive correlation (r=0.447; p<0.001) (Table 2).

**Table 2. Difference of concentration of calcium, urea and creatinine between saliva and blood.**

| Biochemical Parameters | Saliva (mg/dL) | Blood (mg/dL) | p-value |
|---|---|---|---|
| Calcium | 5.41 (3.32-7.61)** | 9.70 (9.25-10.00)** | <0.001* |
| Urea | 118.03 (40.29)*** | 183.22 (36.80)*** | <0.001* |
| Creatinine | 0.59 (0.32-1.13)** | 9.20 (8.05-11.40)** | <0.001* |

*Kruskall Wallis Test; ** and *** Indicate, respectively, quartile and standard deviation.

Correlating the time of hemodialysis treatment with calcium concentration in saliva and serum revealed no statistically significant association (p=0.225 and p=0.245, respectively) (Table 3).

**Table 3. Comparison of calcium concentration in saliva and serum with hemodialysis time.**

| Local | Time | N | Median ($Q_{25}$-$Q_{75}$) | p-value |
|---|---|---|---|---|
| Saliva | < 2 Years | 10 | 7.61 (4.83-11.04) | 0.225 |
| | 2–5 Years | 24 | 5.49 (4.08-7.18) | |
| | > 5 Years | 23 | 4.85 (3.08-7.51) | |
| Serum | < 2 Years | 10 | 9.35 (8.80-10.00) | 0.245 |
| | 2–5 Years | 24 | 9.75 (9.35-10.27) | |
| | > 5 Years | 23 | 9.60 (9.30-9.90) | |

Also, there was no statistically significant association of salivary urea concentrations with time of hemodialysis treatment (p=0.373). On the other hand, a statistically significant association was found between serum urea concentrations with time of hemodialysis treatment (p=0.012). The highest values were observed in patients submitted to hemodialysis treatment for more than five years (Table 4).

There was no statistically significant association of salivary creatinine concentration with time of hemodialysis treatment (p=0.434). In contrast, there was a statistically significant association between serum

creatinine concentration with time of hemodialysis treatment (p=0.025), where the highest values were observed in patients submitted to hemodialysis treatment during two to five years (Table 5).

**Table 4. Comparison of urea concentration in saliva and serum in relation to hemodialysis time.**

| Local | Time | N | Mean (SD) | p-value |
|---|---|---|---|---|
| Saliva | < 2 Years | 10 | 103.00 ± 22.85 | 0.373 |
| | 2–5 Years | 24 | 124.50 ± 42.77 | |
| | > 5 Years | 23 | 117.82 ± 43.11 | |
| Serum | < 2 Years | 10 | 157.00 ± 20.61[a] | 0.012* |
| | 2–5 Years | 24 | 180.75 ± 34.30[a,b] | |
| | > 5 Years | 23 | 197.21 ± 38.98[b] | |

Letters a and b express the results of post hoc tests corrected by the Bonferroni penalty, where different letters indicate a statistically significant difference; *Mann Whitney Test.

**Table 5. Comparison of creatinine concentration in saliva and serum in relation to hemodialysis time.**

| Local | Time | N | Median ($Q_{25}$-$Q_{75}$) | p-value |
|---|---|---|---|---|
| Saliva | < 2 Years | 10 | 0.39 (0.32-0.89) | 0.434 |
| | 2–5 Years | 24 | 0.64 (0.41-1.20) | |
| | > 5 Years | 23 | 0.67 (0.29-1.25) | |
| Serum | < 2 Years | 10 | 7.95 (7.15-9.15) | 0.025* |
| | 2–5 Years | 24 | 9.60 (8.85-11.60) | |
| | > 5 Years | 23 | 9.20 (8.80-13.00) | |

## Discussion

CRF is the most common form of kidney disease, with an estimated prevalence worldwide of about 10.4% among men and 11.8% among women [1]. However, our results differ, since CRF was much more prevalent in men than in women. Concerning age, our findings demonstrated that most patients had an age greater than or equal to 40 years old, which corroborates the results of some studies [5,12,24,25]. In Brazil, the prevalence of CRF is high; approximately 11 to 22 million adults are estimated to have some degree of renal dysfunction in a population of about 200 million and 70% of the adult population [2]. In the Brazilian Northeast exist 134 dialysis units, and our study corresponded to approximately 3% of this totality. Therefore, it is suggested that our results could represent the situation of CRF in this region.

