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***Research Article***

# Assessment of Salivary Creatinine and Urea as Non-Invasive Alternatives to Serum Markers in Healthy Individuals

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**Abstract**

**Background:** Conventional methods for assessing renal function, which rely on serum urea and creatinine, are invasive and can lead to patient compliance issues. Saliva offers a non-invasive alternative, but the correlation between serum and salivary markers in healthy individuals remains unclear.
**Aim:** This study aimed to quantify and compare the concentrations of urea and creatinine in serum and unstimulated whole saliva in a cohort of apparently healthy students, thereby assessing the potential of salivary markers as non-invasive alternatives.
**Methods:** A cross-sectional study was conducted on 60 apparently healthy students. Paired blood and unstimulated whole saliva samples were collected. Urea was estimated using the enzymatic Urease-Berthelot method, and creatinine was measured using the kinetic Jaffe's method. Data were analyzed using T-tests for comparison of means and Pearson's correlation (r), with $p < 0.05$ considered significant.
**Results:** Mean blood urea (3.00 mmol/L) was not significantly different from mean salivary urea (2.50 mmol/L) ($p > 0.05$). Mean blood creatinine (186.20 umol/L) was significantly higher than mean salivary creatinine (59.20 umol/L) ($p < 0.05$). Neither urea ($r = -0.1$, $p > 0.05$) nor creatinine ($r = -0.05$, $p > 0.05$) showed a statistically significant correlation between blood and saliva concentrations.
**Conclusion:** The non-significant difference between mean blood and salivary urea concentrations suggests that salivary urea holds potential as a reliable non-invasive marker for further validation in populations with renal disease. The lack of correlation is likely a statistical consequence of the narrow reference range in the healthy study population.

## 1. Introduction

The accurate and timely diagnosis of renal dysfunction is critical for preventing the progression of chronic kidney disease (CKD) and reducing associated morbidity and mortality. Conventional diagnostic methods rely heavily on the quantification of biomarkers such as urea and creatinine in serum (blood) and urine. While highly effective, the collection of blood is an invasive procedure that can cause psychological distress, physical trauma, and compliance issues, especially in pediatric or elderly populations, or in settings with limited phlebotomy expertise [1, 2]. These challenges often lengthen the turnaround time for laboratory results, thereby delaying patient care.

In response to the need for less invasive and more patient-friendly diagnostic approaches, there has been increasing interest in utilizing alternative biofluids, particularly saliva. Saliva is a clear, viscous fluid secreted by the salivary and mucous glands. Importantly, it is known to contain a wide array of biomarkers, including urea and creatinine, which are filtered from the blood [3, 4].

The potential for saliva to serve as a diagnostic matrix for renal function is supported by the mechanism of transport of low molecular weight compounds. Urea (60 Da) and creatinine (113 Da) are small molecules primarily transported from the blood into the salivary glands

via ultrafiltration, suggesting a direct relationship between their serum and salivary concentrations [5]. Previous studies examining this relationship have shown mixed results; strong positive correlations have been reported in patients with established renal disease, but the correlation is often weaker or non-existent in apparently healthy control groups [2, 6]. For instance, some studies on healthy controls have reported poor correlation for creatinine, which may be attributed to its higher molecular weight and lower lipid solubility compared to urea, limiting its easy transfer across the salivary gland membranes [7]. Conversely, salivary urea has been frequently cited as a highly sensitive marker, even in the early stages of CKD, due to its rapid and proportional diffusion into saliva [8].

Given the conflicting reports in healthy populations, the clinical utility of salivary biomarkers as a general screening tool remains to be conclusively established. This study therefore aimed to precisely quantify and compare the levels of key renal markers—urea and creatinine—in both blood and unstimulated whole saliva in a cohort of apparently healthy young adults. The primary goal was to determine the strength of the correlation and the degree of statistical difference between serum and salivary concentrations for each analyte, specifically investigating which, if any, salivary marker holds promise as a reliable, non-invasive alternative to serum measurements in individuals without overt kidney disease.

## 2. Materials and Methods

### Study Design and Population

This was a cross-sectional study. A total of 60 apparently healthy students in Rivers State, aged 18 years and above, were recruited using a simple random sampling technique. The minimum sample size of 59 was determined. Exclusion criteria included subjects with known oral, kidney, cardiovascular, pulmonary, or liver disease, as well as smokers and diabetic individuals. Ethical approval was obtained from the Rivers State Ministry of Health Ethics Committee, and informed consent was secured from all participants prior to sample collection.

### Sampling Method

Participants enrolled for the study were selected via simple random sampling technique where the participants were given equal opportunity to be chosen using a binary system of “0” and “1” where participants were required to pick from this system such that all those who picked “0” were excluded from the participation while those while those who picked “1” were recruited for the study.

