Long-term haemodialysis and thyroid function

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Summary

Several indices of thyroid function were assessed in 74 patients with chronic renal failure. Sixty patients had undergone haemodialysis for varying periods. Within the first six months of haemodialysis treatment protein-bound iodine and total thyroxine (T4) levels rose, but after this T4 levels and the free thyroxine index fell progressively. Three out of the 12 patients who had undergone haemodialysis for longer than three years had subnormal T4 and supranormal thyrotrophin concentrations and a subnormal response to thyrotrophin stimulation. Long-term haemodialysis may be a cause of biochemical hypothyroidism.

Introduction

It has recently been shown that patients who have undergone haemodialysis for over a year have significantly lower serum thyroxine (T4) concentrations and significantly higher thyrotrophin concentrations than those who have undergone haemodialysis for shorter periods.^{1,2} We have performed a more detailed study of thyroid function in 74 patients undergoing long-term haemodialysis.

Patients and methods

Seventy-five patients with chronic renal failure who were under observation and treatment at the renal unit in Sheffield were studied. They were divided into four groups.

Group 1 consisted of 13 patients who had had renal failure for at least six months but who were not on regular haemodialysis. They had creatinine clearances of 8-15 ml/min.

Group 2 consisted of 18 patients who had been on dialysis for six months or less.

Group 3 consisted of 31 patients who had been undergoing haemodialysis for seven to 35 months.

Group 4 consisted of 12 patients who had been on regular haemodialysis for three years or more.

The patients in group 1 had a protein intake of 30 g/day, and all those on haemodialysis had an intake of 40 g/day. No patient was receiving steroids.

Protein-bound iodine (PBI), total serum thyroxine (T4), protein-binding capacity (T3 resin uptake), and total serum triiodothyroxine (T3) were measured in all patients, and the free thyroxine index (FTI) was calculated. Thyrotrophin-releasing hormone (TRH) tests were carried out on 20 patients, only six of whom were in group 1 or 2. Thyrotrophin-stimulation tests were carried out by measuring serum PBI, T4, and protein-binding capacity before and 24 hours after the injection of 10 units of intramuscular thyrotrophin. PBI was measured by autoanalyser, and T3 and thyrotrophin were measured by immunoassay.

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Results

Four of the 13 patients in group 1 had subnormal total T4 and PBI levels. Their serum albumin levels and protein-binding capacity were also subnormal, however, with the result that the FTI was normal in all patients in this group. Of the 18 patients in group 2 three had a low PBI level, two had subnormal T4, and only one (6%) had a subnormal FTI. In group 3 PBI, T4, and FTI were subnormal in three out of 31 patients, and in group 4 PBI, T4, and FTI were low in four out of 12 patients (tables I and II).

TABLE I—Incidence of subnormal thyroid function in patients with chronic renal failure

Group	No of patients	PBI (μmol/l)	T4 (nmol/l)	T3 resin uptake (%)	FTI (%)
1	13	4 (30%)	1 (8%)	4 (30%)	0
2	18	3 (17%)	2 (11%)	1 (6%)	1 (6%)
3	31	3 (10%)	3 (10%)	1 (3%)	4 (13%)
4	12	4 (33%)	4 (33%)	0	4 (33%)

Conversion: SI to traditional units—PBI: 1 μmol/l ≈ 0.0126 mg/100 ml. T4: 1 nmol/l ≈ 0.078 μg/100 ml. T3: 1 nmol/l ≈ 0.65 ng/ml.

TABLE II—Thyroid function in patients with chronic renal failure

Group	No of patients	PBI (μmol/l)	T4 (nmol/l)	T3 (nmol/l)	T3 resin uptake (%)	FTI (%)	Albumin (g/l)
1	13	0.34*	80*	0.81	88	92*	30
2	18	0.41	103	1.05	97	107	34
3	31	0.40	85*	0.82	99	79*	32
4	12	0.38	70*	0.78	102	70*	34

*P < 0.01 when compared with values for patients on dialysis for under 6 months.

Analysis of the mean PBI, T4, and FTI values in the four groups showed a definite trend. Before haemodialysis (group 1) mean serum albumin, PBI, protein-binding capacity, and total T4 were subnormal, but after less than seven months' haemodialysis these values had become normal (group 2). Albumin, protein-binding capacity, and PBI values remained more or less the same after more than six months' haemodialysis, but T4 levels and the FTI fell progressively (groups 3 and 4) (table III). T3 levels were subnormal in all patients in whom it was measured irrespective of the duration of haemodialysis.

