Salivary Bicarbonate Fails to Mirror Systemic Acid-Base Balance in Pediatric Patients at Risk of Metabolic Disturbances

Articoli originali

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ABSTRACT

Introduction. The utility of salivary bicarbonate as a non-invasive marker of systemic acid-base status in pediatric patients remains unclear. This study investigated the possible correlation between salivary and blood gas analysis at risk for acid-base disturbances, including those with chronic kidney disease (CKD) or receiving acetazolamide.

Methods. In a single-center cross-sectional study (July 2024–March 2025), 94 pediatric patients (6–18 years) underwent simultaneous blood and saliva sampling for gas analysis. Patients were stratified into metabolic acidosis (<22 mmol/L), normal (22–26 mmol/L), or metabolic alkalosis (>26 mmol/L) groups based on serum bicarbonate.

Results. No relationship was observed between salivary and serum bicarbonate ($r = 0.112$, $p = 0.281$), pH, or base excess. However, strong correlations emerged within salivary parameters: bicarbonate was positively associated with salivary pH ($r = 0.682$, $p < 0.001$) and base excess ($r = 0.865$, $p < 0.001$). Patients with eGFR <30 ml/min/1.73m² had significantly higher salivary bicarbonate (13.6 mmol/L vs 6.8 mmol/L, $p = 0.004$), independently of bicarbonate supplementation. This was also negatively associated with calcium ($\beta = -8.67$, $p = 0.004$) and lactate ($\beta = -0.82$, $p = 0.008$). Dialysis status and underlying diagnosis were additional independent predictors. While patients with metabolic acidosis showed higher median salivary bicarbonate than those with normal or alkalotic profiles, this difference was not statistically significant ($p = 0.545$).

Conclusions. Salivary bicarbonate does not reflect systemic acid-base balance but is elevated in advanced CKD, suggesting a local regulatory phenomenon worthy of further exploration.

KEYWORDS: saliva, acid-base equilibrium, chronic renal insufficiency, child, noninvasive diagnostic techniques

Introduction

Saliva plays a key role in maintaining oral pH through its bicarbonate-buffering capacity [1]. Influenced by factors such as hydration status, diet, and underlying medical conditions, salivary flow and composition are dynamic processes that help maintain a stable oral environment [2]. Bicarbonate ions in saliva contribute not only to neutralizing acids from bacterial metabolism and ingested substances, but also serve as part of the broader systemic buffering system [1, 3].

Under physiological conditions, salivary bicarbonate concentrations may range from 1 to 60 mmol/L, depending on glandular source and flow rate, with the highest values observed in parotid and submandibular secretions [3]. However, the extent to which systemic acid-base imbalances influence salivary composition remains unclear. Clinical studies in adult populations have yielded inconsistent findings: Rojas-Morales et al. found no meaningful correlation between salivary and serum bicarbonate or pH in cancer patients [4], while Egboh et al. reported partial alignment of salivary and serum electrolytes in individuals with type II diabetes [5].

At the molecular level, emerging data suggest that salivary glands and kidneys may share adaptive mechanisms in response to acid-base alterations. These include the regulated expression and redistribution of acid-base transporters such as V-ATPase and Rab11b [6], as well as the NBCe1-A and NBCe1-B sodium-bicarbonate cotransporters [7].

These findings support the hypothesis that saliva might serve as a non-invasive indicator of systemic acid-base status, a particularly attractive possibility in pediatric patients for whom repeated blood sampling can be challenging.

This study was therefore designed to evaluate the feasibility and clinical relevance of salivary gas analysis in children at high risk for metabolic acidosis (e.g., chronic kidney disease or acetazolamide therapy) or alkalosis (e.g., tubulopathies).