When considering that oral evidence and symptoms are sometimes the only objective indicators of systemic diseases, dentists could play a key role in the early diagnosis of CRF [26]. In addition, since most of the salivary biomolecules are derived from serum [27,28], laboratory analyses of the components of saliva could be particularly important in the early asymptomatic stages of CRF [26], being the serum calcium, urea and creatinine are widely accepted parameters for assessing CRF status [28]. Some studies demonstrated that saliva could be equivalent to serum, thereby reflecting the physiological state systemic [16-18].

In this perspective, our results have demonstrated that serum and salivary levels of calcium, urea, and creatinine exhibit significant statistical differences (p<0.001). Our findings are consistent with previous studies [2,29-32], adding to the existing data to support the possibility of employing analysis of salivary creatinine and urea for the diagnosis and assessment of CRF [33].

Regardless of the mechanisms responsible for their presence in saliva, evidence of serum/ saliva associations pointed to the possibility that plasma levels of calcium, urea and creatinine play a key role in regulating the secretion and/ or diffusion of these plasma metabolites in saliva [11,21,33]. The practical implications of the study concerned a possible use of saliva for screening or monitoring for renal dysfunction

and associated disorders. Everywhere, analyses of a sample of saliva are promised as diagnostic body fluid in clinical use in endocrinology and dentistry [11,31,33].

Salivary functions, including lubrication, buffer capacity, tooth integrity maintenance, antibacterial activity, taste, and digestion, may be altered by lower salivary flow and biochemical alterations [9,15]. Some oral signs and symptoms are associated with a decreased renal function, such as xerostomia, dysgeusia, and uremic odor, which were the most prevalent oral symptoms among subjects with CRF. The change in taste could be explained by the direct effect of uremic toxins on oral chemoreceptors [10,17,25,26], which is consistent with the finding of increased salivary urea in the present study in relation to the time of hemodialysis, although not statistically significant when compared to serum urea (p=0.373). Another consequence for altered levels of urea is characterized by decreased active metabolite levels of synthesized vitamin D in the kidney. The consequence is an increase in parathyroid hormone synthesis and secretion (secondary hyperparathyroidism), inducing lower calcium levels [16].

Early stages of CRF are characterized by kidney damage and are generally asymptomatic [5,6,12]. As the renal disease worsens, the renal function begins to deteriorate, leading to end-stage renal disease, which requires renal transplantation or hemodialysis [5,10]. Thus, it is important to evaluate salivary composition according to the time of hemodialysis [34].

Regarding the time of hemodialysis, the majority of patients exhibit more salivary alterations the longer the time of treatment [17,18,25]. However, our results no demonstrated this association. There was an association of serum urea and creatinine levels with the time of treatment of patients. Some studies have shown that when there is an increase in serum urea, there is a concomitant increase in salivary urea because the kidneys are unable to excrete urea due to kidney failure [28-30]. As for creatinine, its value increases in saliva, possibly due to a change in the permeability of cells in the salivary gland, creating a concentration gradient that facilitates serum creatinine diffusion in saliva [28-30].

The main limitations found for our study's development were sample size since many patients underwent hemodialysis in the afternoon and evening and the absence of data on the protocol for measuring serum levels in medical records.

## Conclusion

Salivary biochemical levels of urea, creatinine and calcium can indicate the presence of a possible chronic renal failure and the saliva demonstrated to be a potential auxiliary biofluid for clinical monitoring renal alterations.

## Authors' Contributions

| | | |
|---|---|---|
| IMFG | https://orcid.org/0000-0001-6049-2252 | Conceptualization, Writing - Original Draft and Writing - Review and Editing. |
| MBP | --- | Conceptualization, Investigation, Data Curation and Supervision. |
| ASL | --- | Data Curation and Writing - Original Draft. |
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| CFWN | https://orcid.org/0000-0003-2380-109X | Methodology, Formal Analysis, Data Curation and Writing - Review and Editing. |
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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

## Financial Support

None.

## Conflict of Interest

The authors declare no conflicts of interest.

## Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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