DIVALENT ION EXCRETION IN CHRONIC KIDNEY DISEASE: RELATION TO DEGREE OF RENAL INSUFFICIENCY

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SUMMARY

1. The excretory patterns of sodium, calcium, magnesium and phosphorus were evaluated in seventy-eight patients with varying degrees of renal insufficiency, and in twelve normal subjects.

2. In mild renal failure the fractional excretion of filtered sodium, magnesium and phosphorus are significantly higher while that of calcium is significantly lower than values seen in normals. In advanced renal failure the fractional excretions of the filtered loads of all these ions increase steeply. These patterns are not influenced by the type of renal disease.

3. The fractional excretions of filtered sodium and calcium, calcium and magnesium, and sodium and magnesium were plotted against each other. The analysis of the plots showed that the fractional excretions of their filtered loads correlate poorly in patients with mild and moderate renal insufficiency, but closely in patients with severe renal failure.

4. These results indicate that the relation between the renal handling of divalent ions is not uniform at all levels of renal insufficiency. The dissociation between the excretory patterns observed in patients with early renal failure is consistent with the concept that different mechanisms may influence each individual ion separately. This is in contrast to the close association which exists between the excretory patterns of these ions in patients with advanced renal disease, and in which a single common mechanism may underlie the renal handling of these ions.

The fractional renal tubular reabsorption of filtered divalent ions is depressed in chronic kidney disease (Goldman & Bassett, 1954; Better et al., 1967; Steele et al., 1968). The mechanism(s) underlying this phenomenon is not well defined. In a recent study a close relationship between the renal excretion of sodium, calcium and magnesium was observed in patients with advanced renal failure and a common regulatory mechanism was proposed to explain the

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changes in these excretory patterns (Popovtzer et al., 1969a). The relationship between the renal clearances of these ions in other stages of chronic renal failure has not as yet received much attention. Combining patients with varying degrees of renal impairment into one category may obscure different regulating mechanism(s) involved in the renal excretion of divalent ions that might operate at different stages of renal failure. The present study was designed to investigate the renal excretion of calcium, magnesium and phosphorus and their interrelationship at different levels of renal function in patients with chronic renal disease.

**MATERIAL AND METHODS**

Seventy-eight patients with stable chronic renal disease of diverse aetiology with a creatinine clearance (C_c) between 106 and 1 ml/min, and twelve normal individuals, were studied. Data on some patients with advanced renal failure have been reported elsewhere (Popovtzer et al., 1969a); the data from these patients are used for comparison with the observations in patients with mild and moderate renal insufficiency. The patients did not receive diuretics, vitamin D, oral calcium supplements and were not undergoing dialysis. They were divided arbitrarily into five groups according to the severity of the renal failure as follows: (1) C_c 106–40 ml/min, (2) C_c 40–20 ml/min, (3) C_c 20–10 ml/min, (4) C_c 10–5 ml/min, and (5) C_c 5–1 ml/min. The range of the creatinine clearance of each group is approximately half the value of the preceding group. Patients with creatinine clearance below 15 ml/min received a modified 20–40 g protein diet, 400–500 mg phosphorus, 250–250 mg of calcium, and 120–160 mg of magnesium. Sodium intake varied according to the requirements of the individual. Patients with creatinine clearance above 15 ml/min were on a liberal diet. Urine was collected for 24 hr in acid-washed plastic bottles containing small amounts of concentrated hydrochloric acid as preservative. The urines were stored in refrigerators (4–5°) during the day of collection. Samples of venous blood were drawn anaerobically in the fasting state (7 a.m. to 9 a.m.). In all specimens sodium calcium, magnesium and creatinine were measured by methods previously reported from this laboratory (Massry et al., 1967). Phosphorus was determined by the method of Fiske & Subbarow (1925). A portion of each blood sample was processed anaerobically under mineral oil. Diffusible calcium and magnesium levels were determined in the ultrafiltrates from these samples prepared anaerobically in Lavietes chambers at room temperature. The clearances of divalent ions are expressed in the terms of their diffusible fraction.