Methods

Study Design and Subjects

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Padua (approval code 5904/AO/24, July 4, 2024). It is a single-center, cross-sectional study that was conducted between July 2024 and March 2025 on pediatric patients (aged 6–18 years) who were followed at the Pediatric Nephrology or Neurology Unit of the Department of Women's and Children's Health of Padova Hospital. The study adhered to the STROBE statement for observational studies. A total of 108 patients meeting the inclusion criteria were enrolled, but only 94 were able to produce a valid salivary sampling. All participants underwent simultaneous blood and salivary sampling for blood gas analysis. Patients were eligible for inclusion if they met the following criteria: age between 6 and 18 years, diagnosis of chronic kidney disease (CKD) or metabolic acidosis secondary to acetazolamide treatment for idiopathic intracranial hypertension, and scheduled for venous blood gas analysis as part of routine clinical care. To minimize external factors affecting salivary composition, patients were asked to refrain from food, drink, and oral hygiene procedures for at least one hour before sample collection. Exclusion criteria included Sjögren's syndrome, sialolithiasis, diabetes, active oral cavity diseases, or absence of parental/legal guardian consent.

During the sampling session, a venous blood sample and a saliva sample were collected simultaneously. Saliva was obtained using a standardized "whole saliva drooling test": after swallowing residual saliva, patients allowed fresh saliva to accumulate in the sublingual area, which

was then dripped into a sterile urine container while avoiding bubble formation. A minimum of 0.1 mL of saliva was aspirated into a heparinized arterial blood gas syringe, ensuring the removal of air bubbles, and immediately analyzed using a Siemens Healthineers Blood Gas System set to venous mode. The salivary sample was processed within 15 minutes from collection. The venous blood sample underwent analysis using the same platform and protocol. For each participant, the following variables were recorded: age, sex, weight, primary renal or neurological diagnosis (categorized as congenital anomalies of the kidney and urinary tract (CAKUT), glomerulopathy, tubulopathy, ciliopathy, metabolic disease, benign intracranial hypertension or other, eGFR calculated through the Bedside Schwartz formula [8], dialysis status, kidney transplantation status, use of proton pump inhibitors (PPI), and bicarbonate supplementation. Laboratory data included both serum and salivary acid-base parameters: pH, HCO_3^-, base excess (BE), lactate, and calcium.

Patients were divided into three acid-base categories according to their serum bicarbonate values [9]:

- Metabolic acidosis: HCO_3^- < 22 mmol/L
- Normal acid-base balance: HCO_3^- 22–26 mmol/L
- Metabolic alkalosis: HCO_3^- > 26 mmol/L

Endpoints

The primary endpoint of the study was to assess the relationship between salivary and serum pH and HCO_3^- levels, as a measure of diagnostic validity. Secondary analyses explored associations between salivary parameters and other clinical or biochemical variables, including calcium and lactate concentrations. Particular attention was given to the role of clinical covariates such as eGFR category (with “severe” defined by eGFR <30 ml/min/1.73m²), dialysis dependency, and underlying disease type in influencing salivary bicarbonate levels.

Statistical Analysis

Statistical analysis were performed using R software (version 4.4) and jamovi (version 2.6) [10, 11]. The distribution of all continuous variables was assessed on the entire study population using the Shapiro–Wilk test. According to data distribution, continuous variables are reported as mean ± standard deviation when normally distributed and as median with interquartile range (IQR, Q1–Q3) when non-normally distributed. For normally distributed continuous variables, between-group comparisons were performed using parametric tests (Student’s t test or one-way ANOVA, as appropriate). For non-normally distributed variables, non-parametric tests (Mann-Whitney U test or Kruskal-Wallis test) were used. Categorical variables are presented as absolute counts and percentages and were compared using the Pearson χ^2 test or Fisher’s exact test, when appropriate. Descriptive statistics included means, medians, standard deviations, and range values for continuous variables, and frequencies for categorical data. Group comparisons across acid-base categories were conducted using nonparametric Kruskal-Wallis tests and Dwass-Steel-Critchlow-Fligner post hoc procedures. Pearson, Spearman, and Kendall correlation coefficients were calculated to explore relationships between variables, and partial correlation was used to control for confounders. Linear and multinomial logistic regression models were developed to identify independent predictors of salivary bicarbonate levels and acid-base classification. A p-value < 0.05 was considered statistically significant.

