Effects of Expelling of Induced Hypersalivation on Serum Phosphorus, Urea and Creatinine Levels in End Stage Renal Disease Patients

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ABSTRACT

**Introduction:** Saliva has hundreds of components that may serve to detect systemic diseases or as evidence of exposure to various harmful substances, as well as provide biomarkers of health and disease status. Pilocarpine has effects on serum urea, creatinine and phosphorus in patients with chronic kidney disease (CKD) and patients with End Stage Renal Disease (ESRD) on hemodialysis. Pilocarpine is a parasympathomimetic drug used to induce hypersalivation. Parasympathetic stimulation leads to acetylcholine (ACh) release into the salivary acinar cells. ACh causes the salivary gland to release kallikrein, an enzyme that converts kininogen to lysyl-bradykinin. Lysyl-bradykinin acts upon blood vessels and capillaries of the salivary gland to generate vasodilation and increased capillary permeability respectively. The resulting increased blood flow to the acini allows production of more saliva. **Aim of work:** To determine the effects of expelling induced hyper salivation on serum Phosphorus, urea and creatinine levels in CKD and ESRD patients. **Materials and Methods:** It is a case control study which included 80 patients divided into Group A: 40 patients with End Stage Renal Disease on Hemodialysis for at least six months in Assiut University Hospital and Group B: 40 patients with Chronic Kidney Disease (stage 3,4) on conservative medical treatment. Both groups were complaining of hyperphosphatemia. Their ages ranged from 18 to 60 years old with mean age ± SD (51 ± 11), pilocarpine mouth washer (4% concentration, 5 ml pilocarpine which equals 13 mg, three times daily) is given for two months. **Results:** After pilocarpine intake; there was a decrease in serum phosphorus level in CKD patients (33%) than those with ESRD (30%). But there was a decrease in serum creatinine level in ESRD patients (23%) than those with CKD patients (15%). The two groups had the same percentage of decrease in blood urea level (40%). In salivary measures after pilocarpine intake; one hundred percent increase in phosphorus excretion in both group but patients with ESRD showed more creatinine excretion compared to patients with CKD (84% vs. 60%). CKD patients had more urea excretion in saliva versus to patients with ESRD (100% and 55%) respectively. **Conclusion:** Pilocarpine has a role in improving hyperphosphatemia in CKD patients and ESRD patients, also pilocarpine led to decrease in serum urea and creatinine levels so it can be used as an adjuvant therapy in CKD and ESRD patients.

Keywords: End Stage Renal Disease, Phosphorus, Saliva, Urea, Chronic kidney disease, Pilocarpine

1. INTRODUCTION

Chronic kidney disease (CKD) is defined as either abnormality of kidney structure or function for ≥3 months with implications for health\(^1\). Renal excretory function can be assessed by measuring serum levels of compounds excreted by the kidney, commonly the products of protein catabolism (urea and creatinine) and since kidney acts to maintain the constancy of body fluids, by adjusting urine volume and composition, the level of serum electrolytes such as sodium, potassium, and phosphate are also measured as an investigatory tool for diagnosis of renal disease\(^2\).

Saliva has hundreds of components that may serve to detect systemic diseases or as evidence of exposure to various harmful substances, as well as provide biomarkers of health and disease status. Whenever there is an increase in the blood urea, there will be a concomitant increase in the salivary urea. The increase in blood urea concentration could lead to diffusion of nitrogenous waste products into other body fluids like gastric secretions, saliva, and sweat\(^3\).

Chronic kidney disease (CKD) patients have higher salivary pH and higher salivary concentrations of urea, sodium, and potassium than healthy controls. In contrast, their salivary concentration of calcium is significantly lower. The salivary concentration of creatinine, urea, and potassium is conditioned by the severity of the renal failure and/or by hemodialysis treatment\(^4\).

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\(^5\).

Phosphate may be secreted in the saliva, which is then swallowed, and this provides a source of endogenous phosphate and thus contributes to the hyperphosphatemia in ESRD. The level of salivary phosphate may provide a better marker than serum phosphate for the initiation of treatment of hyperphosphatemia in ESRD and hemodialysis (HD) patients\(^6,7\).

The results may also offer a new horizon in the therapy of hyperphosphatemia by inducing hyper salivation. Many medications can be used to induce hyper salivation, e.g., antipsychotics, particularly clozapine and risperidone, parasympathomimetics particularly pilocarpine, anaesthetics like ketamine, and other drugs like yohimbine and mucosa-irritating antibiotics\(^8\).

