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Renal Response to Sodium Restriction in Myxedema[1] (38223)

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(Introduced by Murray Epstein)

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Several observations suggest that the hypothyroid state is characterized by an altered renal handling of sodium. Data indicating excessive sodium reabsorption include increased body wt and total body sodium, edema (1–3), reduced glomerular filtration rate, impaired ability to excrete water (4–7) and the demonstration of a diuresis and natriuresis upon treatment (8). On the other hand, we have found that patients with myxedema have an impaired ability to reabsorb sodium under certain acute conditions (9), an observation consistent with the findings in rats with experimental hypothyroidism (10–13).

Despite this conflicting data, with the exception of sporadic, mostly uncontrolled observations (8, 14, 15) no systematic studies of the adaptation of hypothyroid patients to chronic sodium deprivation have been reported.

In the present study, the renal responses of hypothyroid patients to dietary sodium restriction were compared to those of normal subjects studied under comparable carefully controlled conditions. One myxedematous patient was restudied after a period of partial thyroid replacement.

Material and Methods. Six patients with untreated primary myxedema were studied; Table I summarizes some of their clinical and laboratory findings. Four of these patients had clinically mild to moderate hypothyroidism of variable duration. Patients 1 and 2 had mild symptoms, mostly fatigue and some weight gain. Patients 3 and 4 exhibited well defined but not marked symptoms consisting of various combinations of weight gain, muscular weakness, hair loss, voice change and cold intolerance. Patients 5 and 6 had severe myxedema at the time of initial study, with marked skin, hair and voice changes, increased sensitivity to cold, mental dullness, slow speech, prolonged recovery phase of deep tendon reflexes and severe constipation. They also had the lowest circulating thyroid hormone (Table I). Patient 6 was also studied again 5 mo later, when he was still moderately myxedematous.

For comparison with the myxedema group, four hospitalized euthyroid male patients ranging in age from 48 to 53 years were studied at the same time. Two had mild psoriasis and one each had contact dermatitis in a healing stage and postgastrectomy status. Hypothyroid and euthyroid control subjects gave no history and had no clinical or laboratory evidence of renal, cardiovascular or hepatic disease. The informed consent of each of the control and

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TABLE I. Clinical and Laboratory Findings in Patients with Primary Hypothyroidism.

Patient	Age	Sex	Known duration of disease	PBI[a] μg/100 ml	RAI[b] %	Cholesterol mg/100 ml	Serum creatinine mg/100 ml
1	53	M	1 year	2.2	4.5	300	0.5
2	47	F	7 years	0.7	4	470	1.2
3	24	M	15 years	2.5[c]	<1	350	1.4
4	61	M	3 months	3.5[c]	<1	560	1.4
5	62	F	3 years	0.2	4	266	1.1
6	64	M	4 years	0.2	5	285	1.3

[a] Normal range 4–8 μg/100 ml.
[b] RAI normal range 10–30% uptake at 24 hr.
[c] T_4 determination: normal range 5–12.5 μg/100 ml.

hypothyroid subjects was obtained by a principal investigator.

All subjects were studied as in-patients and were initially provided with diets containing 140–160 mEq of sodium and 80–100 mEq of potassium daily for 5–10 days. Body wt (that was comparable in hypothyroid and control subjects, 78.7 ± 7.1 (SEM) and 78.4 ± 5.1 kg, respectively) and serum sodium concentration were stable in both hypothyroid and control subjects for at least the last 2 days of this period and urinary sodium excretion was similar in both groups (hypothyroid: 140 ± 16 mEq/day; controls: 148 ± 12 mEq/day). After attainment of sodium balance on this regimen, an isocaloric diet containing 14 mEq of sodium and 77 mEq of potassium was substituted for the previous intake for a period of from 4 to 10 days, depending on when sodium balance was again achieved. All subjects lost weight during dietary sodium restriction: controls 1.4–1.8 kg, hypothyroid patients 0.7–2.1 kg. Fluid intake up to 2000 ml per day was permitted *ad libitum* throughout the study.