Data Availability Statement

The datasets are not publicly available due to privacy and ethical restrictions. However, they are

available from the corresponding author on reasonable request and with permission from the Ethics Committee, if applicable.

Results

Population characteristics

A total of 94 pediatric patients were included in the study. Participants were stratified into three groups based on HCO_3-B levels: metabolic acidosis (HCO_3-B < 22 mmol/L), normal acid-base balance (22-26 mmol/L), and metabolic alkalosis (HCO_3-B > 26 mmol/L). At the moment of sample collection, all patients underwent simultaneous blood and salivary gas analysis. Twenty-five (26.6%) in total patients presented a metabolic acidosis, 24 (25.5%) were in metabolic alkalosis, whereas 45 (47.9%) patients had a normal level of bicarbonates. The mean age of participants was 12.8 (±4.1) years. 44 patients (46.8%) had no kidney function impairment; 14 displayed an eGFR < 30 ml/min/1.73m^2 or lower (14.9%). According to the underlying disease, most of the patients had a form of glomerulopathy (30.9%) or a CAKUT (29.8%), either in the whole group or according to the venous serum bicarbonate, except for the metabolic alkalosis part where tubulopathies were more frequent than CAKUT (7 vs 5, respectively 29.2% vs 20.9%). 4 samples were collected from patients on dialysis regimens, 3 receiving hemodialysis (HD) and 1 receiving peritoneal dialysis (PD). Twelve patients (12.8%) underwent kidney transplantation, the majority of whom had normal venous serum HCO_3-B (58.3%). Approximately one third of all patients was on HCO_3-B oral supplementation (34%), mostly in the metabolic acidosis group but also in the normal serum HCO_3-B group. Fourteen patients were on anti-acid therapy, mostly in the normal HCO_3-B group and most of them were the transplanted kids. Clinical characteristics are summarized in Table 1, and acid–base parameters in Tables 2 and 3.

Blood and salivary acid-base parameters

We explored the relationship between blood and salivary acid-base parameters in terms of pH, bicarbonates and BE. No significant correlation was observed between serum and salivary bicarbonate concentrations (Pearson's r = 0.112, p = 0.281, Figure. 1), nor did we find any relationship between serum and salivary pH values (r = -0.008, p = 0.938), nor between BE values in saliva did not significantly reflect their venous counterparts (r = -0.163, p = 0.116). In contrast, relationships within salivary parameters themselves were considerably stronger. Salivary bicarbonate showed a strong positive association with salivary pH (r = 0.682, p < 0.001) and salivary base excess (r = 0.865, p < 0.001), indicating an internally coherent local regulation. In addition, salivary bicarbonate was negatively correlated with both salivary calcium and salivary lactate, with the association reaching statistical significance for calcium (r = -0.373, p < 0.001), while the trend with lactate did not attain significance (r = -0.180, p = 0.100). We then analyzed whether salivary parameters varied among patients with different serum acid-base status. At a descriptive level, median salivary bicarbonate was higher in patients with metabolic acidosis (8.4 mmol/L) compared to those with normal bicarbonate levels (7.1 mmol/L), while values in patients with metabolic alkalosis were slightly lower (6.9 mmol/L), as shown in Figure 2. However, these differences did not reach statistical significance. The Kruskal-Wallis test showed no significant differences in salivary bicarbonate across the three metabolic groups (p = 0.545), nor in salivary pH (p = 0.224) or base excess (p = 0.427). These results are likely influenced by the relatively small sample size of the acidosis group and the high variability of salivary bicarbonate values within each category.

