Studies on the Intestinal ^{47}Ca-absorption in Normal Persons and Patients Undergoing Peritoneal Dialysis, Haemodialysis and Vitamin D Treatment

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An impaired action of Vitamin D on its target organs, bone and intestine, probably caused by a disturbance in vitamin D metabolism has been suggested as the initial disorder leading to osteodystrophy in chronic renal failure. Our understanding of the role of metabolic acidosis in the genesis of renal osteodystrophy remains still incomplete and requires further investigation (Lennon, 1969). According to Schaefer and Opitz (1970) an early disturbance of intestinal calcium absorption has to be expected at a reduction of the glomerular filtration rate to 25 – 30 ml/min. The duration and severity of renal insufficiency, however, does not correlate well with the severity or the extent of renal osteodystrophy (Liu & Chu, 1943; Stanbury & Lumb, 1966). Studies performed by Stanbury and Lumb (1962) showed that an impairment of intestinal calcium absorption does not lead unconditionally to a negative calcium balance, so that the early development of osteomalacia must not be absolutely referred to a mineral deficit (Stanbury, 1968). A regular finding in the investigations of Garner and Ball (1966) on bone histology in uraemic patients were the signs of destruction in the bone adjacent to the osteoid. Although ions participating in bone mineralisation are made available by this process, the osteoid seams remain uncalcified.

According to these results the calcification of osteoid in renal insufficiency does not appear in spite of a normal (Ca) x (PO_4) product in plasma. If one considers renal osteodystrophy to be a consequence of decreased intestinal calcium absorption and defective bone mineralisation, a primary disturbance of vitamin D metabolism seems to be the most probable cause. The resistance to vitamin D due to an altered vitamin D metabolism together with an antagonism to or a failure of end organ response to the vitamin points out the complex nature of this disorder. The mode of action of vitamin D on the bone in uraemia and its interaction with parathyroid hormone, calcitonin, magnesium and phosphorus is far from decided (De Luca, 1967; De Luca et al, 1968; Jackson & Dancaster, 1962; Norman, 1968; Pechet et al, 1968), but a

stimulating effect on bone mineralisation seems to be most probable (Stanbury, 1968). The vitamin D resistance in uraemia is followed by an inhibition of the so called permissive action of vitamin D on parathyroid hormone (Haas, 1965). By these means over a long period the decrease in plasma calcium levels leads to the development of relative hypoparathyroidism or hypocalcemic hyperparathyroidism (Stanbury, 1968). This regulation, however, is not able to maintain calcium homeostasis for a long time and besides osteomalacia the characteristic bone lesions of renal osteodystrophy finally occur. Early administration of sufficient vitamin D therapy may not only heal osteomalacia but may also lead to a diminution of osteitis fibrosa (Schaefer & Opitz, 1970). Further investigations have to find out at which exact moment of early renal failure vitamin D therapy should be started with a good chance of success. Besides this, problems arise with vitamin D therapy in autonomous (tertiary) hyperparathyroidism, especially those concerned with the risks of metastatic calcifications and this needs satisfactory clarification. Secondary hyperparathyroidism which is still subject to homeostasis may, after a variable period, and induced by unknown factors, embrace the morphological and functional features of an autonomous (tertiary) hyperparathyroidism and surgical treatment may be required. Since the vitamin D resistance underlying renal osteodystrophy is not influenced by parathyroidectomy, vitamin D therapy is necessary subsequent to the operation. Surgical treatment may be indicated as well when, in patients under vitamin D therapy, the (Ca) x (PO_4) product in plasma exceeds the critical limit of 70 as a result of an improved intestinal calcium absorption, thus favouring metastatic calcification. The therapeutic effect of calcium administration during haemodialysis and peritoneal dialysis, respectively, and the advantage of a high calcium intake without vitamin D treatment are not commonly advocated (Curtis et al, 1969; Wing, 1968; Clarkson et al, 1966; Dent et al, 1961).

MATERIALS AND METHODS

In our studies on intestinal calcium absorption we used the assay method of Nordin (1968). ^{47}Ca, obtained from the Radiochemical Centre, Amersham, England, with a specific activity of > 150 μCi ^{47}Ca/mg Ca was used as a tracer dose of 10 – 15 μCi in a carrier amount of 50 mg $CaCl_2$, dissolved in 30 ml demineralised water. The admixture of ^{47}Se in this preparation is evident from the data sheet of the Radiochemical Centre.