TABLE III—Percentage changes in mean values between each group

Change from:	Albumin	T3 resin uptake	PBI	T4	FTI
Group 1-2	+13.3	+10.2	+20.6	+28.7	+16.3
Group 2-3	-5.9	+2.1	-2.4	-17.5	-26.2
Group 3-4	+6.2	+3	-5	-17.6	-11.4

Serum thyrotrophin concentrations were raised in all patients with low T4 levels; in those patients with normal levels thyrotrophin concentrations were either normal or high normal. In all patients with a clearly raised serum thyrotrophin concentration (who also tended to be those with a low or low normal T4 levels and who had been undergoing dialysis for more than a year) TRH-induced increases in thyrotrophin were extremely low or absent (table IV). The increase in serum PBI and T4 levels after thyrotrophin was significantly smaller in these patients than in normal subjects. Three patients who had subnormal T4 and raised thyrotrophin concentrations showed a significantly reduced response to thyrotrophin stimulation (table V).

TABLE IV—Results of TRH tests in patients with chronic renal failure

Time (min):	Thyrotrophin concentrations (mU/l)		
	0	20	60
Groups 1 and 2 ..	3.7 ± 0.6	5.7 ± 1.7	7.3 ± 2.1
Groups 3 and 4* ..	7.5 ± 0.9	8.0 ± 1.2	7.9 ± 1.4

*Patients with subnormal T4 concentrations did not have a significantly different basal thyrotrophin or TRH stimulation pattern.

TABLE V—Effect of thyrotrophin stimulation on thyroid function. Results show values before and after thyrotrophin

				Controls (n = 12)	Uraemia (n = 16)	"Hypothyroid" (n = 3)
PBI						
Before	..	..	..	0.49 ± 0.19	0.40 ± 0.14	0.30
After	..	..	..	0.92 ± 0.38	0.63 ± 0.28*	0.43
T4						
Before	..	..	..	112 ± 15.9	96 ± 23.4	53.5
After	..	..	..	195 ± 23.9	145 ± 70.1*	65.0
Protein-binding capacity						
Before	..	..	..	96 ± 6.3	92.8 ± 10.7	96.3
After	..	..	..	91 ± 7.4	85.6 ± 13.9	89.3
FTI						
Before	..	..	..	116 ± 5.8	102.0 ± 21.9	55.7
After	..	..	..	215 ± 10.5	189 ± 57.3	73.0

*P < 0.05 when compared with controls.

Discussion

Our results show clearly that the incidence of abnormalities of thyroid function increases with the duration of haemodialysis. A third of the patients who had been on haemodialysis for over three years (group 4) had subnormal serum PBI and T4 levels, a low FTI, and raised thyrotrophin concentrations, while only one of the patients from group 2 and none from group 1 had a low FTI. T3 concentrations were subnormal in all patients in whom they were measured.

When the mean T4 and FTI values were considered similar trends were observed. There was a graded fall of mean T4 and FTI from group 2 to group 4 in spite of a persistently normal PBI. There may be two reasons for this. Firstly, our observations did not reflect the evaluation of thyroid function in the same patients over a period of time but merely compared the thyroid function of patients who had undergone haemodialysis for different periods. Secondly, the thyroid gland secretes iodinated products other than T4 and T3, which may maintain PBI concentrations within the normal range in the face of diminishing T4 and T3 levels; this would be consistent with the recent demonstration that 3'35' triiodothyronine (rT3) levels are relatively high in uraemic patients because of the preferential conversion of T4 to rT3 rather than to T3.³ Silverberg *et al*² also observed that T4 and FTI fell in patients on haemodialysis, but they did not find significant correlation between the fall in T4 and the duration of haemodialysis.

We tried to assess the functional reserve of the thyroid gland by performing thyrotrophin-stimulation tests. This procedure is better than the usual isotope uptake tests because the latter provide no information on actual thyroid hormone synthesis and release. The increase in PBI and T4 concentrations in uraemic patients after thyrotrophin stimulation was less than that observed in normal subjects. The response of two patients who had subnormal T4 and raised thyrotrophin concentrations was significantly smaller than that of other patients.