Variable	Total (n = 94)	Metabolic acidosis (HCO_3^- <22; n = 25)	Normal (HCO_3^- 22–26; n = 45)	Metabolic alkalosis (HCO_3^- >26; n = 24)	p-value
Age, years Shapiro–Wilk p 0.046	13.0 (10.0– 16.0)	12.0 (9.0–15.0)	13.0 (10.0–16.0)	14.0 (10.0–16.0)	0.622
Male sex, n (%)	59 (62.8)	13 (52.0)	30 (66.7)	16 (66.7)	0.430
Weight, kg Shapiro–Wilk p 0.009	46.2 (34.7– 60.8)	43.4 (29.0–50.6)	46.6 (36.4–61.0)	47.2 (32.5–64.2)	0.405
Main diagnosis, n (%)					0.010
Glomerulopathy	29 (30.9)	4 (16.0)	16 (35.6)	9 (37.5)	
CAKUT	28 (29.8)	11 (44.0)	12 (26.7)	5 (20.8)	
Tubulopathy	12 (12.8)	0 (0.0)	5 (11.1)	7 (29.2)	
Other diagnosis	25 (26.6)	10 (40.0)	12 (26.6)	3 (12.5)	
eGFR category, n (%)					0.018
> 89 ml/min/1.73m^2	44 (46.8)	9 (36.0)	24 (53.3)	11 (45.8)	
60-89 ml/min/1.73m^2	17 (18.1)	0 (0.0)	11 (24.4)	6 (25.0)	
30-59 ml/min/1.73m^2	19 (20.2)	8 (32.0)	5 (11.1)	6 (25.0)	
15-29 ml/min/1.73m^2	3 (3.2)	2 (8.0)	1 (2.2)	0 (0.0)	
< 15 ml/min/1.73m^2	11 (11.7)	6 (24.0)	4 (8.9)	1 (4.2)	
Renal replacement status, n (%)					0.215
Conservative	78 (83.0)	20 (80.0)	37 (82.2)	21 (87.5)	
Dialysis	4 (4.3)	3 (12.0)	1 (2.2)	0 (0.0)	
Kidney transplantation	12 (12.8)	2 (8.0)	7 (15.6)	3 (12.5)	
Oral bicarbonate therapy, n (%)	32 (34.0)	13 (52.0)	13 (28.9)	6 (25.0)	0.082
PPI use, n (%)	14 (14.9)	1 (4.0)	10 (22.2)	3 (12.5)	0.113

Table 1. Demographic characteristics of the study population stratified by serum bicarbonate and mean values of the analytics. p-values refer to between-group comparisons (Kruskal–Wallis for continuous variables; χ^2/Fisher for categorical variables).
Abbreviations: BE = base excess; CAKUT = congenital anomalies of the kidney and urinary tract; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HCO_3^- = bicarbonate; IQR = interquartile range; PPI = proton pump inhibitor; SD = standard deviation.

Variable	Total (n=94)	Metabolic acidosis (HCO_3^- <22; n=25)	Normal (HCO_3^- 22–26; n=45)	Metabolic alkalosis (HCO_3^- >26; n=24)	Shapiro–Wilk W	Shapiro–Wilk p	p-value
pH	7.33 ± 0.05	7.31 ± 0.04	7.35 ± 0.05	7.33 ± 0.06	0.991	0.760	0.019
HCO_3^-, mmol/L	24.1 ± 3.25	20.4 ± 1.60	24.0 ± 1.12	28.2 ± 2.17	0.983	0.243	<0.001
BE, mmol/L	−1.99 ± 2.85	−5.20 ± 1.95	−1.71 ± 1.47	0.82 ± 2.25	0.988	0.536	<0.001
Ca^{2+}, mmol/L	1.24 ± 0.06	1.22 ± 0.07	1.26 ± 0.05	1.24 ± 0.06	0.981	0.174	0.057
Lactate, mmol/L	1.2 (0.9–1.5)	1.2 (0.9–1.6)	1.2 (1.0–1.5)	1.2 (0.9–1.5)	0.761	<0.001	0.810

Table 2. Venous blood gas parameters stratified by serum bicarbonate. Continuous variables are shown as mean ± SD if Shapiro–Wilk p≥0.05, otherwise as median (IQR, Q1–Q3). Abbreviations: BE = base excess; HCO_3^- = bicarbonate.

