THE DISTURBANCE OF CALCIUM METABOLISM IN CHRONIC RENAL FAILURE

IB HORNUM

Medical Department P, University Hospital, Copenhagen, Denmark

Some aspects of calcium metabolism in renal failure have been studied in 9 females and 5 males in the age range from 25 to 63 years. Endogenous creatinine clearance was above 40 ml per min. in 3, between 40 and 10 ml per min. in 5, and between 10 and 3 ml per min. in 6 patients. Ten had chronic pyelonephritis, 3 chronic glomerulonephritis and 1 polycystic kidneys.

Metabolic balances of 5–7 weeks' duration were carried out (Reifenstein et al., 1945). During each balance regime a tracer study was performed. The decay in plasma activity following an intravenous injection of Ca$^{47}$ or Ca$^{45}$ was followed and the tracer data calculated on the basis of a simple one compartment model originally suggested by Heaney and Whedon (1958).

From the combined balance and tracer data the following parameters are obtained: (1) the exchangeable pool of calcium; (2) the accretion rate, i.e. the rate of deposition of calcium in calcified tissues; (3) the resorption rate, i.e. the rate of removal of calcium from calcified tissues; (4) the urinary calcium excretion; (5) the endogenous faecal calcium, i.e. the calcium excreted and not reabsorbed by the intestinal tract; (6) the intestinal absorption of calcium (in mg per day and in % of dietary intake); and (7) the balance of calcium.

![Graph](image)

*Fig. 1.* Urinary calcium excretion (mg per 24 hrs.) correlated with the endogenous clearance of creatinine (ml per min.).

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![Graph showing accretion rate of calcium (mg per 24 hrs.) correlated with the endogenous clearance of creatinine (ml per min.).](image)

Fig. 2. Accretion rate of calcium (mg per 24 hrs.) correlated with the endogenous clearance of creatinine (ml per min.).

*Urinary calcium excretion* showed a direct proportionality to the glomerular filtration rate (Fig. 1). One patient (indicated by a circle around the black dot) was omitted from the regression calculation in this and in the following figure since he had a pronounced sodium losing nephropathy, a condition which is known to increase urinary calcium excretion even at low clearance levels (Walker *et al.*, 1965).

*Accretion rate* was inversely correlated to glomerular filtration rate (Fig. 2). The accretion was low at the higher clearance levels and increased at low clearance levels (Dymling, 1964).

![Graph showing intestinal absorption of calcium (% of dietary intake) correlated with the endogenous clearance of creatinine. Solid lines indicate area of normal absorption levels.](image)

Fig. 3. Intestinal absorption of calcium (% of dietary intake) correlated with the endogenous clearance of creatinine. Solid lines indicate area of normal absorption levels.

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Intestinal absorption (Fig. 3) was uniformly low at the higher clearance levels, whereas 3 out of 6 patients with severe renal failure had a very high intestinal absorption (Milhaud et al., 1961; Heaney and Skillmann, 1964).

Calcium balance was zero or slightly negative in all patients with the exception of the three patients with severe renal failure and a high intestinal absorption. In these cases the balances were +123, +186 and +566 mg per 24 hours, respectively.

Parathyroid hormone is known to increase skeletal turnover, intestinal absorption and renal tubular reabsorption of calcium (Rasmussen, 1961).

Accordingly, the finding of a low intestinal absorption and a low accretion rate of calcium with moderate renal failure is compatible with a functional hypoparathyroidism and the tendency towards a high accretion rate and a high intestinal absorption in severe renal failure is compatible with a functional hyperparathyroidism (Dymling, 1964; Milhaud and Bourichon, 1964).

It is well-known that the serum calcium tends to drop in the late stages of renal failure. This suppression represents a stimulus to increased parathyroid activity, which has also been directly demonstrated by determination of PTH in the serum of patients with severe renal failure (Berson and Yalow, 1966).

There is, however, no universal agreement regarding the pathogenesis of hypocalcaemia in advanced renal failure. Most authors stress the primary role of an intestinal malabsorption of calcium (Stanbury, 1963).

Apparently the present results do not support the theory of such primary malabsorption as the cause of the secondary hyperparathyroidism for the following 3 reasons: (1) Three patients with severe renal failure have both a high rate of accretion and a high intestinal absorption of calcium. (2) The low intestinal absorption in early renal failure is not accompanied by high accretion rate (suggesting hyperparathyroidism), but is accompanied by a low accretion rate. (3) The low intestinal absorption of calcium found in early renal insufficiency is not accentuated by increasing renal failure. This has been demonstrated in an earlier figure representing the whole material and appeared also from the course of events in a single patient who developed a spontaneous aggravation of her renal failure during the balance regime. With the reduction of her clearance rate a fall of the total serum calcium level was

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**Fig. 4.** Illustration of the possible course of events in the development of osteomalacia in severe renal failure.

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observed. This drop was accompanied by a change in her intestinal absorption from low to high values. There was a simultaneous increase of the inorganic phosphorus.

That a phosphorus retention occurs in late renal failure is well-known. This hyperphosphatemia in severe renal failure has led some authors to suggest that the secondary hyperparathyroidism is due to the formation of metastatic deposits of calcium phosphates (Albright and Reifenstein, 1948).

This theory seems generally to have been rejected due to the fact that it seemingly did not explain the osteomalacic features which today are known to occur in many patients with renal failure. This osteomalacia may, however, also be explained as a result of the formation of metastatic calcifications (Fig. 4).

In normal man the bone turnover rate is governed by the ionized serum calcium via the parathyroid glands. For a person in balance this accretion rate equals the resorption rate.

When phosphate retention takes place, metastatic calcification starts. The ionized serum calcium tends to fall and the parathyroid glands will be stimulated. Parathyroid hormone will perform its usual homeostatic actions to the extent that the end-organs can react to the hormone.

The thus increased influx of calcium to the extracellular fluid is, however, accompanied by a similar increase in inorganic phosphorus and the metastatic calcification will increase. The return to the skeleton of calcium and of phosphorus will be lowered and the mineral contents of the skeleton will decrease, unless the intestinal absorption of calcium can fully compensate for the loss of calcium and phosphorus to the metastatic deposits.

In summary the material presented here indicates that a state compatible with a functional hypoparathyroidism exists in slight renal insufficiency. This might be due to the lowered urinary output of calcium which is a consequence of the lowered GFR.

In severe renal failure a state compatible with a functional hyperparathyroidism is present. Our findings, however, do not indicate that a low intestinal absorption is the primary cause of the secondary hyperparathyroidism. That a low intestinal absorption is probably an important feature in the development of the skeletal disease seems reasonable, but the primary cause of the secondary hyperparathyroidism is rather to be found in the process of metastatic calcification.

REFERENCES