Radioactive measurements were carried out in a sample changer of the Tracerlab (Gamma/Guard, Model GG 5331 and Gamma/Guard 150 Spectro/Matic, Model SC 535, respectively) in a γ-peak of 1.31 MeV. Counting efficiency in the Gamma/Guard Model GG 5331 was about 4.5% and 10.5% in the Gamma/Guard 150. Blood samples (20 ml in heparinised tubes) were taken 30, 60, 120 and 240 minutes following oral administration of the labelled

calcium (between 8 and 12 hrs a.m.) from fasting patients after 12 hours of starvation. After centrifugation the plasma radioactivity was measured in glass tubes and calculated in per cent of the administered dose of ^{47}Ca/litre of plasma. An additional calculation was carried out according to the method of Nordin et al (1968), so that the size of the extracellular calcium pool could be taken into consideration. We did not employ the double isotope method because we intended to repeat the absorption test several times during treatment with increasing doses of vitamin D and therefore wished to minimise the radiation exposure. Experiments with the double isotope method carried out by Gregory and Messner (1969) have shown that changes in the early miscible calcium pool do not influence statistically the values obtained with the absorption test.

Intestinal calcium absorption was studied in 20 control persons with normal renal function and in 19 patients with chronic renal insufficiency. In the latter group 10 patients were on regular haemodialysis, 9 patients were treated in our chronic peritoneal dialysis programme. At the beginning of our studies the patients were on haemodialysis treatment from six months to one and a half years, being dialysed twice weekly for 12 to 14 hours, with a bath calcium concentration of 5.6 mg/100 ml. Peritoneal dialysis treatment at the beginning of our investigations had been performed for three to six months, once a week for 24 to 36 hours with a calcium concentration of 5.4 mg/100 ml in the dialysing fluid. None of the patients had been treated with vitamin D or phosphate binders prior to our investigations.

RESULTS

1. Control group:

The absorption values of 20 normal persons are shown in Figure 1 (upper curves). In agreement with the findings of other authors (Nordin et al, 1968; Mautalen et al, 1969; Gregory & Messner, 1969) the maximum absorption peak is shown to be reached 2 hours after oral ^{47}Ca administration and we also used the 2 hour values for the comparison with the results obtained in patients with chronic renal failure.

2. Patients on haemodialysis:

Figure 1 (lower curve, HD) shows the absorption values of 10 patients on regular haemodialysis. The intestinal calcium absorption in these patients was found to be significantly lowered when compared with the control group (30 min $p=0.025$, 60 min $p=0.005$, 120 min $p=0.0025$, 240 min $p=0.005$) with the maximum peak four hours after oral calcium administration. Possible causes for this delayed absorption besides vitamin D resistance might be uraemic gastro-enteropathy, possibly with villous atrophy, and a disturbance in calcium transport. Possibly the shape of the disappearance rate (Tothill et al, 1970) may also be important. We did not measure this in our study for the reasons mentioned above.

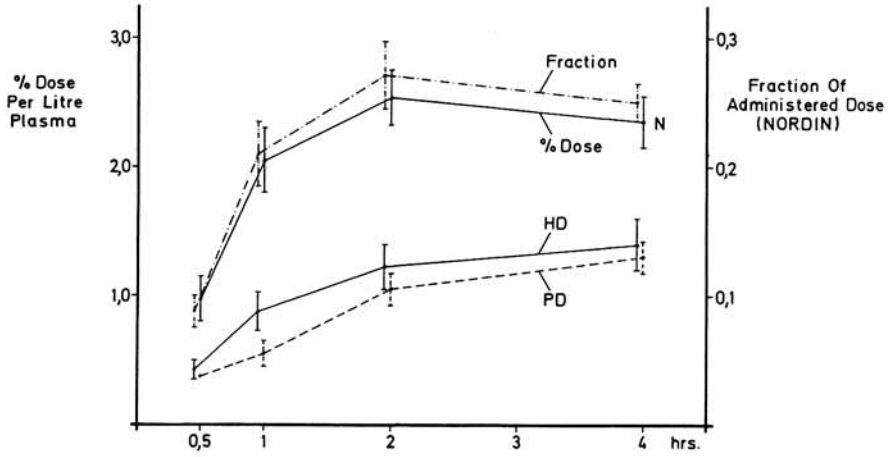

Figure 1. Intestinal ^{47}Ca absorption in 20 normal subjects (N) and patients with chronic renal failure on dialysis treatment (HD = haemodialysis, n=9; PD=peritoneal dialysis, n=10; hrs = hours after oral ^{47}Ca administration). Mean $\pm$ s.e.m.