**RESULTS**

The individual values for serum concentration and excretory rates of sodium, calcium, magnesium and phosphorus are available in a table (Clinical Science Table 38/4) deposited with the Librarian, the Royal Society of Medicine, London, W.1, from whom a copy may be obtained on request. The mean values with SD of the fractional excretions of filtered sodium (C_Na/C_c), calcium (C_Ca/C_c), magnesium (C_Mg/C_c) and phosphorus (C_P/C_c) are shown on Figs. 1(a), 1(b), 1(c) and 1(d) respectively. In mild renal impairment (C_c 107–40 ml/min) the fractional excretions of filtered sodium, magnesium and phosphorus are significantly higher while that of calcium is significantly lower than values seen in normal subjects. The fractional excretion of filtered calcium increases as renal failure decreases and becomes significantly higher than normal only when C_c falls below 10 ml/min. C_Na/C_c and C_Mg/C_c gradually
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Fig. 1 (a) Mean and SD values for the fractional excretion of filtered sodium ($C_{\text{Na}}/C_{\text{Cr}}$) at different levels of creatinine clearance ($C_{\text{Cr}}$). $n =$ number of patients, $P$ refers to the relation between normal subjects and patients as determined by $t$ test.

(b) Mean and SD values for the fractional excretion of filtered calcium ($C_{\text{Ca}}/C_{\text{Cr}}$) at different levels of creatinine clearance ($C_{\text{Cr}}$). $n =$ number of patients, $P$ refers to the relation between normal subjects and patients, as determined by $t$ test.

(c) Mean and SD values for the fractional excretion of filtered magnesium ($C_{\text{Mg}}/C_{\text{Cr}}$) at different levels of creatinine clearance ($C_{\text{Cr}}$). $n =$ number of patients, $P$ refers to the relation between normal subjects and patients, as determined by $t$ test.

(d) Mean and SD values for the fractional excretion of filtered inorganic phosphorus ($C_{\text{P}}/C_{\text{Cr}}$) at different levels of creatinine clearance ($C_{\text{Cr}}$). $n =$ number of patients, $P$ refers to the relation between normal subjects and patients, as determined by $t$ test.
increase as creatinine clearance diminishes and their values at all levels of renal function are significantly higher than those seen in normals. A steep rise is observed in these parameters when $C_Cr$ falls below 10 ml/min. These changes in the excretory patterns were not related to changes in levels of diffusible fractions of calcium and magnesium.

The relationship between $C_{Na}/C_{Cr}$ and $C_{Cal}/C_{Cr}$, $C_{Na}/C_{Cr}$ and $C_{Mg}/C_{Cr}$, and $C_{Cal}/C_{Cr}$ and $C_{Mg}/C_{Cr}$ in normal subjects and patients with renal disease is shown in Figs. 2, 3 and 4.
Fig. 3. The relationships between the fractional excretion of filtered sodium ($C_{Na}/C_{Cr}$) and magnesium ($C_{Mg}/C_{Cr}$) in normal subjects and in patients with different degrees of renal insufficiency. $P$ refers to the significance of $r$. 
Fig. 4. The relationships between the fractional excretion of filtered calcium (Ca/Cr) and magnesium (Mg/Cr) in normal subjects and in patients with different degrees of renal insufficiency. P refers to the significance of r.
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respectively. It is apparent that the relations between the excretory patterns are subject to considerable variations at different stages of renal impairment. A significant correlation between $C_{Ca}/C_{cr}$ and $C_{Na}/C_{cr}$ exists in normal subjects with preponderance of fractional excretion of filtered calcium on that of sodium. The relationship between these parameters becomes less significant in mild renal failure with less calcium being cleared for any given level of $C_{Na}/C_{cr}$. A close and highly significant relationship exists in patients with advanced renal failure ($C_{cr}$ less than 10 ml/min) with a slope near unity. The relation between $C_{Ca}/C_{cr}$ and $C_{Mg}/C_{cr}$ is also significant in normal subjects; however, it is poor in mild and moderate renal failure and becomes highly significant ($P<0.01$) in patients with advanced renal insufficiency ($C_{cr}$ less than 10 ml/min). The slope for the relationship between $C_{Ca}/C_{cr}$ and $C_{Mg}/C_{cr}$ is 1.86 in patients with $C_{cr}$ 9-5 ml/min and 1.05 in patients with $C_{cr}$ 4-1 ml/min. $C_{Na}/C_{cr}$ and $C_{Mg}/C_{cr}$ are closely related in normal subjects (Fig. 4). There is no correlation between them in patients with mild impairment of renal function ($C_{cr}$ 106-47) and a close correlation exists in severe renal insufficiency ($C_{cr}$ <10 ml/min).

A significant inverse relationship between $C_{ph}/C_{cr}$ and $C_{Ca}/C_{cr}$ is observed in patients with mild renal failure indicating that those with the lowest fractional excretion of filtered calcium tend to have the highest fractional excretion of filtered phosphorus and vice versa (Fig. 5). No significant correlation between $C_{ph}/C_{cr}$ and $C_{Ca}/C_{cr}$ was observed in other levels of chronic renal disease.

