Taste changes and saliva composition in chronic kidney disease
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Abstract
Objective: To determine whether there is an association between changes in salivary composition and altered taste perception in chronic kidney disease (CKD) patients.

Design: Cross-section observational study.

Setting: Tertiary hospital renal outpatient clinic.

Subjects: Thirty CKD patients (24 males, six females, age 69.7 ± 14.2 years), with glomerular filtration rate (GFR) <25 mL/min and five controls, (one male, four females, age 44.6 ± 10.3 years) with GFR >80 mL/min.

Intervention: Participants performed a taste identification task to assess perception of the five primary tastes: sweet, salty, bitter, sour and umami. Perceived intensity was rated on a 100 mm visual analogue scale to determine sensitivity, and liking was rated using a nine-point hedonic scale. A saliva sample was collected to determine biochemical composition.

Main outcome measure: Recognition, perceived intensity and liking of the five primary tastes.

Results: It was observed that CKD patients have increased salivary bicarbonate, potassium and urea concentrations (p<0.05) and a poorer ability to perceive sour, umami and bitter tastes (p<0.05) when compared to controls. Bicarbonate concentration in saliva was inversely related to both liking and intensity of umami taste and to the intensity of sour taste (p<0.05), whilst salivary urea was linked to the perceived intensity of bitter taste (p<0.05).

Conclusion: This study provides evidence that taste active compounds are present in the salivary fluid. In particular bicarbonate and urea are associated with altered taste perception and may influence food consumption, specifically for protein rich foods.

Keywords
Saliva, taste, umami, uraemia.

Support and financial disclosure
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Introduction
Chronic kidney disease (CKD) is a common disorder affecting approximately 10% to 15% of the adult population worldwide. CKD appears to be increasing and is associated with a high prevalence of comorbidities which accompanies high economic costs, causing major challenges to health care systems (Bolton et al., 2000).

Issues of malnutrition in CKD patients are well established and associated with an increase in incidence of morbidity and mortality (Muscaritoli et al., 2009). Dietary protein spontaneously decreases in progressively uraemic patients (Mitch, 2000) as food avoidance, especially for animal protein, is common in this patient group. The mechanisms of why this occurs are not fully understood.

The sense of taste is important for consumption and enjoyment of food. It is well known there are five primary tastes. Bitter and sour tastes deter the ingestion of strong acids and potential toxic substances (Kim, 2004). Sweet taste is appetitive and indicates...
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energy-dense carbohydrate food sources. Umami (glutamate) taste serves as an indicator of protein-rich foods and palatability of food is enhanced when glutamate is added (Kurihara, 2009). Salt taste is also appetitive and informs about sodium and other minerals in foods (Mese & Matsuo, 2000). Taste perceptions are mediated by receptors on taste cells usually located in taste buds on specialised papillae in the oropharynx region, but taste receptors are also scattered within the alimentary tract and respiratory passageways (Finger & Kinnamon, 2011). Taste perception of the five qualities is highly variable between individuals with genetic, physiological, nutritional, environmental and sociocultural factors all playing a role within the individual (Matsuo, 2000). Previous research has shown CKD patients have an impaired ability to recognise four of the primary tastes (Fornari & Avram, 1978; Ciechanover et al., 1980). Umami taste has not previously been tested.

Studies have shown CKD patients have altered salivary composition when compared to those without renal failure, with significantly higher concentrations of sodium, potassium, urea, phosphate and pH levels (Tomás et al., 2008; Bots et al., 2007). It is unknown what causes taste changes in renal patients but alterations in salivary composition may play a role.

To support a link between kidney function, salivary composition and taste, an improvement in taste thresholds has been observed following commencement of haemodialysis (Burge et al., 1979). The aim of this study was to determine whether there is an association between changes in salivary composition and altered taste perceptions in CKD patients.

**Subject and methods**

CKD patients (n=30, 24 males, six females, age 69.7 ± 14.2 years, GFR <25 mL/min) and healthy controls (n=5, one male, four females, age 44.6 ± 10.3 years, GFR > 80 mL/min) were recruited from the Austin Hospital outpatient renal clinic. Group characteristics are shown in Table 1. The study was approved by the Austin Human Research Ethics Committee and the Deakin University Human Research Ethics Committee.