3. Patients on peritoneal dialysis:

The same effect of a lowered calcium absorption (30 min p=0.015, 60 min p=0.0006, 120 min p=0.0005, 240 min p=0.0025) and a shifting of the maximum absorption time was observed in nine patients on our peritoneal dialysis programme (Figure 1, lower curve, dotted line, PD). A significant difference of the absorption values between the haemodialysed group and the patients on

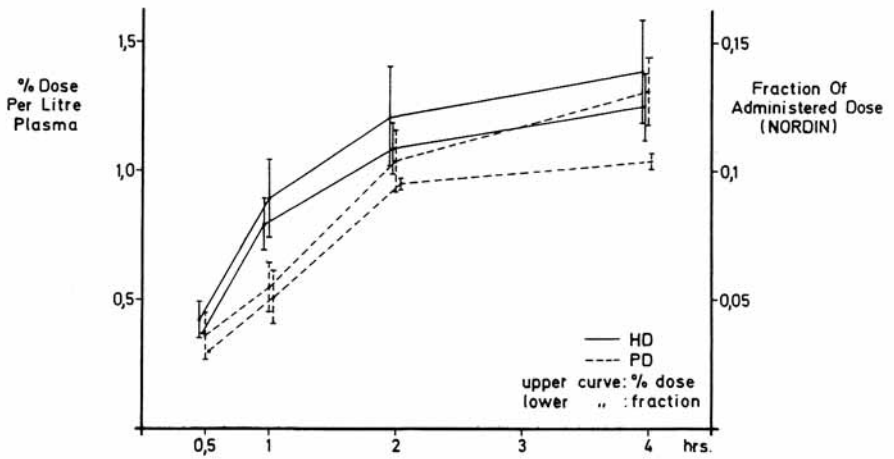

Figure 2. Intestinal ^{47}Ca absorption in patients on regular dialysis (PD = haemodialysis, n=9; PD = peritoneal dialysis, n=10; hrs = hours after oral ^{47}Ca administration). Figure 2 shows the same values as Figure 1 (lower curves), but in another scale. Mean $\pm$ s.e.m.

peritoneal dialysis (Figure 2) could not be obtained (30 min p=0.2, 60 min p=0.025, 120 min p=0.23, 240 min p=0.35). Figure 1 in addition shows that regular dialysis treatment as performed in our renal unit whether peritoneal or haemodialysis is unable to correct the impaired intestinal calcium absorption in our patients with chronic renal failure.

4. Vitamin D treatment:

Subsequently vitamin D treatment was carried out in 7 of the 10 haemodialysed patients and in 8 of the 9 patients on peritoneal dialysis. Figures 3 and 4 show the individual changes (2 hour reference values) of calcium absorption during vitamin D treatment. In two of the 15 dialysed patients the calcium

Patients	% dose/l plasma, prior to vitamin - D (2 hrs values)	VITAMIN - D (I U) | TIME (Weeks) % dose/l plasma, 2 hrs values (Hemodialysis)			
M.H-D., ♂	0.551	100 000 | 21 1.296	-	-	-
K.A., ♂	-	50 000 | 13 0.8983	100 000 | 4 0.916	-	-
E.H., ♂	-	20 000 | 5 0.575	30 000 | 3 -	100 000 | 3 0.971	
K.D., ♂	1.390	20 000 | 8 1.583			Transplantation
G.U., ♀	1.1539	50 000 | 14 1.3692	100 000 | 4 2.57	-	-
S.H., ♀	0.712	50 000 | 6 0.914		-	Transplantation
B.H., ♀	1.199	100 000 | 21 1.2316	-	-	-

Figure 3. Individual changes (2 hours reference values) of calcium absorption during vitamin D treatment. Patients on regular haemodialysis

absorption was normalised by oral application of the vitamin at a dose of 50.000 to 100.000 IU per day. An improvement of calcium absorption of up to 50% of the normal range could be observed in 4 more patients investigated on a daily dose of 20.000 to 100.000 IU of vitamin D. (Figure 5)