To circumvent a possible error that might be introduced into the results and their interpretation due to the use of $C_{cr}$ as an estimate of glomerular filtration rate and the factoring of all quantities analysed by $C_{cr}$, the absolute clearances of these ions were analysed against each other as well. The relationships are essentially the same as those for the fractional excretion of their filtered loads (Table 1):
Table 1. Interrelationships between $C_{Ca}$, $C_{Na}$, $C_{Me}$ and $C_p$ in normal subjects and in patients with chronic renal disease

<table>
<thead>
<tr>
<th></th>
<th>Slope (b)</th>
<th>Coefficient of correlation (r)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL SUBJECTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{Ca}$ vs $C_{Na}$</td>
<td>5.0</td>
<td>0.59</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>$C_{Me}$ vs $C_{Ca}$</td>
<td>1.0</td>
<td>0.65</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>$C_{Me}$ vs $C_{Na}$</td>
<td>9.0</td>
<td>0.58</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td><strong>PATIENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{Cr}$ 106-47 ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{Ca}$ vs $C_{Na}$</td>
<td>0.73</td>
<td>0.54</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>$C_{Me}$ vs $C_{Ca}$</td>
<td>0.23</td>
<td>0.06</td>
<td>$P$ NS</td>
</tr>
<tr>
<td>$C_{Me}$ vs $C_{Na}$</td>
<td>0.56</td>
<td>0.12</td>
<td>$P$ NS</td>
</tr>
<tr>
<td>$C_p$ vs $C_{Ca}$</td>
<td>$-5.50$</td>
<td>0.59</td>
<td>$P &lt; 0.05$</td>
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<tr>
<td>$C_{Cr}$ 37-20 ml/min</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$C_{Ca}$ vs $C_{Na}$</td>
<td>0.09</td>
<td>0.09</td>
<td>$P$ NS</td>
</tr>
<tr>
<td>$C_{Me}$ vs $C_{Ca}$</td>
<td>2.40</td>
<td>0.50</td>
<td>$P$ NS</td>
</tr>
<tr>
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<td>0.62</td>
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<tr>
<td>$C_{Cr}$ 16-10 ml/min</td>
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<td></td>
<td></td>
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<tr>
<td>$C_{Ca}$ vs $C_{Na}$</td>
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<td>$C_{Me}$ vs $C_{Ca}$</td>
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<td>0.44</td>
<td>$P$ NS</td>
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<td>1.80</td>
<td>0.42</td>
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<td>$C_{Cr}$ 9-5 ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{Ca}$ vs $C_{Na}$</td>
<td>0.85</td>
<td>0.94</td>
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<td>$C_{Me}$ vs $C_{Ca}$</td>
<td>1.90</td>
<td>0.75</td>
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<td>$C_{Me}$ vs $C_{Na}$</td>
<td>1.60</td>
<td>0.73</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>$C_{Cr}$ 4-1 ml/min</td>
<td></td>
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<td></td>
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<tr>
<td>$C_{Ca}$ vs $C_{Na}$</td>
<td>0.94</td>
<td>0.90</td>
<td>$P &lt; 0.001$</td>
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<td>0.60</td>
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<td>$C_{Me}$ vs $C_{Na}$</td>
<td>1.40</td>
<td>0.76</td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{Ca}$, clearance of diffusable calcium; $C_{Na}$, sodium clearance; $C_{Me}$, clearance of diffusable magnesium; $C_p$, phosphate clearance; $C_{Cr}$, endogenous creatinine clearance; NS, not significant. $P$ refers to the significance of $r$.

**DISCUSSION**

The results of the present investigation confirm previous observations that the fractional excretion of filtered sodium, calcium, magnesium and phosphorus increases as renal failure progresses (Goldman & Bassett, 1954; Better et al., 1967; Steele et al., 1968; Slatopolsky et al., 1968). However, a wide variation is apparent when the excretory interrelationships between these ions are examined at different degrees of renal failure. These excretory patterns were not influenced by the type of renal disease.

The excretory pattern of calcium is distinct from that of other ions in that the fractional excretion of its filtered load is less than normal in early renal disease, in contrast to the increase
in the fractional excretion of filtered sodium magnesium and phosphorus. A significant rise in $C_Ca/C_Cr$ above values seen in normal subjects is noticed only in patients with $C_G$ of less than 10 ml/min. Several possible factors may account for the differences in these excretory patterns. Kleeman et al. (1961) demonstrated in human subjects, and Talmage, Krantz & Buchanan (1955) and Massry et al. (1968) in experimental animals, that parathyroid hormone enhances renal tubular reabsorption of calcium. Recently, Reiss, Canterbury & Bilinsky (1968) have found high levels of parathyroid hormone in the blood of patients with mild impairment of renal function. The presence of secondary hyperparathyroidism in early renal disease may contribute to the decreased fractional excretion of filtered calcium. Our observation in this group of patients, that those who have the lowest fractional excretion of filtered calcium exhibited the highest phosphorus clearance, lends support to the role of the high blood levels of parathyroid hormone in affecting the excretory pattern of calcium in early renal insufficiency. The changes in osseous metabolism of calcium in renal disease may also be important. The avidity of the skeleton for calcium may play a role in regulating renal excretion of calcium. A depletion in bone calcium may contribute, by mechanism(s) yet unknown, to the enhanced tubular reabsorption independent of parathyroid activity. Such a situation may exist in osteomalacia often seen in renal disease (Stanbury & Lumb, 1966).

