ORIGINAL ARTICLE

Effects of chronic hemodialysis on thyroid function in chronic renal failure

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Summary: Thyroid function was studied in 54 patients undergoing chronic hemodialysis. Serum thyroxine, triiodothyronine and free thyroxine and the free thyroxine index were significantly lower than normal. The levels of both serum thyroxine and the free thyroxine index tended to fall progressively the longer the patients were on hemodialysis. These findings, in association with low serum TSH levels and normal increase in radioactive iodine uptake by the thyroid after TSH injection, suggest that a defect in pituitary secretion of TSH may be responsible. Although some patients experienced symptomatic improvement after treatment with L-thyroxine the efficacy of this form of treatment in patients on chronic hemodialysis has not yet been established.

Résumé: *Les effets de l'hémodialyse chronique sur la fonction thyroïdienne dans l'insuffisance rénale chronique*

Nous avons étudié la fonction thyroïdienne chez 54 malades soumis à des hémodialyses répétées pour insuffisance rénale chronique. Il a été constaté que les taux sériques de la thyroxine, de la triiodothyronine et de la thyroxine libre et l'indice de thyroxine libre étaient notablement inférieurs à la normale. A mesure que les hémodialyses se multipliaient, le taux de la thyroxine sérique et l'indice de la thyroxine libre avaient tendance à baisser graduellement. Ces diverses constatations, rapprochées des faibles niveaux de thyrotrophine (TSH) sérique et de l'augmentation de la fixation par la thyroïde d'iode radioactif après injection de TSH, laissent supposer l'existence d'une insuffisance de sécrétion hypophysaire de TSH. Nous avons noté que certains malades présentaient une amélioration symptomatique après traitement à la L-thyroxine, mais il n'a pas encore été possible d'établir l'efficacité de ce mode de traitement chez des malades soumis à des hémodialyses répétées.

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Studies of thyroid function in patients in chronic renal failure and patients on chronic hemodialysis or peritoneal dialysis have produced conflicting results. In some patients in chronic renal failure findings consistent with hyperthyroidism have been reported. These include elevated levels of protein-bound iodine (PBI) and free thyroxine, increased T_3 resin uptake and an increased thyroxine pool.[1-3] In other patients findings consistent with hypothyroidism have been reported, including low levels of PBI, decreased ^{131}I uptake, reduced basal metabolic rate, prolonged tendon reflex time, symptoms of hypothyroidism, and a prolonged half-life and turnover rate of triiodothyronine and thyroxine.[1,3-5] The hypothyroidism has been variously attributed to reduced TSH (thyrotropin, thyroid-stimulating hormone) secretion by the pituitary[4] and to abnormalities primarily within the thyroid itself.[6]

Similar conflicting information exists for patients on chronic hemodialysis. In some, findings consistent with hyperthyroidism have been reported. These include elevated levels of free thyroxine, increased ^{131}I uptake, and exophthalmos.[1,7,8] In other patients findings consistent with hypothyrodism have been found, including low levels of PBI, serum thyroxine and serum triiodothyronine, and decreased T_3 resin and ^{131}I uptake.[1,8-10] The hypothyroidism has been attributed to reduced secretion of TSH by the pituitary.[6,10]

We have studied thyroid function in 54 patients on chronic hemodialysis.

Materials and methods

The 54 patients in this study, 36 men and 18 women, were receiving hemodialysis three times weekly for periods of 6 to 10 hours on a standard Kiil dialyzer with dialysate flow rates of 500 ml./min. One quarter of the patients had internal arteriovenous fistulas; the rest had silastic shunts. The length of time on dialysis ranged from two weeks to six years. The underlying renal disease was glomerulonephritis in 38, polycystic kidney in 6, obstructive pyelonephritis in 2, phenacetin nephritis in 2, lupus nephritis in 2 and other disease in 4. No patients were being given testosterone. The patients' ages ranged from 6 to 60 years.

The local water supply was fluoridated and the calcium concentration of the dialysis fluid was 3 mEq./l. The dialysis fluid was not softened or deionized.