Because of the small number of our investigations we cannot give a statistical statement on whether a correlation exists between the initial calcium absorption values and the increase of the absorption caused by the individual vitamin

Patients	% dose/l plasma, prior to vitamin -D (2 hrs values)	VITAMIN -D (I U) | TIME (Weeks) — % dose/l plasma, 2 hrs values (Peritoneal Dialysis)			
Th.A., ♀	0.745	50 000 | 8 — 0.5271	75 000 | 3 — -	100 000 | 6 — 0. 9049	
Str.,E., ♂	0.6628	50 000 | 6 — -	40 000 | 1 — 0.728	-	
K.G., ♀	1.954	30 000 | 4 — -	50 000 | 2 — 2.4826	-	
H.H., ♂	0.5569	20 000 | 10 — -	50 000 | 4 — -	75 000 | 7 — 0.7567	
A.E., ♀ PTX subtotal	1.000	200 000 | 4 — Ca: 14.1	100 000 | 1.5 — Ca: 12.0	50 000 | 4 — 1.13	Ca:11.2
B.M., ♀	0.895	50 000 | 5 — 1.235	-	-	
H.W., ♂	1.514	20 000 | 2 — 0.7224	30 000 | 1.5 — -	50 000 | 1 — 0.6003	
H.H., ♂	0.979	20 000 | 12 — 1.1587	-	-	

Figure 4. Individual changes (2 hours reference values) of calcium absorption during vitamin D treatment. Patients on regular peritoneal dialysis.
Patient A. E., treated after subtotal parathyroidectomy, showed a sudden increase in plasma calcium levels so that vitamin treatment had to be interrupted several times

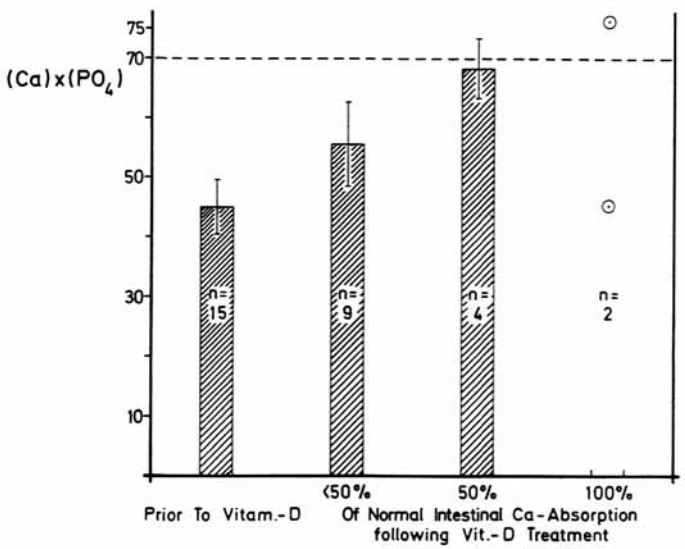

Figure 5. (Ca) x (PO_4) products in plasma prior to and during vitamin D treatment. Patients on regular dialysis

doses. According to our experience so far we do not think a standard dose of vitamin D is justified. The dosage of vitamin should be adjusted upwards individually for each patient from an initial dose of about 20.000 IU per day. Vitamin D treatment in patients with chronic renal insufficiency designed to inhibit secondary hyperparathyroidism should be controlled by measurement of intestinal calcium absorption. When plasma calcium levels are elevated up to a high normal range the (Ca) x (PO_4) product should be observed as a coarse parameter because of the danger of the development of metastatic calcification. In one of our patients the (Ca) x (PO_4) product exceeded the limit of 70 (Figure 5) after increase of the plasma calcium level as a result of an improved intestinal absorption. In such cases vitamin D treatment seems to be inopportune and should only be considered following parathroidectomy.

We also tried to find some correlation between the 2 hour calcium absorption values and the following parameters: duration of the renal insufficiency, the plasma level of urea nitrogen and the creatinine level, respectively. In contrast to the findings of other authors (Schaefer et al, 1969) who nevertheless worked with the more sensitive technique of whole body counter measurements, we were unable to detect a correlation between intestinal calcium absorption and the duration or severity of chronic renal failure.

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