The excretion of calcium and magnesium are interrelated, both in experimental animals and in human subjects (Wesson, 1962; Better et al., 1967; Massry et al., 1967). Therefore, the dissociation between the renal handling of these divalent ions seen in patients with early renal failure is worth special comment. Renal failure affects significantly intestinal absorption of calcium (Liu & Chu, 1943; Stanbury & Lumb, 1962; Ogg, 1968), presumably due to changes in the metabolism of vitamin D (Avioli et al., 1968). Studies in humans with normal kidney function showed that vitamin D influenced calcium absorption but had minimal, if any, effect on the urinary or faecal excretion of magnesium (Heaton, Hodgkinson & Rose, 1964). Furthermore, intestinal absorption of magnesium is apparently not affected by renal insufficiency (Clarkson et al., 1965). The above differences in the intestinal absorption and its metabolic consequences may at least partly account for the differences in renal excretion of these ions. In addition, experimental data indicate that the renal tubular reabsorption of magnesium exhibits a maximum capacity (Tm) (Averill & Heaton, 1966; Massry, Coburn & Kleeman, 1969a). Observation in humans also suggests that under normal conditions the tubular transport of magnesium operates at, or near, saturation and that any increments in the filtered load of magnesium are excreted almost completely in the urine (Barker, Elkinton & Clark, 1959). The presence of increased filtration rate per residual nephrons in renal insufficiency (Bricker, Klahr & Rieselbach, 1964) and the consequent increase in filtered load of magnesium may thus be another tentative explanation for the early augmentation in the fractional excretion of magnesium, as opposed to that of calcium. Although experimental (MacIntyre, Boss & Troughton, 1963; Arnard, Rasmussen & Anast, 1966; Massry et al., 1969a) and clinical (Shelp, Steele & Rieselbach, 1969) evidence suggests that parathyroid hormone affects the renal handling of magnesium in a similar fashion to its effect on calcium, it is possible that the increase in filtered magnesium per nephron has a greater effect on fractional magnesium excretion and overshadows the effect of parathyroid hormone.

Our data are consistent with previous reports that an increase in fractional excretion of filtered phosphorus occurs as renal failure progresses (Goldman & Basset, 1954). In early renal failure the fractional excretion of filtered phosphorus is high in the absence of any demon-
strable elevation of serum phosphorus and is presumably due to high circulating levels of parathyroid hormone. Although the role of parathyroid hormone in regulating renal excretion of phosphorus is well documented in renal failure (Slatopolsky et al., 1968), other factors may still be operative (Popovtzer et al., 1969b). Recently, the presence of a factor(s) other than parathyroid hormone in uraemic sera which might influence fractional excretion of filtered phosphorus has been suggested (Massry, Coburn & Kleeman, 1969b). Studies in three of our patients with advanced renal failure failed to show a return of fractional phosphate excretion to normal values after total parathyroidectomy. The $C_p/C_{cr}$ in the patients were 0.95, 0.80 and 0.88 before surgery and 0.48, 0.50 and 0.56 respectively, 1 month after the removal of the parathyroid glands.

When the nephron population becomes critically reduced leading to severe renal failure, two new phenomena become apparent: (1) there is an increase in the fractional excretion of filtered calcium and steep rise in that of sodium and magnesium, and (2) the excretory patterns of sodium and calcium become intimately correlated with a slope near unity. Likewise, the fractional excretion of filtered sodium and magnesium, and calcium and magnesium show a close and significant correlation. These close interrelationships between $C_{Na}/C_{cr}$, $C_{Ca}/C_{cr}$ and $C_{Mg}/C_{cr}$ in advanced renal failure are consistent with our previous suggestion (Popovtzer et al., 1969a) that a common mechanism(s) may control the renal excretion of sodium, calcium and magnesium in these patients. Such mechanism(s) may overshadow the effect of several other factors that may affect the excretory patterns of these ions in early renal failure.

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