The PBI was measured by a method based on that of Riley and Gochman,[11] serum thyroxine by a modification of the method of Murphy,[12] T_3 resin uptake by the Triosorb method,[13] free thyroxine by the method of Sterling and Brenner,[14] serum triiodothyronine by the method of Wahner

and Gorman,[15] serum thyrotropin by the method of Mayberry *et al*,[16] and the free thyroxine index (FTI) by the method of Howorth and Maclagan,[17] in which the FTI equals the product of the serum thyroxine and the ratio of the patient's T_3 resin uptake to control T_3 resin uptake. Antithyroglobulin antibodies were measured by the method of Roitt and Doniach,[18] plasma vitamin A by the method of Thompson *et al*,[19] serum carotene by a modification of the method of Wenger, Kirsner and Palmer,[20] serum cholesterol by the method of Black, Jarrett and Levine,[21] and plasma inorganic iodide by the method of Harden, Mason and Buchanan,[22] using saliva instead of urine. Photomotograms of the Achilles tendon reflex were obtained by the method of Gilson,[23] using the Burdick photomotograph. The half-relaxation point was determined, i.e. the time from the hammer tap to the half-way point of tendon relaxation. The results are recorded in milliseconds.

The thyrotropin stimulation test was performed as described by Burke,[24] using 10 units of thyrotropin hormone (Thyrotron, Nordic Biochemicals) given intramuscularly once daily for three days; 24-hour ^{131}I uptake was determined before administration of thyrotropin and again after three days of treatment.

Scanning of the thyroid was done in 20 patients after intravenous injection of 1.5 mCi of ^{99m}Tc-sodium pertechnetate. Scanning was performed five minutes later with a gamma camera (Nuclear Chicago Pho-gamma) using a pinhole collimator. Blood samples were taken during dialysis to measure the difference in concentration of various substances on the arterial and venous side of the dialyser. These samples were taken five minutes after starting dialysis, during which time the patient was receiving heparin. The removal of ^{131}I-sodium iodide from the circulation during dialysis was studied one hour after patients had been given an oral dose of 10 μCi of ^{131}I. Ten patients with low values of serum thyroxine and free thyroxine index received 100 μg. thyroxine daily. After three weeks the dose was increased to 200 μg. per day and the patient remained on this dose for up to six months. In two patients, after receiving 200 μg. per day for three weeks, the dose was increased to 300 μg. per day. In four patients thyroid tissue was obtained during parathyroidectomy and examined histologically.

The analyses were done by Anova 14 and Anova 15 programs of the DERS 360/67 Program Library. The data were organized and edited by the Department of Statistics of the W.W. Cross Cancer Institute, Edmonton. All calculations were based on those outlined by Snedecor and Cochran.[25]

Results

1. *Comparison of chronic hemodialysis patients with normal subjects*

From Table I it can be seen that levels of PBI, plasma inorganic iodide and serum cholesterol and Achilles tendon reflex time were not significantly different from normal. Serum levels of thyroxine, free thyroxine, triiodothyronine, TSH, carotene, albumin and total protein and the free thyroxine index were all significantly lower than normal. The T_3 resin uptake, free thyroxine fraction and plasma vitamin A levels were greater than normal.

2. *Comparison of pre- and post-dialysis blood values*

The levels of PBI, serum thyroxine, triiodothyronine and TSH, T_3 resin uptake and the free thyroxine index were not significantly different before and after dialysis. The mean free thyroxine fraction, measured in five patients, increased from 0.046 to 0.083% and the mean serum free thyroxine in these patients rose from 1.43 to 2.75 ng./100 ml. Both of these increases may be due to the effect of heparin on the binding of thyroxine by protein.[7] The mean counts per minute of ^{131}I of the blood fell from 1534 pre-dialysis to 278 post-dialysis.