<table>
<thead>
<tr>
<th>Table 1. Participant characteristics.</th>
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<tbody>
<tr>
<td>CKD</td>
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<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td><strong>Gender (% male)</strong></td>
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<td><strong>GFR (mL/min)</strong></td>
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A taste assessment task was designed to assess taste perception of the five primary tastes and was performed in accordance with the International Standards Organisation (ISO), ISO 3972:1991 – Sensory analysis – Methodology – Method of investigating sensitivity of taste (International Organisation for Standardisation, 1991). Solutions for salty, sweet, sour, bitter and glutamate tastes were prepared in the sensory laboratory at Deakin University on the day prior to testing. These were made from common food ingredients and deionised water using salt, sucrose, citric acid, caffeine and monosodium glutamate (MSG).

Patients were seated in a quiet clinical room with minimal visual distraction and provided with both verbal and written instructions prior to testing. Each of the five solutions were labelled with a three-digit code and presented in a randomised order. The participant was informed of possible taste qualities and instructed to taste the samples from left to right. The testing procedure required the participant to taste 10 mL of the testing solution and expectorate after 5–10 seconds. The taste quality was identified by circling one of six options; sweet, salty, savoury, bitter, sour or none if no taste was detected. The patient then rated the perceived intensity of each solution on a 100 mm visual analogue scale anchored at each end with the attributes “water like” for the absence of taste to “very strong”. The patient was required to place a vertical mark on the line where they considered most appropriate. After completing identification and intensity ratings, participants also rated their liking of the solution on a nine-point hedonic scale ranging from “dislike extremely” (one) to “like extremely” (nine). Room temperature water was provided and participants were directed to rinse their mouth between sampling.

Saliva samples were collected to determine biochemical composition and salivary pH. Saliva (1 mL) was collected from each participant by chewing on a cylindrical cotton-wool swab from a saliva collection kit (Salivette, Sarstedt, Nümbrecht, Germany). Collection was carried out no earlier than 30 minutes after a meal and participants also rinsed their mouth with water to ensure no contamination of saliva with interfering substances occurred. The swab was placed inside the mouth of the participant and they were instructed to gently chew for approximately one minute or until a sufficient quantity of saliva was produced. The swab was then withdrawn and placed into a polypropylene tube. Biochemical analysis of the saliva samples was carried out by pathology at Austin Health on the same day of testing using Beckman UniCel DXC800/600 system. Samples were centrifuged at 4000 rpm for 10 minutes after which the cotton wool was withdrawn. Sodium, potassium, bicarbonate, calcium, urea and zinc were analysed using a number of techniques including indirect potentiometry, using selective electrode enzymatic rate and colorimetric methods. Electrolyte concentrations were expressed as mmol/L and zinc in µmol/L.

**Statistical analysis**

Descriptive statistics (mean and standard error) were used to summarise continuous data. Frequency of response was used for categorical data. Responses from the taste identification task were analysed using Chi-square. Non parametric statistics including Mann–Whitney U test were used to compare data between control and CKD groups. Spearman correlation was used to assess associations between taste perception and saliva composition. Statistical significance was set at p<0.05. All statistical analyses were conducted using SPSS statistical software.
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Ver. 17.0 (SPSS Inc, Chicago, IL, USA). A power calculation was conducted prior to the study and determined 23 subjects were required to achieve 90% power. A 10% b (90% power) was set and the standard deviation for the nine-point hedonic scale was set at one-scale point and the desired detection difference was 0.75 units on the nine-point hedonic scale.

Results

Saliva composition

Biochemical parameters measured in saliva are shown in Table 2. The salivary composition of CKD patients differed to controls. Levels of potassium, bicarbonate and urea were found to be significantly higher in the CKD group (p=0.006, p=0.01, p<0.001, respectively).

Taste identification

Results from the taste identification task are shown in Figure 1. Salt and sweet tastes were correctly identified by most CKD patients 30 (100%) and 28 (90%) respectively, while sour taste was often confused for bitter and correctly identified by 17 (57%) of patients. Only 14 (43%) of CKD patients were able to identify the umami taste quality, which was confused with all other tastes, while the bitter taste quality was recognised from the other four primary tastes by 21 (70%) of patients. Controls were significantly better at identifying sour (p= 0.05), glutamate (p<0.001) and bitter (p= 0.02) tastes indicating CKD patients had a poorer ability to recognise three of the five primary taste qualities.