### Sample Collection and Processing

**Saliva Collection:** Unstimulated whole saliva (4–5 mL) was collected by the spitting method, where subjects were instructed to spit into an open-mouthed universal container with their heads tilted downward. The collected saliva was centrifuged, separated, and stored at 4°C in a 5 mL plain container.

**Blood Collection:** Venous blood (5 mL) was drawn from the median cubital vein using a standard venipuncture procedure. The sample was transferred to a plain container, allowed to clot, centrifuged, and the resulting serum was separated and stored at 4°C.

### Laboratory Analysis

All biochemical analyses were performed at the Chemical Pathology laboratory of PUMS using a BOSCH 752N UV VIS Spectrophotometer. Commercially available, quality-controlled diagnostic kits were used for the estimation of the analytes. The primary methodology for the markers was as follows:

**Urea:** Estimated using the enzymatic Urease-Berthelot method. Urea is hydrolyzed by urease into ammonia and carbonic acid; the ammonia is then measured spectrophotometrically at 550nm after reacting with phenol and hypochlorite to form a blue color.

**Creatinine:** Estimated using the kinetic colorimetric Jaffe’s method. Creatinine reacts with picric acid in an alkaline solution to form a colored complex, the intensity of which is directly proportional to the creatinine concentration, read at 500nm.

### Statistical Analysis

Data were collated in a spreadsheet and analyzed using SPSS version 21.0. Descriptive statistics were used to determine the mean and standard deviation SD for all measured parameters. Inferential statistics included an independent samples T-test to compare the mean concentrations between blood and saliva, and Pearson’s correlation analysis to determine the linear relationship between the two biofluids. A p-value of $<0.05$ was considered statistically significant.

## 3. Results

Figure 1: Mean Comparison of Blood and Salivary Urea Concentrations This bar chart displays the mean blood urea concentration (3.00 mmol/L) and mean salivary urea concentration (2.50 mmol/L), showing no statistically significant difference (P=0.05).

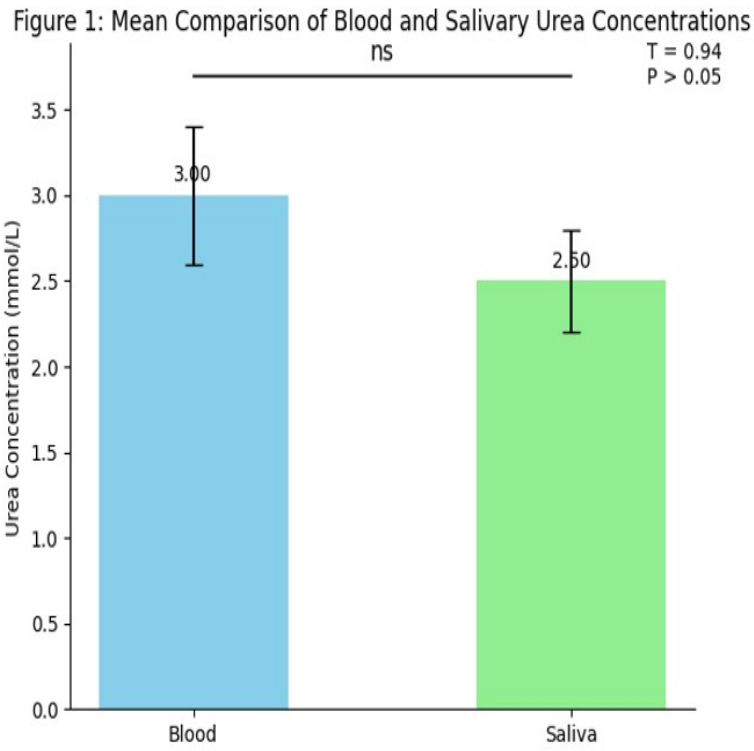



Figure 2: Mean Comparison of Blood and Salivary Creatinine Concentrations This bar chart illustrates the mean blood creatinine concentration (186.20 µmol/L) and mean salivary creatinine concentration (59.20 µmol/L), indicating a statistically significant difference ($P<0.05$).