Table I—Values in patients on chronic hemodialysis

		Chronic hemodialysis patients			Normals			
Test	Units	Number	Mean value	Sample standard deviation	Number	Mean value	Sample standard deviation	Level of significance (P value)
PBI	μg./100 ml.	24	6.8	3.7	15	5.8	0.3	NS
Serum thyroxine (measured as the iodine)	μg./100 ml.	54	3.4	1.1	46	4.9	0.75	<0.01
T_3 resin uptake	%	54	32.2	5.0	46	29.9	3.1	<0.01
Free thyroxine index		54	3.6	1.09	46	4.9	0.98	<0.01
Serum free thyroxine fraction	% of total thyroxine	21	0.053	0.009	21	0.047	0.005	<0.01
Serum free thyroxine	ng./100 ml.	21	1.42	0.612	21	2.72	0.455	<0.01
Serum triiodothyronine	ng./100 ml.	29	160	56	26	243	40	<0.01
Serum TSH	μunits/ml.	35	4.4	2.7	209	6.7	3.9	<0.01
Plasma inorganic iodide	μg./100 ml.	11	5.9	9.2	5	0.6	0.42	NS
Serum cholesterol	mg./100 ml.	24	160	34	220	160	40	NS
Serum carotene	mg./100 ml.	25	77.2	30.6	100	185	58	<0.01
Plasma vitamin A	mg./100 ml.	30	176	59.5	100	50	12.5	<0.01
Achilles half-relaxation time	msecs.	19	296	68	11	288	44	NS
Serum albumin	g./100 ml.	29	3.65	0.52	200	4.3	0.4	<0.01
Total serum protein	g./100 ml.	29	6.5	0.73	200	7.1	0.35	<0.01

NS = not significant

3. *Comparison of values from the arterial and venous side of the dialyzer*

In seven patients the levels of PBI, serum thyroxine, free thyroxine and TSH, T_3 resin uptake, the free thyroxine index and the free thyroxine fraction at the arterial side of the dialyzer were not different from those on the venous side. The mean serum levels of triiodothyronine, however, fell from 187.8 to 138.8 ng./100 ml. The mean counts per minute of ^{131}I in the blood fell from 1534 on the arterial side to 514 on the venous side of the Kiil dialyzer, and the dialyzer clearance rates averaged 75 ml./min. at a blood flow rate of 140 ml./min.

4. *Effect of heparin on blood values*

In five patients, blood samples taken five minutes after the beginning of dialysis, while the patient was receiving heparin, showed no significant changes in the levels of PBI, serum thyroxine or TSH from the pre-dialysis values. The mean free thyroxine fraction rose from 0.046 to 0.102% and the mean serum free thyroxine from 1.43 to 3.26 ng./100 ml.

5. *Comparison of results over a one-year period*

In 25 patients who had been on dialysis for variable lengths of time, values of serum thyroxine, T_3 resin uptake and the free thyroxine index were obtained one year apart (Table II). The mean free thyroxine index, calculated from the serum thyroxine and T_3 resin uptake, fell significantly over the one-year period from 3.36 to 2.68.

6. *Comparison of results in patients on the dialysis program for different periods of time*

Seven parameters of thyroid function were compared (Table III) in patients on dialysis for 0 to 12 months, 13 to 24 months and 25 or more months. Significantly lower levels of serum thyroxine and the free thyroxine index were found in patients on dialysis for 25 months or longer compared with those on dialysis for 12 months or less.

7. *Effect of TSH on ^{131}I uptake*

The 24-hour ^{131}I uptake was measured in three patients on chronic hemodialysis whose levels of serum thyroxine and free thyroxine index were lower than normal. In all three the uptake was normal (11, 17 and 17%) as judged by the normal range of 10 to 40%. When the 24-hour ^{131}I uptake was repeated after three days of TSH administration, it increased to 12, 32 and 36% respectively in the three patients. This response is greater than that seen in hypothyroidism caused by primary thyroid failure and is in the range seen in normal subjects or in patients with pituitary hypothyroidism.[24]

8. *Histology of the thyroid tissue*

Histopathological examination of thyroid tissue from four patients demonstrated no abnormalities.

9. *Antithyroglobulin antibodies*

Antithyroglobulin antibodies were absent in 26 cases and present in low titre (1:5) in four cases.

10. *Clinical findings and response to treatment*

All patients complained of some degree of cold intolerance and skin dryness. Only one patient had thyroid enlargement as judged independently by two clinicians. In this patient thyroid enlargement had been present for several years before onset of renal failure. In 20 patients sodium pertechnetate scans of the thyroid also failed to reveal any enlargement. In the patients without clinical evidence of peripheral neuropathy reflexes were judged to be normal.

Ten patients with a low level of serum thyroxine and free thyroxine index were treated with L-thyroxine. On daily doses of 100 μg. five noted reduction of fatigue and improved cold tolerance within a few weeks. When, after three weeks, the dosage was raised to 200 μg., three of these five patients experienced excessive sweating, increased nervousness or palpitations. Reducing the dose to the former level of 100 μg. per day caused these side effects to disappear. In the other two a further reduction in fatigue was noted at the dosage of 200 μg. per day. In one of these, raising the dose to 300 μg. per day produced palpitations necessitating reduction of the dose.