Like Cuttler *et al*,⁴ we found that thyrotrophin concentrations in uraemic patients were either high normal or clearly raised. The kidneys are known to participate in the removal and degradation of circulating polypeptide hormones, including

thyrotrophin. In uraemic patients the degradation and removal of circulating thyrotrophin is diminished, which may account for the raised thyrotrophin levels. Cuttler *et al*⁴ also showed that thyrotrophin secretion rates were subnormal in uraemic patients in spite of the raised serum thyrotrophin levels. This explains the raised thyrotrophin concentrations, but it does not account for the fact that thyrotrophin was clearly raised in our patients with low normal or subnormal T4 levels but normal or high normal in those with normal T4 concentrations. This indicates that the integrity of the thyroid-pituitary feedback mechanism is intact in these patients and that this feedback operates against a background of diminished thyrotrophin clearance from the circulation.

The TRH-induced thyrotrophin release was subnormal in all patients, there being no release at all in those patients who had clearly raised basal thyrotrophin concentrations. This is paradoxical in view of the low or low normal T4 concentrations observed in many of these patients. Cuttler *et al*⁴ also found subnormal responses to TRH in uraemic patients.

The diminution in the response of thyrotrophin to TRH might be the result of either a diminished thyrotrophin reserve in the thyrotroph or to an alteration in the excitability of the thyrotroph cell membrane. Gonzales *et al*⁵ observed that 200 µg of TRH given intravenously induced no significant rise in serum thyrotrophin in uraemic patients, whereas an infusion of 800 µg did. This observation suggests that the thyrotrophs of uraemic patients have a raised threshold (or diminished excitability) to TRH.

A raised threshold is indeed possible in view of the low protein intake of these patients. Rats maintained on low-protein diets have raised serum thyrotrophin concentrations associated with diminished thyrotrophin contents in their pituitary glands.⁶

These findings suggest a combined abnormality in the function of the thyroid and pituitary glands. The thyroid gland seems to be relatively insensitive to thyrotrophin, as indicated by low T4 levels and high thyrotrophin concentrations in the presence of a residual functional reserve (shown by the thyrotrophin-stimulation test). Two patients also had a subnormal thyroid response. Higher than usual doses of TRH have been found to induce thyrotrophin release, which would suggest that the pituitary gland is relatively insensitive to TRH. At present we cannot comment on the possibility that there are diminished thyrotrophin stores in the pituitary glands of uraemic patients.

It is interesting that this report of an apparent increase in the incidence of biochemical hypothyroidism in patients on long-term haemodialysis should be from Sheffield, where many patients come from Derbyshire—an area renowned for goitre and the lack of iodide in tap water. A combination of leaching out of iodide from patients' blood during haemodialysis and the salt restriction (table salt is the main source of iodide) that these patients are subjected to probably results in progressive depletion of body iodide. Our findings are not entirely consistent with those observed in iodide deficiency, however. In this condition the ratio of T3 and T4 rises, whereas all our patients had subnormal T3 concentrations. Serum PBI levels were maintained in association with progressively diminishing serum T4 concentrations after haemodialysis, and the sensitivity of the thyroid gland to thyrotrophin was diminished, which would indicate that an intrinsic defect of thyroid hormone synthesis rather than iodide depletion underlay the thyroid function abnormality in these patients. Other factors like ionic abnormalities, chronic low protein intake, and the effect of uraemic toxins would also have to be considered to explain this abnormality. Carter *et al*⁷ have suggested that the subnormal T3 may be due to a diminished peripheral conversion of T4 to T3.

The clinical significance of these data is not entirely clear, especially since the patients with low T4 and raised thyrotrophin concentrations did not have symptoms specifically related to hypothyroidism. But marginal hypothyroidism is often extremely difficult to diagnose clinically. A study of ankle reflex durations in these patients is in progress to assess the presence of hypothyroidism at the end organs. A trial of treatment with iodine

or thyroid hormones, or both, in patients who prove to be hypothyroid is also being considered.