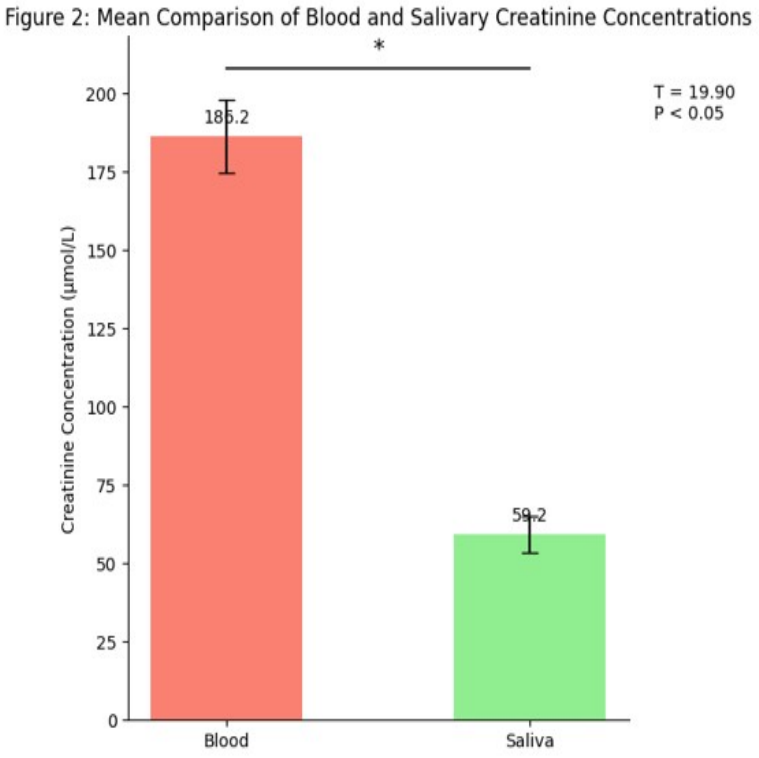
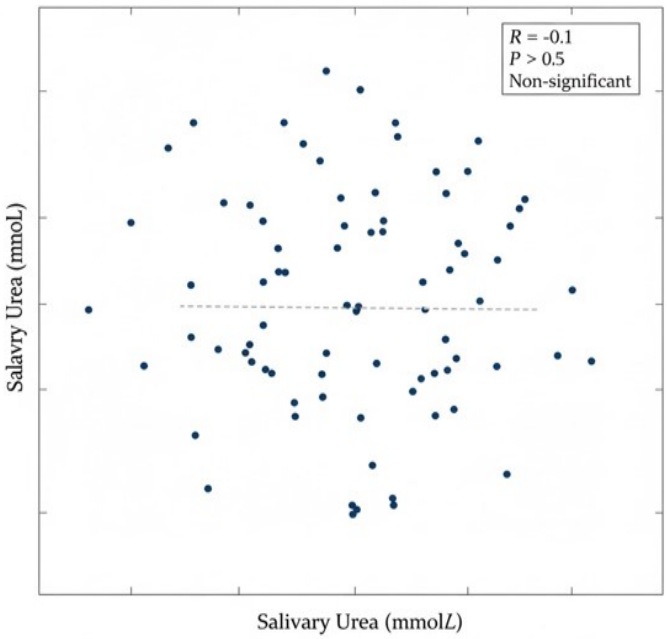



Figure 3: Correlation Between Blood and Salivary Urea Concentrations This scatter plot shows the individual paired values for blood urea and salivary urea, with a reported Pearson's correlation coefficient of R = -0.1 and a P-value $> 0.05$, indicating a non-significant inverse correlation.

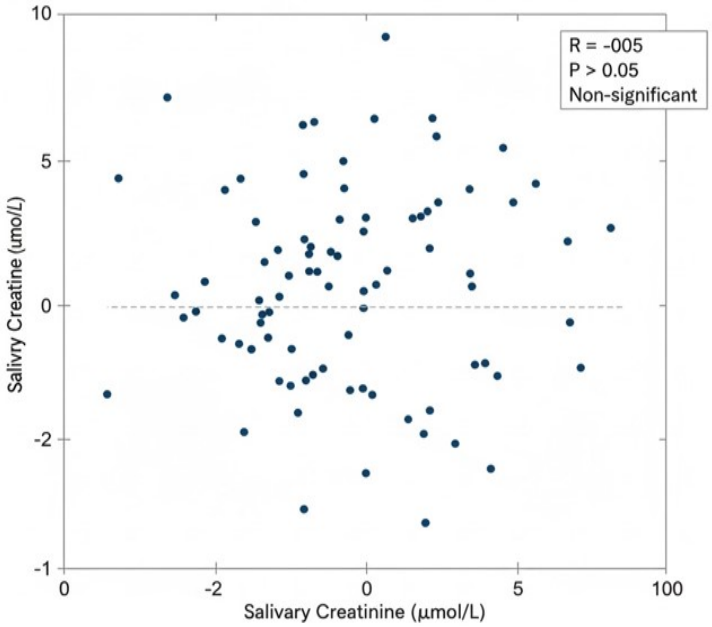
Figure 3: Correlation Between Blood and Salivary Urea Concentations




Scatter plot illustrating the correlation between blood urea and salivary concentations. The Pearson's correlation coefficient (R) value and P-value are indicated.