The other five patients had no subjective improvement on 100 μg. L-thyroxine daily. Raising the dosage to 200 μg. per day failed to cause any symptomatic improvement even after six months of treatment. In one of these patients, raising the dosage to 300 μg. per day also failed to produce symptomatic improvement.

Discussion

The levels of serum thyroxine, triiodothyronine, free thyroxine and the free thyroxine index were frequently low when first measured in our patients receiving chronic hemodialysis. In addition, the levels of serum thyroxine and free thyroxine index (FTI) tended to fall further the longer the patient was on dialysis (Tables II and III). These findings suggest that hypothyroidism may be present in many of the patients. Yet there are problems in confirming the diagnosis clinically. Most of our dialysis patients complain of cold intolerance, fatigue and skin dryness, symptoms which could be due equally well to uremia. It was impossible to distinguish clinically between those in whom the levels of the thyroid hormones were low and those in whom

Table II—Comparison of thyroid values over one-year period

			Initial values		Values one year later		
Test	Units	Number	Mean	Sample standard deviation	Mean	Sample standard deviation	Level of significance
Serum thyroxine	μg./100 ml.	25	3.18	0.94	2.7	1.15	NS
T_3 resin uptake	%	25	32.5	8.16	30.24	4.03	NS
Free thyroxine index		25	3.36	0.95	2.68	1.08	$P<0.01$

NS = not significant

they were normal. In addition, in all patients without a significant neuropathy, the Achilles tendon reflexes were normal as judged clinically and by actually measuring the half-relaxation time. Some of the laboratory data were also not consistent with hypothyroidism. Serum carotene and cholesterol levels are usually higher than normal in hypothyroidism[26] while in our patients serum carotene levels were lower than normal and serum cholesterol levels were normal. Plasma vitamin A levels, which are usually lower than normal in hypothyroidism[26] were greatly elevated in our patients. This may be due, however, to the retention of retinol-binding protein which occurs in renal failure.[27] The ^{131}I uptake was normal in the three patients tested but this test may be a poor indicator of thyroid function in renal failure since failure to excrete the ^{131}I through the urine may cause blood levels to remain elevated longer than in normal individuals, resulting in increased uptake by the thyroid. The response to therapy varied. Some patients noted increased strength and improved cold intolerance; some did not.

If hypothyroidism is indeed present in many of our hemodialysis patients, what role does it play in the uremic syndrome? If it were contributing to the anemia, one would expect a direct correlation between blood levels of hemoglobin and the levels of thyroxine, free thyroxine and triiodothyronine. In fact a negative correlation was found. In addition, treatment with L-thyroxine for up to six months failed to raise the hemoglobin level significantly in any patient. There was also no correlation between the level of the thyroid hormones and the serum cholesterol, serum carotene, plasma vitamin A levels, or the motor nerve conduction velocities of the lateral peroneal nerves.

It is unlikely that the low levels of TSH or the thyroid hormones are due to their loss through a dialyzer. The levels of serum thyroxine, free thyroxine and TSH did not change in passage through the Kiil dialyzer, and at the end of dialysis the levels of serum thyroxine, TSH and triiodothyronine were not significantly different from those determined before dialysis.

It is also unlikely that primary thyroid failure is responsible for the low level of thyroid hormones. Low levels of the hormones would stimulate TSH production causing it to be present in high concentration in the serum.[15] In our patients, however, the mean TSH levels were lower than normal. In addition, if primary thyroid failure were responsible for low levels of thyroid hormones, the radioactive iodine uptake would not increase after TSH stimulation.[24] In our patients, however, a normal increase in ^{131}I uptake was noted after TSH stimulation. Similar responses to TSH have been noted by others in non-dialyzed uremic patients[4] and in chronic hemodialysis patients.[10] All this evidence suggests that a defect in TSH secretion may be responsible for the abnormal thyroid function. Some investigators[6] have demonstrated that the serum TSH concentrations were lower after injection of thyrotropin-releasing hormone (TRH) during dialysis than in a control group, which also suggests reduced secretion. Defects in pituitary function involving hormones such as ACTH[4] and growth hormone[9] have also been reported in renal failure, and pathological alterations in the pituitary have been found.[28]

Pituitary abnormalities could be due to the effect of uremic toxins. In our study, however, there was no correlation between the level of TSH and the level of either BUN or creatinine. Malnutrition, a not uncommon problem in patients on chronic hemodialysis, can cause a reduction in thyroid function[29] which may be secondary to reduced TSH secretion.[30] Many of our patients have failed to achieve their ideal weight since starting chronic hemodialysis, and are suffering from some degree of malnutrition. This is reflected in their low levels of serum albumin, total protein and carotene (Table I). However, none of these three parameters nor the patient's clinical state of nutrition showed any correlation with the level of TSH.