Variable	Total (n=94)	Metabolic acidosis (HCO_3^- <22; n=25)	Normal (HCO_3^- 22–26; n=45)	Metabolic alkalosis (HCO_3^- >26; n=24)	Shapiro–Wilk W	Shapiro–Wilk p	p value
pH	7.33 (7.10–7.50)	7.33 (7.20–7.60)	7.35 (7.10–7.50)	7.27 (7.00–7.40)	0.973	0.046	0.224
HCO_3^-, mmol/L	7.1 (4.4–11.5)	8.4 (4.0–14.1)	7.1 (4.7–10.0)	6.9 (4.3–9.9)	0.855	<0.001	0.545
BE, mmol/L	−16.5 ± 11.2	−14.2 ± 13.4	−16.4 ± 9.94	−19.3 ± 10.7	0.980	0.151	0.427
Ca^{2+}, mmol/L	0.745 ± 0.194	0.728 ± 0.177	0.741 ± 0.213	0.767 ± 0.179	0.975	0.096	0.638
lactate, mmol/L	0.5 (0.4–0.7)	0.6 (0.5–0.9)	0.4 (0.3–0.6)	0.6 (0.5–0.8)	0.253	<0.001	0.012

Table 3. Saliva blood gas parameters stratified by serum bicarbonate. Continuous variables are shown as mean ± SD if Shapiro–Wilk p≥0.05, otherwise as median (IQR, Q1–Q3). Abbreviations: BE = base excess; HCO_3^- = bicarbonate.

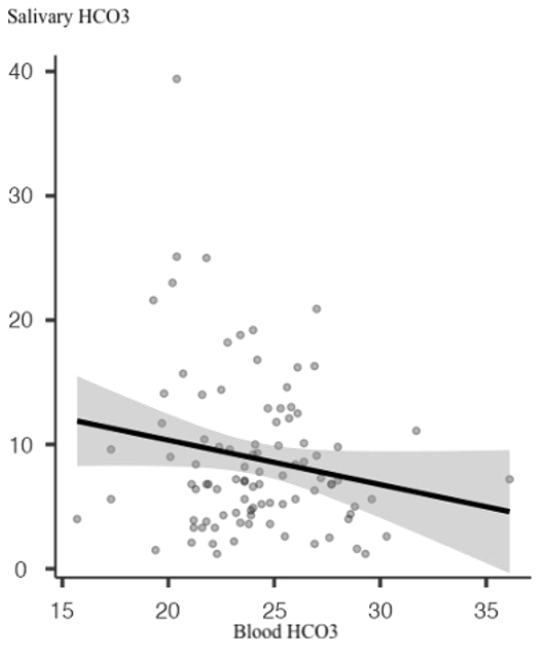

Figure 1. Correlation between salivary and serum bicarbonate levels in our population. Scatter plot showing the relationship between salivary (HCO_3-S) and serum bicarbonate (HCO_3-B) levels. No significant correlation was observed (Pearson's r = 0.112, p = 0.281).

In patients with normal acid–base balance (serum bicarbonate 22–26 mmol/L), salivary bicarbonate showed a median value of 7.1 mmol/L (IQR 4.7–10.0), which was considered an internal reference within the study population. Median salivary bicarbonate values were slightly higher in patients with metabolic acidosis (8.4 mmol/L, IQR 4.0–14.1) and lower in those with metabolic alkalosis (6.9 mmol/L, IQR 4.3–9.9), although these differences did not reach statistical significance (Kruskal–Wallis p = 0.545). Similarly, no significant differences were observed across groups for salivary pH (p = 0.224) or salivary BE (p = 0.427). Salivary calcium and lactate concentrations were also compared across systemic acid–base categories.