2. METHODS

The present study is a case control study which carried out on 80 patients divided into two groups (40 patients with End Stage Renal Disease on Hemodialysis for at least six months and 40 patients with Chronic Kidney Disease stage 3,4 on conservative medical treatment) who were complaining of hyperphosphatemia. Their ages ranged from 18 to 60 years old with mean age ± SD (51 ± 11) The study was from march 2016 to march 2017. Those 80 patients were divided into:

1. Forty patients with ESRD were sub grouped into: Group A: 20 ESRD patients on hemodialysis receiving phosphate binders in the form of calcium acetate 500 mg 3 times daily and received pilocarpine mouth washer (4% concentration, 5 ml pilocarpine which equals 13 mg, 3 times daily) for 2 months, Control A: included 20 ESRD patients on hemodialysis receiving only phosphate binders in the form of calcium acetate 500 mg 3 times daily for 2 months.

2. Forty patients with CKD stage 3 or 4 on medical conservative treatment were sub divided into: Group B: 20 CKD patients stage 3 or 4 receiving phosphate binders in the form of calcium acetate 500 mg 3 times daily and receive pilocarpine mouth washer (4% concentration, 5 ml pilocarpine which equals 13 mg, 3times daily) for 2 months, Control B: 20 CKD patients stage 3 or 4 receiving only phosphate binders in the form of calcium acetate 500 mg 3 times daily for 2 months.

We excluded all patients suffering from any systemic disease that could affect the saliva characteristics e.g DM, Sjogren disease, rheumatoid arthritis and SLE or receiving any type of medication that could affect the saliva production e.g: antipsychotics, particularly clozapine and risperidone, parasympathomimetics particularly pilocarpine, anaesthetics like ketamine, and other drugs like yohimbine and mucosa-irritating antibiotics and patients known to be smoker and/or habitual drinker.

The studied patients were subjected to Laboratory investigations including:

1. Serum urea, creatinine, and phosphorus.
2. Salivary urea, creatinine, and phosphorus.

These investigations were done five times through the duration of the study (at the start of the study, every two weeks and the end of the 8th week) Each time 5ml

saliva was collected by passive drool technique and stored in -80 freezer.

**Statistical analysis**

The results of the study were tabulated, and statistical analysis was carried out using statistical package spss version 12, using significant level (p<0.05).

### 3. RESULTS

A total 80 patients who fulfilled the inclusion criteria attending to Assiut university hospital. The mean of their ages in the study is 51 ± 11 for group A and 50 ± 10 for group B, most of them were males (70% in group A and 65% in group B).

The demographic data of the patients (Table 1, Figures 1-2).

### Table 1: Demographic data of all groups included in our study

<table>
<thead>
<tr>
<th></th>
<th>ESRD (n=40)</th>
<th></th>
<th>CKD (40)</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Control A</td>
<td>P1 value</td>
<td>Group B</td>
<td>Control B</td>
<td>P2 value</td>
<td>P3 value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 11</td>
<td>49 ± 12</td>
<td>0.32 (NS)</td>
<td>50 ± 10</td>
<td>52 ± 10</td>
<td>0.06 (NS)</td>
<td>0.11 (NS)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (37.5%)</td>
<td>13 (32.5%)</td>
<td>0.97 (NS)</td>
<td>12 (30%)</td>
<td>14 (35%)</td>
<td>0.09 (NS)</td>
<td>0.07 (NS)</td>
</tr>
<tr>
<td></td>
<td>5 (12.5%)</td>
<td>7 (17.5%)</td>
<td></td>
<td>8 (20%)</td>
<td>6 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (10%)</td>
<td>4 (10%)</td>
<td>0.65 (NS)</td>
<td>8 (20%)</td>
<td>3 (7.5%)</td>
<td>0.39 (NS)</td>
<td>0.31 (NS)</td>
</tr>
<tr>
<td></td>
<td>4 (10%)</td>
<td>6 (15%)</td>
<td></td>
<td>8 (20%)</td>
<td>5 (12.5%)</td>
<td>0.11 (NS)</td>
<td>0.97 (NS)</td>
</tr>
</tbody>
</table>