There is also some evidence that uremia may interfere directly with thyroid function. Ramirez *et al*[10] reported a high incidence of colloid goitre in patients on chronic hemodialysis. Others[6] have found elevated levels of TSH in some patients with chronic renal failure and have noted

Table III—Comparison of thyroid values after varying times on dialysis

Test	Units	0-12 months on dialysis	13-24 months on dialysis	25 or more months on dialysis	Level of significance
Serum thyroxine	μg./100 ml.				
Number of cases		31	8	13	Significant difference
Mean		3.7	3.1	2.7	(<0.01) between 0-12 months
Standard deviation		1.04	0.76	0.95	and 25 months or more
T_3 resin uptake	%				
Number of cases		31	8	13	No significant difference
Mean		32.3	31.2	33.3	between the groups
Standard deviation		3.4	7.5	6.7	
Free thyroxine index					
Number of cases		31	8	13	Significant difference
Mean		4.0	3.2	2.8	(<0.01) between 0-12 months
Standard deviation		1.1	0.76	0.68	and 25 or more months
Serum free thyroxine	ng./100 ml.				
Number of cases		9	4	7	No significant difference
Mean		1.7	1.35	1.04	between the groups
Standard deviation		0.6	0.73	0.41	
Serum triiodothyronine	ng./100 ml.				
Number of cases		13	6	10	No significant difference
Mean		139.2	162.8	184.6	between the groups
Standard deviation		48.6	51.1	60.9	
Serum TSH	μunits/ml.				
Number of cases		16	8	10	No significant difference
Mean		4.2	3.9	5.1	between the groups
Standard deviation		2.0	2.0	3.9	
PBI	μg./100 ml.				
Number		12	4	7	No significant difference
Mean		6.5	9.1	6.2	between the groups
Standard deviation		3.3	5.8	3.4	

an exaggerated release of TSH after stimulation by TRH in these patients, suggesting that a primary defect of thyroid function may be present. In our patients there was a negative correlation between the serum creatinine and the level of thyroid hormones, also suggesting that uremic toxins may interfere directly with thyroid function. We have not observed goitres in our dialysis patients, either by clinical examination or by sodium pertechnetate scanning, except in one patient in whom a goitre was present prior to onset of renal failure. Others also have found goitre to be uncommon in dialysis patients.[8]

Thyroid function may be directly affected by many factors in renal failure. Malnutrition could interfere directly with thyroid function but we could find no correlation between the thyroid hormone levels and the patients' state of nutrition, serum albumin, total protein or carotene. Autoimmunity is unlikely to be related. Histological examination of the thyroid yielded normal findings in four patients with low levels of thyroid hormones. In addition, thyroglobulin antibodies were absent in 26 cases and present in low titre in only four, and their presence did not correlate with the levels of thyroid hormones. Plasma inorganic iodide may be elevated in the blood of patients with chronic renal failure[31] or patients on chronic hemodialysis[9] and could interfere with thyroid function.[32] Some of our patients had elevated plasma inorganic iodide levels but they failed to show any correlation with the levels of the thyroid hormones. Fluoride may also interfere with thyroid function[33] and our local water has been fluoridated since 1967. The fluoride ion passes from the dialysis fluid into the patient's blood through the cellophane membrane in the dialyzer, and the blood fluoride levels rise steadily in patients dialyzed with floridated water.[34] Some aliphatic compounds present in drinking water may also interfere with thyroid function.[35] It is of interest that in a group of patients treated by chronic peritoneal dialysis, a method which employs distilled water, serum thyroxine levels were normal.[36]

From the evidence presented it seems that an abnormality of thyroid function is present in many of our patients on chronic hemodialysis and that this abnormality may be due to a defect in pituitary function. Although some of the patients noted symptomatic improvement after treatment with L-thyroxine, assessment of this form of treatment must await controlled clinical trials.

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