Mean blood calcium was higher than salivary one (1.24 ± 0.06 mmol/l vs 0.745 ± 0.19 mmol/l, p < 0.001), although salivary calcium values were comparable among patients with metabolic acidosis

(0.7 mmol/L, IQR 0.6–0.8), normal acid–base balance (0.7 mmol/L, IQR 0.6–0.9), and metabolic alkalosis (0.8 mmol/L, IQR 0.7–0.8), with no statistically significant differences (p = 0.638). In contrast, blood and salivary lactate levels did not differ significantly (1.2 mmol/l, IQR 0.9–1.5 vs 0.4 mmol/L, IQR 0.4–0.7, p = 0.072). Saliva lactates differed significantly across groups (Kruskal–Wallis p = 0.012), with higher median values observed in patients with metabolic acidosis (0.6 mmol/L, IQR 0.5–0.9) and metabolic alkalosis (0.6 mmol/L, IQR 0.5–0.8) compared with those with normal acid–base balance (0.4 mmol/L, IQR 0.3–0.6), even if are lower than blood lactate (1.2 mmol/l, IQR 0.9–1.5).

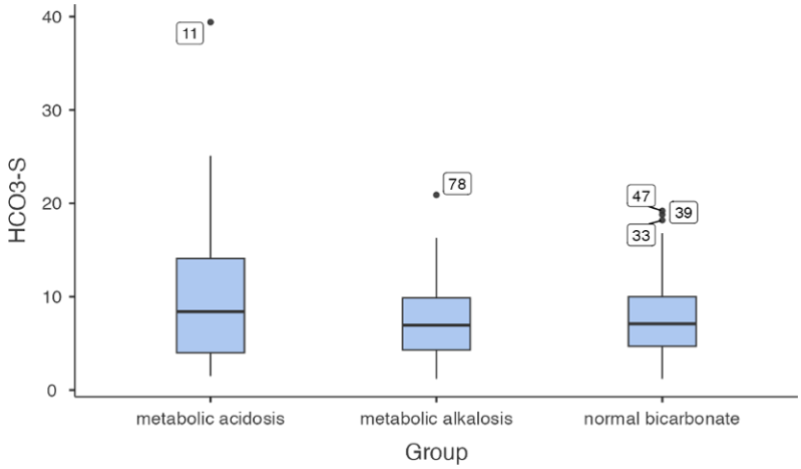

Figure 2. Distribution of salivary bicarbonate levels across serum acid-base groups.

Linear regression model for prediction of salivary bicarbonate

To better understand which variables might influence salivary bicarbonate, we constructed a linear regression model. Several factors emerged as independent predictors of salivary bicarbonate concentrations. Children on dialysis had significantly lower salivary bicarbonate values compared to those under conservative management (β = –9.91, p = 0.003). The underlying renal diagnosis also influenced salivary bicarbonate levels: patients with asphyxiating kidney disease, glomerulopathies, and tubulopathies exhibited lower values compared to those with congenital anomalies of the kidney and urinary tract (CAKUT). Salivary calcium and lactate concentrations were also inversely associated with salivary bicarbonate (β = –8.67, p = 0.004 and β = –0.82, p = 0.008, respectively). Patient weight was positively associated with salivary bicarbonate levels (β = 0.125, p = 0.007), while serum bicarbonate was not a significant predictor (β = 0.0075, p = 0.975), further supporting the absence of a direct systemic-salivary relationship.

Salivary bicarbonate and reduced eGFR

An additional finding of clinical interest emerged when comparing patients based on kidney function. Those with severe reduction of eGFR lower than 30 ml/min/1.73m^2 (n = 14), showed significantly elevated salivary bicarbonate concentrations, with a median value of 13.6 mmol/L (IQR 8.2-21.3), compared to 6.8 mmol/L (IQR 4.2-9.8) in patients with better preserved renal function (p = 0.004). Notably, this difference persisted regardless of whether patients were receiving oral bicarbonate supplementation as shown in Figure 3. Serum bicarbonate values, by contrast, did not differ significantly between these groups (eGFR < 30 ml/min/1.73m^2, 22.6 ± 2.4 mmol/l vs eGFR > 30 ml/min/1.73m^2, 24.4 ± 3.3 mmol/l, p = 0.051).