Comorbidities

| HTN                  | 12 (30%)    | 10 (25%) | 0.98 (NS) | 8 (20%)  | 12 (30%)  | 0.23 (NS) | 0.09 (NS) |
| DM                   | 4 (10%)     | 10 (25%) | 0.87 (NS) | 4 (10%)  | 5 (12.5%) | 0.11 (NS) | 0.97 (NS) |
| Both                 | 12 (30%)    | 10 (25%) | 0.98 (NS) | 8 (20%)  | 12 (30%)  | 0.23 (NS) | 0.09 (NS) |

Data were expressed either in the form of frequency (%) (nominal data) or mean ± SD (continuous data). P value was considered statistically significant if less than 0.05 (NS; non-significant; S). A and B indicated in that patients received pilocarpine while control A and B indicated to those didn’t. HTN; hypertension, DM; diabetes mellitus. P1; measure statistical difference between group A and its control while P2 between group B and its control and P3 between group A and group B.

![Figure 1: Sex distribution of patients included in our study where data was expressed in the form of percentage](https://www.example.com/figure1.png)
This study showed no statistically significant differences between group A and its control as regard age, duration of illness, sex and comorbidities with P value (0.32, 0.43, 0.97 and 0.31 respectively). The same results were noticed in group B and its control with P value (0.06, 0.11, 0.09 and 0.39 respectively). Also, there were no statistically significant differences as regard age, sex, and comorbidities when comparing group A and group B where P value was more than 0.05. While there was a significant statistical increase in the mean of the duration of illness in group A (9 ± 2.5) when compared with group B (5 ± 1.1) with P value 0.01 (as shown in Table 1).

In serum measures after pilocarpine intake; patients with chronic kidney disease (group B) had more decrease in phosphorus level; 33% vs. 30% for those with end stage renal disease (group A) but group A had more decrease in creatinine level; 23% vs. 15% for group B. the same percentage of decrease was noticed with urea level in both groups (40%).

In the case of salivary measures after pilocarpine intake; one hundred percent increase in phosphorus excretion in both group but group A showed more creatinine excretion compared to group B; 84% vs. 60%. Group B patients had more urea excretion in saliva compared to group A; 100% and 55% respectively. As shown in the table (2).

Table 2: Percentage of change in serum and salivary level of phosphorus, creatinine, and urea in both group A and B after pilocarpine intake

<table>
<thead>
<tr>
<th></th>
<th>Percentage of change in serum measures</th>
<th>Percentage of change in salivary measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>30 % (decrease)</td>
<td>33 % (decrease)</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>40% (decrease)</td>
<td>40% (decrease)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>23% (decrease)</td>
<td>15% (decrease)</td>
</tr>
</tbody>
</table>

Group A patients are those with end stage renal disease while Group B patients are those with chronic kidney disease.
In ESRD patients (group A), there was statistical significant increase in salivary levels of phosphorus, urea and creatinine (mean ± SD= 3.5 ± 1.4, 11 ± 2.9, 22 ± 2.5 respectively) after pilocarpine intake compared to (mean ± SD=1.5 ± 0.9, 7 ± 3.7, 14 ± 1.3 respectively) before pilocarpine intake with P value (0.04, 0.00 and 0.03 respectively).

Also, There was significant decrease in serum levels of phosphorus, urea and creatinine (mean ± SD = 1.4 ± 0.65, 9.1 ± 1.4, 633 ± 121 respectively) after pilocarpine intake compared to (mean±SD= 1.9 ± 1.81, 13.7 ± 1.3, 956.6 ± 213 respectively) before pilocarpine intake with P value (0.00, 0.01 and 0.00 respectively). As shown in the table (3).

In CKD patients (group B), there was statistical significant increase in salivary levels of phosphorus, urea and creatinine (mean ± SD = 2.4 ± 1.3, 7 ± 1.9, 14 ± 3.1 respectively) after pilocarpine intake compared to (mean ± SD = 1.1 ± 0.78, 4 ± 2.1, 10 ± 2.3 respectively) before pilocarpine intake with P value (0.01, 0.04 and 0.03 respectively).

Also, There was significant decrease in serum levels of phosphorus, urea and creatinine (mean ± SD = 1.1 ± 0.65, 7.1 ± 1.4, 319 ± 100 respectively) after pilocarpine intake compared to (mean ± SD = 1.4 ± 0.78, 10.7 ± 2.3, 416.6 ± 123 respectively) before pilocarpine intake with P value (0.02, 0.02 and 0.00 respectively). As shown in the table (4).

