Proc EDTA–ERA (1985) Vol 22

REDUCED $1,25(OH)_2D_3$ MAY BE RESPONSIBLE FOR THE DEVELOPMENT OF HYPERPARATHYROIDISM IN EARLY CHRONIC RENAL FAILURE

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Summary

Serum $1,25(OH)_2D_3$ was measured in 29 subjects with chronic renal failure. Glomerular filtration rate (GFR) was measured by single injection of ^{51}Cr EDTA. Eleven had filtration rates in the range 50–90ml/min/1.73m^2 (mean 69.5). None had more than 1g/24hr proteinuria. In the range 20–90ml/min/1.73m^2 $1,25(OH)_2D_3$ was correlated with GFR ($r=0.54$, $p<0.01$). Compared with normal subjects, the early chronic renal failure group had lower mean $1,25(OH)_2D_3$ (30.9±9.9 versus 38.0±7.9pg/ml, $p<0.05$) and similar mean serum phosphate. Within this group, reduced $1,25(OH)_2D_3$ tended to be associated with lower serum phosphate. Thus reduction in $1,25(OH)_2D_3$ occurred early in chronic renal failure in some patients and may have led to the development of hyperparathyroidism.

Introduction

Hyperparathyroidism is known to develop early in the course of chronic renal failure [1], but the pathogenetic mechanisms involved remain controversial. In advanced chronic renal failure, plasma $1,25(OH)_2D_3$ is low and a reduction occurring in early chronic renal failure could theoretically give rise to hyperparathyroidism, either directly or indirectly by changes in serum calcium. Surprisingly few reports have appeared as to plasma $1,25(OH)_2D_3$ early in the course of chronic renal failure at the time hyperparathyroidism starts to develop [2,3]. We therefore addressed this question, utilizing a method of assessing renal function which avoided the inaccuracies attendant on 24-hour urine collections.

Subjects and methods

Glomerular filtration rate was measured by single injection of ^{51}Cr EDTA [4] and corrected for surface area. No subject had proteinuria of greater than 1g

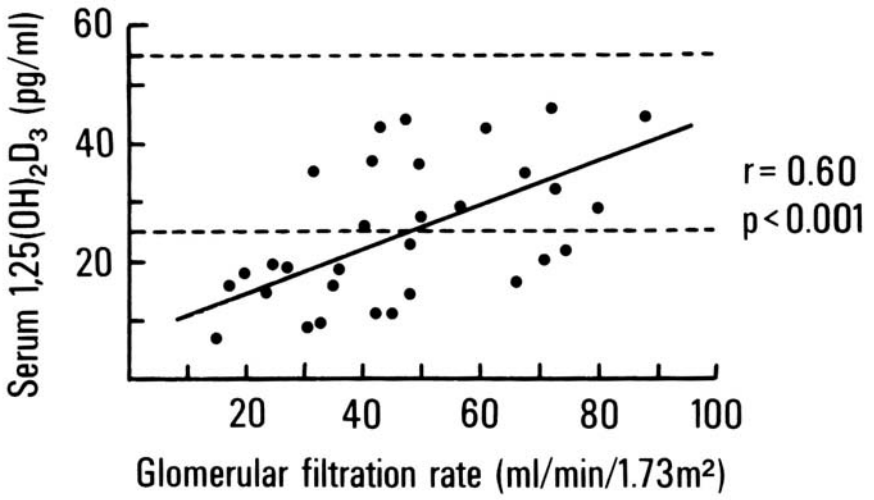

Figure 1. Relationship between serum $1,25(OH)_2D_3$ and glomerular filtration rate in subjects with chronic renal failure with glomerular filtration rates from 15–90ml/min/1.73m²

daily or had received vitamin D or its metabolites. Metabolites of vitamin D_3 were measured by radio-immunoassay following lipid extraction (acetonitrile) and HPLC (partisil 5μ developed in hexane: 2-propanol: methanol, 90:5:5 v/v) ([5] with modifications). Antiserum (02282) was kindly provided by Professor AD Care. Normal $1,25(OH)_2D_3$: 22–54pg/ml (mean±2SD, n=23) (Figures 1,2),