To assess whether the lack of correlation between blood and salivary acid–base parameters was driven by patients with advanced kidney dysfunction, a sensitivity analysis was performed after excluding subjects with eGFR <30 ml/min/1.73m². In this cohort (n = 80), no significant associations were observed between serum and salivary bicarbonate (r = −0.072, p = 0.525), serum and salivary pH (r = −0.024, p = 0.835), or serum and salivary base excess (r = −0.041, p = 0.717). In contrast, strong correlations among salivary parameters persisted, including the associations between salivary bicarbonate and salivary pH (r = 0.743, p < 0.001) and between salivary bicarbonate and salivary base excess (r = 0.840, p < 0.001), confirming the internal coherence of salivary acid–base regulation independent of systemic acid–base status.

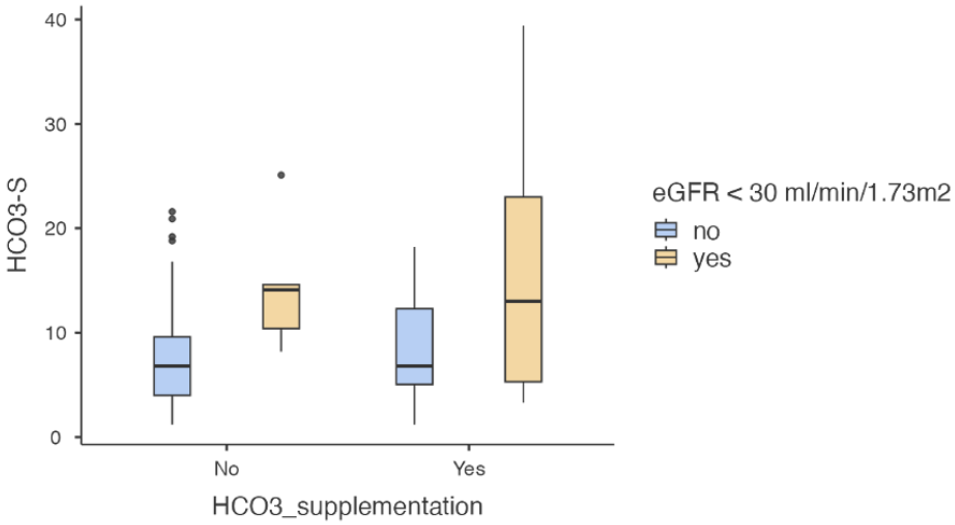

Figure 3. Salivary bicarbonate concentrations by eGFR and bicarbonate supplementation status. Boxplot of salivary bicarbonate levels (HCO_3-S) stratified by eGFR < 30 ml/min/1.73m² and use of oral bicarbonate supplementation. Patients with eGFR < 30 ml/min/1.73 m² (beige boxes) exhibited significantly higher HCO_3-S values compared to those with preserved renal function, regardless of bicarbonate supplementation status.

Discussion

This study aimed to evaluate whether salivary gas measurements could serve as a non-invasive proxy for systemic acid-base status in pediatric patients with CKD or other metabolic disorders. Our findings demonstrate a dissociation between salivary and venous acid-base parameters, with no significant relationships observed between salivary and serum bicarbonate, pH, or base excess values. This aligns with previous studies reporting poor concordance between saliva and blood for pH and bicarbonate levels in clinical populations, including patients with malignancies [4].

Despite this systemic dissociation, internal correlations within salivary parameters were strong: salivary bicarbonate was significantly associated with salivary pH and base excess. This supports the concept that salivary composition is governed predominantly by local factors such as ductal transporter activity, oral environment, and secretory rate, rather than systemic acid-base demands [2, 3].