Figure 4: Correlation Between Blood and Salivary Creatinine Concentrations This scatter plot presents the individual paired values for blood creatinine and salivary creatinine, with a reported Pearson's correlation coefficient of r = -0.05 and a P-value $> 0.05$, indicating a non-significant inverse correlation.

Figure 4: Correlation Between Bloodd Salivary Creatinine Concentrations




Scatter plot illustrating the corrolation between blood and salivary concentrations. The Pears correlation coepfticient (R) value and are indicated.

## 4. Discussion

The aim of this study was to assess the potential of salivary urea and creatinine as non-invasive alternatives to serum markers in apparently healthy individuals. The findings provide crucial insights into the translational potential of these biomarkers in a non-diseased state.

### Comparison of Mean Concentrations

The most striking finding was the non-significant difference between the mean blood urea (3.00 mmol/L) and salivary urea (2.50 mmol/L) concentrations ($p > 0.05$). This suggests that in healthy individuals, salivary urea levels are remarkably close to those found in the blood. This result aligns with existing literature, which posits that urea's low molecular weight (60 Da) facilitates its easy and proportional passive diffusion or ultrafiltration from the plasma into the salivary glands [5, 8]. The close proximity of these mean values supports the premise that salivary urea can accurately reflect serum levels in a healthy setting.

In contrast, the mean blood creatinine concentration (186.20 umol/L) was significantly higher than the mean salivary creatinine concentration (59.20 umol/L) ($p < 0.05$). The salivary creatinine level was approximately one-third of the blood concentration. This significant difference is likely due to creatinine's higher molecular weight (113 Da) compared to urea, which restricts its transport across the acinar cell membranes into the saliva [7]. This finding suggests that salivary creatinine does not closely mirror serum creatinine levels in healthy individuals, thus, possibly limiting its utility as a direct non-invasive surrogate marker in screening contexts.

### Correlation Between Blood and Saliva

Despite the close mean values for urea, the correlation analysis showed a non-significant relationship between blood and salivary urea concentrations ($r = -0.1$, $p > 0.05$). Similarly, the correlation between blood and salivary creatinine was also non-significant ($r = -0.05$, $p > 0.05$). This outcome, while initially counterintuitive, is consistent with several studies conducted on healthy cohorts [2, 6].

In healthy subjects, serum urea and creatinine levels fall within a narrow normal reference range. When the range of analyte concentrations is very narrow (i.e., minimal variation), correlation analysis tends to yield low values, even if the salivary and serum values track each other perfectly in an absolute sense. The lack of a strong, positive correlation is therefore likely a statistical artifact of the narrow concentration range in this healthy population, rather than a reflection of a breakdown in the underlying transport mechanism. The primary clinical utility of these markers emerges in disease states (CKD) where serum concentrations are significantly elevated, creating a much wider range of values that typically results in a strong positive correlation, as demonstrated by other studies [6].

## 5. Conclusion

This study demonstrates that in apparently healthy individuals, salivary urea concentration is statistically indistinguishable from blood urea concentration, affirming the ease of urea transport into saliva. Salivary creatinine, however, shows a significant difference in concentration, being much lower than its blood counterpart. Despite the close mean values for urea, neither salivary urea nor creatinine showed a statistically significant correlation with their respective serum concentrations, a finding likely attributed to the narrow, normal reference range characteristic of the healthy study population. Overall, the negligible difference in mean values for urea highlights its potential as a more reliable non-invasive marker for further investigation in a diseased population.

### Recommendations

Based on the finding that salivary urea is not significantly different in concentration from blood urea in healthy individuals, it is recommended that future studies focus on:
Determining the diagnostic accuracy of salivary urea (e.g., establishing a cut-off value) in subjects with confirmed chronic kidney disease (CKD) across different stages; investigating the relationship between salivary urea and serum urea in patients with elevated serum levels to confirm the positive correlation that is expected in disease states.; exploring the use of salivary urea as a first-line screening tool in low-resource settings where invasive blood collection may be challenging.

### Limitation

A key limitation of this study is the inherent difficulty in establishing a significant correlation between salivary and serum renal markers in a cohort of apparently healthy individuals, as the biomarker concentrations fall within a narrow, normal range. Furthermore, the study did not measure the salivary flow rate, which is a key factor influencing the concentration of salivary analytes.

### Article Information

**Disclaimer (Artificial Intelligence):** The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

**Competing Interests:** Authors have declared that no competing interests exist.

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