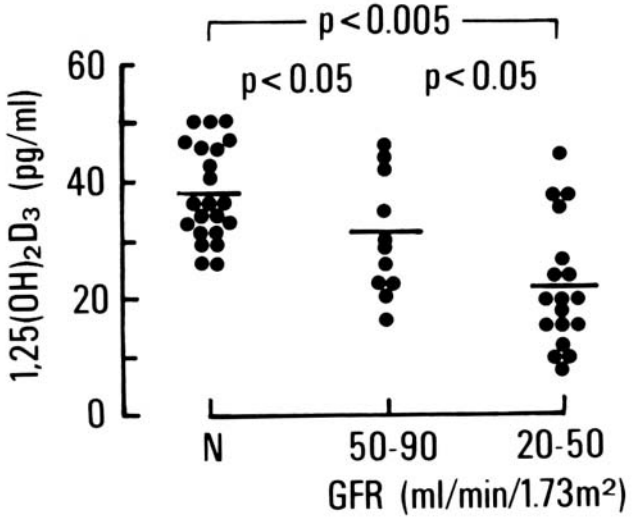

Figure 2. Serum $1,25(OH)_2D_3$ in 23 normal subjects and in subjects with early and moderate chronic renal failure

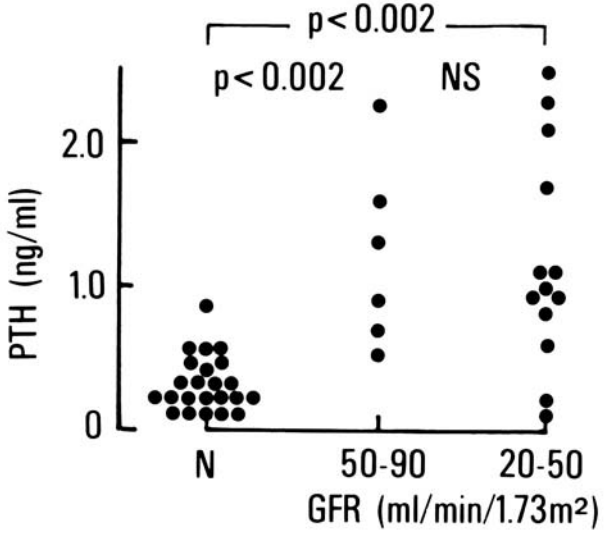

Figure 3. Serum PTH in 18 normal subjects and in subjects with early and moderate chronic renal failure

$25(OH)_2D_3$ 6–36ng/ml (n=23). Serum iPTH was measured by immunoradiometric assay [6] which recognizes the intact molecule. Normal serum iPTH <0.7ng/ml (Figure 3, Table I).

Results are expressed as mean ± SD. Two tailed tests of significance are used throughout except in the single instance of the use of the Spearman rank correlation coefficient (r_S). Between group comparisons were made using the Mann-Whitney U test.

Results

Over the range of glomerular filtration of 20–90ml/min/1.73m^2, there was a positive correlation between glomerular filtration rate and $1,25(OH)_2D_3$ ($r=0.54$, $p<0.01$). When subjects were divided by GFR, those with a GFR from 50–90ml/min/1.73m^2 (mean GFR 69.5±9.9) had a lower mean plasma $1,25(OH)_2D_3$ than normal: 30.9±9.9 versus 38.0±7.9pg/ml ($p<0.05$), but a higher mean than those with GFR in the range 20–50ml/min/1.73m^2 (mean GFR 36.1±9.8): 30.9±9.9 versus 21.1±10.9 ($p<0.05$). The latter group had a lower mean plasma $1,25(OH)_2D_3$ than normal ($p<0.005$) (Figure 2). Both the early and moderate chronic renal failure groups had elevated PTH compared with normal ($p<0.002$) (Figure 3). Within the early chronic renal failure group there was a tendency for serum phosphate to be correlated with plasma $1,25(OH)_2D_3$ (Figure 4) ($r_S=0.56$, $p<0.05$, one tailed test).