Taste intensity

Mean taste intensity values are presented in Figure 2. Significant differences were observed on comparison between CKD patient and controls with sour and bitter tastes rated significantly less intense by CKD patients (CKD patients: 3.70 ± 1.82 and 4.66 ± 2.85, respectively) than controls (control: 5.36 ± 1.21 and 7.42 ± 1.16, p= 0.02 and p= 0.03, respectively). Intensity for salt, savoury and sweet tastes were on average rated lower by CKD patients; however, these values were not statistically significant between groups, p=0.07, p=0.07 and p=0.13 respectively.

Liking

Liking ratings are presented in Table 2. Liking for salt rated lower by CKD patients, while liking for the other tastes tended to be greater; however, these values were not statistically significant between control and CKD groups (p>0.05).

Relationship between saliva composition and taste

A number of correlations were found between biochemical parameters measured in saliva and liking or intensity ratings. Bicarbonate concentration negatively correlated with both umami liking (r = –0.307, p=0.02) and umami intensity (r = –0.317, p=0.02) as well as with the intensity of sour taste (r = –0.288, p=0.03). A negative correlation between salivary urea and the perceived intensity of bitter was detected (r = -0.381, p=0.04). Zinc concentration was found to negatively correlate with sweet intensity (r = –0.317, p=0.02).

Discussion

Results from the current study support the hypothesis that taste active compounds found in saliva alter taste perceptions in CKD patients. This study suggests CKD patients have an impaired ability to identify sour, bitter and umami tastes. We found 17

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>CKD n=30</th>
<th>Control n=5</th>
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<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>16.57 ± 2.33</td>
<td>9.60 ± 1.72</td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>37.30 ± 2.17</td>
<td>25.12 ± 2.05†</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>11.48 ± 1.85</td>
<td>3.20 ± 0.58†</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>29.42 ± 1.93</td>
<td>7.50 ± 0.64†</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>3.03 ± 0.43</td>
<td>3.23 ± 0.37</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>9.86 ± 1.21</td>
<td>6.83 ± 1.56</td>
</tr>
<tr>
<td>Zinc (µmol/L)</td>
<td>0.51 ± 0.34</td>
<td>0.64 ± 0.13</td>
</tr>
<tr>
<td>pH</td>
<td>6.98 ± 0.24</td>
<td>6.72 ± 0.21</td>
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</tbody>
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Significant differences were observed between CKD and control salivary bicarbonate, potassium and urea as Mann-Whitney U test

†Denotes significant difference in CKD and control saliva composition at p<0.05
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Table 3. Mean liking ratings of the five basic tastes of CKD patients compared to control group

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td>n=30</td>
<td>n=5</td>
</tr>
<tr>
<td>Salt</td>
<td>4.27 ± 0.31</td>
<td>5.80 ± 0.60</td>
</tr>
<tr>
<td>Sour</td>
<td>5.77 ± 0.30</td>
<td>5.00 ± 0.67</td>
</tr>
<tr>
<td>Glutamate</td>
<td>5.63 ± 0.36</td>
<td>4.40 ± 0.60</td>
</tr>
<tr>
<td>Bitter</td>
<td>4.37 ± 0.31</td>
<td>3.00 ± 0.67</td>
</tr>
<tr>
<td>Sweet</td>
<td>6.97 ± 0.41</td>
<td>4.20 ± 0.62</td>
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Subjects rated liking on a 9-point hedonic scale ranging from dislike extremely (1) to like extremely (9). Liking ratings did not significantly differ between control and CKD groups (p>0.05) as detected by Mann-Whitney U test.

Figure 2. Taste intensity.

Mean intensity scores for the five primary tastes of CKD patients (n=30) and comparison to control group (n=5). Participants rated perceived intensity on a 100 mm line scale ranging from 'water like' (0) to 'very strong' (10). CKD patients rated sour and bitter tastes significantly less (p<0.05) intense compared to control subjects as detected by Mann-Whitney U test.

(60%) of the CKD patients had difficulty identifying umami taste compared to one (20%) of the control group and 27% of healthy subjects found in a previous study (Lugaz et al., 2002). Twelve (40%) of the CKD patients were found to have difficulty identifying bitter taste compared to none of the control group and approximately 20% in healthy subjects found earlier studies (Mese & Matsuo, 2000; Lugaz et al., 2002).