**Table 3: comparison between Salivary and serum levels of Phosphorus, Urea and Creatinine level in patients with ESRD (group A) before and after pilocarpine intake**

<table>
<thead>
<tr>
<th></th>
<th>Before pilocarpine intake</th>
<th>After pilocarpine intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saliva</td>
<td>Serum</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.5 ± 0.9</td>
<td>1.9 ± 1.81</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>7 ± 3.7</td>
<td>13.7 ± 1.3</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>14 ± 1.3</td>
<td>956.6 ± 213</td>
</tr>
</tbody>
</table>

Data were expressed in the form of mean ± SD. P1, P2; Student t test was used to compare between phosphorus, urea, and creatinine level in serum and saliva before and after pilocarpine intake respectively, p value <0.05.

**Table 4: Comparison between Salivary and serum level of Phosphorus, Urea and Creatinine level in patients with CKD (group B) before and after pilocarpine intake**

<table>
<thead>
<tr>
<th></th>
<th>Before pilocarpine intake</th>
<th>After pilocarpine intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saliva</td>
<td>Serum</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.1 ± 0.78</td>
<td>1.4 ± 0.78</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>4 ± 2.1</td>
<td>10.7 ± 2.3</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>10 ± 2.3</td>
<td>416.6 ± 123</td>
</tr>
</tbody>
</table>

Data were expressed in the form of mean ± SD. P1, P2; Student t test was used to compare between phosphorus, urea, and creatinine level in serum and saliva before and after pilocarpine intake respectively, p value <0.05.

**4. DISCUSSION**

We hypothesized in this study that saliva could act as an excretory pathway helping failed kidneys in patients with CKD or ESRD, we used pilocarpine (parasympathomimetic) to increase salivation, and we asked our patients to expel this saliva based on previous studies which approved that urea and phosphorus are secreted in saliva.

Our results showed that, group A patients (ESRD patients who received calcium acetate and pilocarpine) had decreased serum urea, creatinine and phosphorus levels when compared with control group (ESRD patients who received calcium acetate only) with P value <0.002 for all comparisons, and also had increased salivary urea, creatinine and phosphorus levels when compared with control group with P value < 0.03 for all comparisons. These results were in

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agreement with Vincenzo Savica et al., 2009(9) who observed an approximate average of 2-mg/dl reduction in serum Phosphorus after 15 day of salivary Phosphorus binding (Chewing chitosan Gum) during fasting periods, and found that chewing gum preparation that contains 20 mg of chitosan for 1 h twice daily, controlled the serum phosphorus level of 13 hemodialysis patients who continued their usual regimen of phosphate binders with meals and thrice-weekly hemodialysis and approved that adding salivary phosphate binding (Chewing chitosan Gum) to traditional phosphate binders could be a useful approach for improving treatment of hyperphosphatemia in HD patients. These results also are in agreement with Paolo Monardo et al., 2008(9) who found that serum phosphate significantly decreased during the first weeks of chewing chitosan gum in ESRD patients and returned to baseline after discontinuing the chewing gum.

Our results were not in agreement with Akizawa T et al., 2014(10) who found that chewing gum and expelling saliva does not affect serum and salivary phosphorus levels in Japanese HD patients with hyperphosphatemia. On the other hand, our study showed that group patients (CKD patients stage 3 or 4 who received calcium acetate and pilocarpine) had increased salivary urea, creatinine, and phosphorus levels when compared with control group (CKD patients stage 3 or 4 who received calcium acetate only) with p value <0.06 for all comparisons, and also had decreased serum urea, creatinine and phosphorus levels when compared with control group with p value <0.03 for all comparisons.

These results were in agreement with Block GA et al., 2013(11) who found that salivary phosphorous is approximately 4-5 times that of serum Phosphorus and is not related to glomerular filtration rate. Also Chitosan chewing gum resulted in a reduction of serum Phosphorus by approximately 0.05-0.065 mmol/l.

Our results showed a significant value to use parasympathomimetic drugs (pilocarpine) as an add on the drug in CKD and ESRD patients complaining of hyperphosphatemia. Our observations are preliminary and require confirmation in a randomized, double-blind, placebo-controlled study on a larger HD population, in which fecal phosphorus elimination needs to be determined.

5. CONCLUSION

Based on the results of this study, we can conclude that: Pilocarpine has a good role in improving the refractory hyperphosphatemia in CKD patients and ESRD patients. Also, pilocarpine led to decrease in serum urea and creatinine levels so it can be used as an adjuvant therapy in CKD and ESRD patients.

REFERENCES