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Apparent resistance to hypotensive effect of clonidine

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Summary

Clonidine failed to reduce the blood pressures of two patients with essential hypertension. One was given 5.4 mg/day and the other 6 mg/day, and their respective peak plasma clonidine concentrations were 26.2 ng/ml and 14.4 ng/ml. Several months after the end of clonidine treatment a single oral dose of 0.3 mg of clonidine produced maximum falls in blood pressure of 30/22 mm Hg and 88/41 mm Hg with peak plasma clonidine concentrations of 1.4 ng/ml and 0.9 ng/ml. Resistance to the hypotensive effect of high doses of clonidine may be due to stimulation of peripheral alpha-adrenoceptors causing vasoconstriction, which maintains a raised blood pressure.

Introduction

Clonidine is a hypotensive agent widely used to treat patients with high blood pressure.¹ The reported range of daily doses for optimum blood pressure control is 0.15-4.8 mg.² When used in conjunction with a diuretic, however, the maximum effective dose of clonidine may be considerably lower in many patients.³ In some patients small initial doses of clonidine have lowered blood pressure but when the dose has been increased the blood pressure has risen and become refractory to the drug.^{2,4} We describe here two hypertensive patients whose blood pressures were apparently resistant to high doses of clonidine and the results of studies of both high and low doses of clonidine.

Case 1

A 44-year-old man presented with accelerated hypertension in May 1967, when his blood pressure was 200/140 mm Hg. He had electrocardiographic (ECG) evidence of left ventricular hypertrophy but no cardiac enlargement or impairment of cardiac or renal function. He

had a family history of hypertension, but further investigation failed to show any primary cause. For two years he was treated with several antihypertensive drugs, including guanethidine, methyldopa, guanoxan, reserpine, and bethanidine. Blood pressure control was unsatisfactory, and side effects, particularly impotence, were unacceptable. In March 1969 clonidine (0.225 mg/day) was introduced. The dose was gradually increased over the next two and a half years to 7.2 mg/day in an attempt to obtain adequate blood pressure control. His impotence improved but he developed side effects of clonidine, including sedation, dry mouth, and constipation. Control of his blood pressure remained difficult despite the addition of propranolol, debrisoquine, and hydralazine. In October 1975 he was admitted to hospital for further assessment of treatment. His blood pressure was 170/120 mm Hg supine and 122/70 mm Hg erect, and he was receiving clonidine 5.4 mg, bendrofluazide 10 mg, propranolol 960 mg, and hydralazine 600 mg daily. Hydralazine and propranolol were stopped three days before the first (high-dose) clonidine study. After this study clonidine was withdrawn and blood pressure was controlled over the next eight months with labetalol 3.2 g and bendrofluazide 10 mg daily. This treatment was interrupted 16 hours before the second (low-dose) clonidine study.

Case 2

A 51-year-old woman had been hypertensive since her first pregnancy in 1959 (aged 34). There was a family history of hypertension, but investigation had shown no primary cause. Antihypertensive treatment was started with rauwolfia alkaloids in 1962, when her blood pressure was 190/125 mm Hg. This treatment was continued until 1972, when, with a blood pressure of 210/130 mm Hg, treatment was changed to a thiazide diuretic, debrisoquine, and clonidine, the latter in an initial daily dose of 0.2 mg. Blood pressure control remained difficult, however, despite the subsequent use of methyldopa, bethanidine, propranolol, and an increased dose of clonidine to a maximum of 6 mg/day by June 1974. She complained of sedation, dry mouth, and constipation on clonidine. In November 1975 she was admitted to hospital for further changes of treatment. At this time blood pressure was 186/122 mm Hg supine and 173/126 mm Hg erect, and she was receiving clonidine 6 mg, propranolol 480 mg, and bendrofluazide 10 mg daily. Propranolol was withdrawn three days before the first clonidine study. After this study clonidine was withdrawn, and her blood pressure was controlled on labetalol 2.4 g and bendrofluazide 10 mg daily. Seven months later the second clonidine study was performed 16 hours after the last dose of labetalol.

Method

Each patient was investigated twice: once during long-term clonidine treatment and again seven to eight months after stopping clonidine. In the first study both patients received their usual morning dose of clonidine—1.8 mg (case 1) and 1.5 mg (case 2) orally. In the second they were given a single 0.3-mg dose of clonidine orally. Both patients gave their informed written consent to the procedures. The investigation was performed in a quiet clinical laboratory, where the

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