The significant elevation of salivary bicarbonate in patients with reduced eGFR (<30 mL/min/1.73m²) represents a novel and clinically relevant finding (13.6 mmol/L vs 6.8 mmol/L, p = 0.004). Notably, patients with reduced eGFR exhibited salivary bicarbonate concentrations exceeding the study-specific internal reference value (7.1 mmol/L) irrespective of their systemic acid–base status, whereas individuals with eGFR >30 mL/min/1.73 m² showed salivary bicarbonate levels consistent with this internal reference. A sensitivity analysis excluding patients with advanced chronic kidney

disease confirmed that the lack of correlation between blood and salivary acid-base parameters was not attributable to severe renal impairment. Taken together, these findings support the concept that salivary acid–base regulation operates largely independently of systemic acid–base balance. From a pathophysiological perspective one could hypothesize an adaptive decrease in glandular bicarbonate secretion in response to systemic acidosis, as prior studies in animal models have demonstrated that salivary glands exhibit transporter redistribution, such as NBCe1-A and NBCe1-B isoforms, under systemic acid-base disturbances [6, 7]. However, in our study, this rise in salivary bicarbonate was related to low serum bicarbonate, suggesting alternative mechanisms. A plausible explanation is that the elevated salivary bicarbonate in advanced CKD may be mediated by microbial metabolism rather than epithelial adaptation. Several studies have documented that CKD is associated with increased salivary urea concentrations, which may be hydrolyzed by urease-positive bacteria in the oral cavity, generating ammonia and bicarbonate and leading to secondary alkalinization of saliva [12–14]. The resulting shift in oral microbiota and local pH may influence bicarbonate levels independently of systemic acid-base status.

Additionally, our data revealed a negative correlation between salivary bicarbonate and both calcium and lactate concentrations. While these associations are not fully understood, it is possible that elevated bicarbonate reduces free calcium solubility or reflects compensatory changes in oral metabolism. Manley et al. similarly found that reduced salivary buffering capacity was associated with increased oral symptoms in adult CKD patients, including dry mouth and nausea, which could be linked to changes in calcium or mucosal homeostasis [13].

Although PPI use was recorded, it showed no significant association with salivary parameters. However, we did not investigate gastrointestinal symptoms or dyspepsia scores, which have been linked to salivary composition in previous studies [13]. This represents a potentially relevant unmeasured variable in our cohort.

Study strengths and limitations

This study has several strengths. First, it represents, to our knowledge, the largest pediatric cohort to date evaluating salivary gas analysis in relation to systemic acid–base parameters, with a rigorously standardized sampling protocol minimizing pre-analytical variability. Both saliva and blood samples were collected simultaneously and analyzed using the same platform, thereby reducing inter-instrumental bias. The inclusion of patients across a wide spectrum of kidney function, from normal eGFR to dialysis, allowed us to explore associations along the full continuum of renal impairment. Moreover, the study adhered to the STROBE guidelines for observational research, ensuring methodological transparency.

However, some limitations should be acknowledged. The sample size, particularly within the metabolic acidosis subgroup, was modest, limiting statistical power for subgroup analyses. The cross-sectional design precludes assessment of causal relationships or longitudinal changes in salivary parameters following correction of acid–base imbalance. The lack of data on oral microbiota, salivary flow rate, urea, and ammonia prevents detailed mechanistic interpretation of elevated salivary bicarbonate in CKD. Additionally, potential selection bias may have occurred, as only patients able to provide adequate saliva samples were included. Finally, while efforts were made to standardize sample collection, residual confounding from dietary or circadian variability cannot be excluded.

Conclusions

Salivary gas analysis did not prove to be a reliable indicator of systemic acid–base balance in pediatric patients. Although salivary parameters showed consistent internal correlations, they did not mirror blood values. Interestingly, children with advanced CKD exhibited markedly higher salivary bicarbonate concentrations, independent of systemic levels or supplementation, suggesting local or microbiota-driven mechanisms. These findings highlight the need for further studies to clarify the physiological and clinical significance of salivary alterations in renal disease.

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