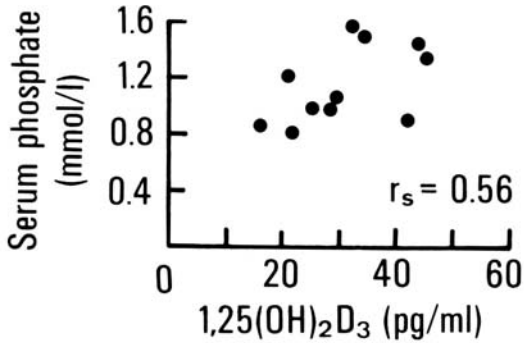

Figure 4. Relationship between serum phosphate and 1,25(OH)$_2$D$_3$ in subjects with early chronic renal failure (GFR 50–90ml/min/1.73m^2)

TABLE I. Clinical and biochemical characteristics of subjects with early renal failure

Subject	Sex	GFR ml/min/ 1.73m^2	Renal disease	1,25(OH)$_2$D$_3$ pg/ml	25(OH)D$_3$ ng/ml	PTH	P mmol/L	Ca^{2+}
ED	F	88	Partial lipodystrophy	43.7	11.4	0.9	1.44	2.09
AH	M	80	Focal sclerosing glomerulonephritis	28.8	33.4	0.54	0.96	2.05
MB	F	75	Diabetes	21.5	19.4	0.7	0.8	2.37
JS	F	73	Glomerulonephritis	32.2	11.0	1.3	1.55	2.22
VH	F	72	Chronic pyelonephritis	45.8	27.3	–	1.35	2.17
MH	M	71	Unilateral nephrectomy	20.2	12.3	2.3	1.21	2.13
JA	F	68	Reflux nephropathy	34.5	19.2	–	1.50	2.46
MR	F	66	Hypertension	16.2	12.5	–	0.87	2.17
AH	M	61	Hypertension	42.3	8.3	–	0.90	2.31
TA	F	57	Focal proliferative glomerulonephritis	29.2	16.1	–	1.01	2.24
MJ	F	53	Reflux nephropathy	25.2	27.9	1.6	0.96	2.09
mean ±SD		69.5 ±9.9		30.9 ±9.9	18.8 ±8.2		1.14 ±0.28	2.21 ±0.13

Discussion

Our findings indicate that early in the course of chronic renal failure plasma 1,25(OH)$_2$D$_3$ may be reduced. Wilson et al [7] recently reported a study of subjects with a mean GFR of 62ml/min in whom they found abnormalities

of calcium and phosphate handling, correctable by $1,25(OH)_2D_3$ administration, which suggested a mild deficiency of $1,25(OH)_2D_3$. Our data support their conclusion by direct measurement of $1,25(OH)_2D_3$ in similar subjects.

Our findings are also consistent with those of Malluche et al [8], who investgated intestinal calcium absorption in chronic renal failure and found 23 per cent of subjects of glomerular filtration rates between 50 and 70ml/min to have calcium absorption values more than two standard deviations below the mean. Their distribution of calcium absorption values over the whole range of glomerular filtration rates is very similar to that which we report for $1,25(OH)_2D_3$ and both studies indicate the relative heterogeneity of the chronic renal failure population until a late stage.

Possibly because subjects with early chronic renal failure are usually asymptomatic, remarkably few data are available as to plasma $1,25(OH)_2D_3$ at the stage we have reported. Of six subjects with glomerular filtration rates between 50 and 90ml/min, Ogura et al [4] found two with reduced $1,25(OH)_2D_3$. In 12 subjects with a mean GFR of 50ml/min, Slatopolsky et al [3] found levels in the upper normal range. Although our subjects appeared to have normal plasma $25(OH)D_3$, it is possible that differences in either sunlight or $25(OH)D_3$ intake could explain the difference between the latter data and our own.

The serum phosphate values deserve comment. Considering all the subjects with chronic renal failure together, we found the expected tendency of serum phosphate to rise with decreasing renal function (and falling $1,25(OH)_2D_3$ values). Within the early chronic renal failure group, however, the subjects with lower plasma $1,25(OH)_2D_3$ tended to have lower serum phosphate values (Figure 4), a finding consistent with a greater degree of parathyroid activity in these subjects and hence with the hypothesis that reduced $1,25(OH)_2D_3$ may be responsible for the development of hyperparathyroidism in early chronic renal failure.

References

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