We observed that such variations in taste function are associated with the various electrolytes, excreted in the saliva. Major salivary electrolytes such as sodium, potassium, zinc and bicarbonate (Mese & Matsuo, 2000) or other biochemical markers such as urea (Keast & Breslin, 2002) may influence taste perception as they are taste-active substances. Taste receptors are constantly exposed to low concentrations of electrolytes including sodium, potassium and bicarbonate ions and as a result, will normally adapt to the salivary environment (Bradley & Beidler, 2003). This constant exposure to salivary electrolytes can result in an increase or decrease in sensitivity; for example, salt taste is detected only when above salivary sodium-chloride concentrations (Mese & Matsuo, 2000; Keast & Breslin, 2002).

The CKD patients were found to have increased salivary potassium, bicarbonate and urea when compared to healthy individuals confirming results from other studies (Burge et al., 1979; Dong & Guo, 2010). Previous research showed that removal of urea and other toxins via dialysis results in improved taste function (Middleton & Allman-Farinelli, 1999; Dobell et al., 1993), indicating circulating toxins in the blood and the ability to taste may be mediated via saliva. Presumably, it is the parameters that differed from “normal” composition, such as bicarbonate and urea that influence taste function.

A significant negative correlation was observed between bicarbonate level and both sour and umami intensity, and umami liking. Food avoidance for animal proteins is common in CKD and the inability to identify umami taste could possibly explain why CKD patients develop an aversion for these types of foods. This may influence food consumption, specifically for protein containing foods, as glutamate has a major role in signalling protein-rich foods. It has been proposed that as bicarbonate ions in the saliva increase, there is a subsequent decrease in the concentration of free hydrogen ions, resulting in diminished sour taste intensity (Tomás et al., 2008). The same hypothesis may be true for umami taste, with increasing bicarbonate removing sodium ions thereby reducing umami taste perception. If salivary bicarbonate is decreasing the concentration of sodium ions, we would also expect to see a reduction in salt taste and while this was observed, it was not statistically significant.

Our study also suggests saliva urea level affects perceived intensity of the bitter taste quality with the higher the concentration of urea, the lower the perceived intensity of bitter taste. Genetic variation in sensitivity to 6-n-propylthiouracil, a bitter compound, or variations in sensitivity to mono sodium glutamate will impact consumption of bitter foods (Tepper et al., 2009) and dietary proteins (Luscombe-Marsh, Smeets & Westerterp-Plantenga, 2008), respectively. These genetic subgroups may be more sensitive to changes in urea and pH levels. The lower bitter taste associated with increased salivary urea would occur through the adaptation or habituation process as the bitter taste system would become less sensitive to bitterness (Mese & Matsuo, 2000).

In addition, zinc levels in saliva, although not significantly different from healthy controls, were negatively associated with the intensity of sweet taste, supporting previous research showing zinc ions are potent sweetness inhibitors (Keast et al., 2004). Zinc deficiency was believed to contribute to diminished taste perception in CKD patients. Early studies demonstrated an improvement in hypoguesia in chronic dialysis patients following supplementation with oral zinc capsules (Atkin-Thor et al., 1978; Mahajan et al., 1980), but no significant increment in plasma zinc levels or improvement in taste disturbance was observed in later studies (Matson et al., 2003). In fact, excessive zinc has been associated with taste dysfunction with a decrease in sweet taste perception (Middleton & Allman-Farinelli, 1999).
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and an increase in oral astringency (Keast, 2003). Sweet taste is appetitive and any increases in salivary zinc could have significant influence on acceptance of foods as sweet perception would be reduced (Keast et al., 2004).

Limitations
The low number of participants in the control group were not age- or sex-matched. Although the control numbers were low, studies looking at taste recognition and saliva composition in healthy individuals obtained similar results (Mese & Matsuo, 2000; Bradley & Beidler, 2003; Lugaz et al., 2002). Despite evident differences in age and gender balance, research has been controversial but suggests the process of taste itself is robust across the lifespan and gender. Any age effect found could be attributed predominately to a generic taste loss (Mojet et al., 2003) and therefore was not expected to influence results greatly.

Conclusion
This is the first study to evaluate perception of umami taste in the CKD population, with the results showing less than half of the patient group were able to clearly distinguish umami taste from the other four primary taste qualities. In addition, increased bicarbonate and urea concentrations in the saliva were associated with decreased intensity of sour, umami, and bitter tastes. Larger prospective studies including estimations of dietary intake are required to assess if taste abnormalities experienced by CKD patients influence the amount and types of foods eaten and if this is the body’s response to reduce the urea load in the CKD patient nearing end-stage renal failure.

Acknowledgements
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References


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