Twenty-four hour urine collections were made daily and analyzed for creatinine, sodium and potassium. Blood was obtained at regular intervals for creatinine, sodium and potassium determinations. Creatinine was measured in serum and urine by a method adapted to the Autoanalyzer, sodium and potassium with an IL flame photometer. Student's *t* test was used for statistical evaluation of the data (16).

Results. As shown in Table II and Fig. 1 urinary Na excretion fell to the level of intake in the control subjects within four to five days of institution of the low Na diet. The half-time of reduction of urinary Na excretion (Na $t_{½}$) in these subjects was 34 ± 5 hr. During the first 5 days of the diet, mean cumulative urinary Na loss was 148 ± 11 mEq.

The 4 patients with mild to moderate hypothyroidism (patients 1–4) achieved Na balance in 3–7 days, with a mean Na $t_{½}$ of 34 ± 4 hr and a mean cumulative Na loss of 153 ± 11 mEq, values not significantly different from those of the control subjects ($P > 0.70$) (Table II). The 2 patients (5 and 6) with clinically severe hypothyroidism, however, demonstrated impaired ability to conserve salt. Urinary Na excretion still exceeded intake in patient 5 at the end of 7 days of low Na intake, with a Na $t_{½}$ of 81 hr and a cumulative urinary Na loss of 233 mEq over 5 days. Patient 6 achieved Na balance on day 10 of Na restriction, with a Na $t_{½}$ of 96 hr and a cumulative urinary Na loss of 436 mEq for the first 5 days. When restudied after 5 mo of modest thyroid replacement (desiccated thyroid 60 mg/day) his PBI was 0.8 μg/100 ml and clinically he was still moderately hypothyroid (hoarseness, dry skin, definitely delayed recovery phase of deep tendon reflexes). At this time his ability to conserve Na although improved remained clearly abnormal (Fig. 1).

Prior to salt restriction, mean serum Na concentration was lower in the hypothyroid patients (137 ± 1 mEq/liter) than in the

TABLE II. Renal Response to Sodium Restriction in Hypothyroid and Control Patients.

Patients	Time to achieve Na balance (days)	Na $t_{1/2}$[a] (hr)	Cumulative urinary Na loss[b] (mEq/5 days)	Creatinine clearance (ml/min)[c]		Serum sodium (mEq/liter)		Urinary, potassium (mEq/day)	
				B[d]	A[d]	B[d]	A[d]	B[e]	A[e]
Controls									
1	5	47	173	122	102	142	132	79	79
2	4	35	127	99	102	142	135	57	51
3	5	24	158	113	125	138	136	31	46
4	4	30	135	126	92	144	142	65	76
Mean ± SE		34 ± 5	148 ± 11	115 ± 6	105 ± 7	142 ± 1	136 ± 2	58 ± 10	63 ± 8
Hypothyroid Mild to moderate									
1	7	30	136	61	52	138	136	51	50
2	4	38	133	113	108	141	147	44	40
3	3	27	166	81	73	138	137	37	66
4	5	43	176	61	66	135	134	41	45
Severe									
5	7[f]	81	233	36	39	134	136	36	53
6	10	96	436	57	59	136	133	51	55
Mean ± SE (all hypothyroid patients)				68 ± 11	66 ± 10	137 ± 1	137 ± 2	43 ± 3	52 ± 4

[a] Time in hours required to decrease urinary sodium excretion to 1/2 of the control value.
[b] Cumulative urinary sodium excretion in excess of dietary sodium intake during the first 5 days of sodium restriction.
[c] 24-hr endogenous creatinine clearance.
[d] B: Before salt restriction; A: After salt restriction.
[e] Average urinary potassium excretion before (B) and during the last 2 days during sodium restriction (A).
[f] Did not achieve Na balance by day 7.

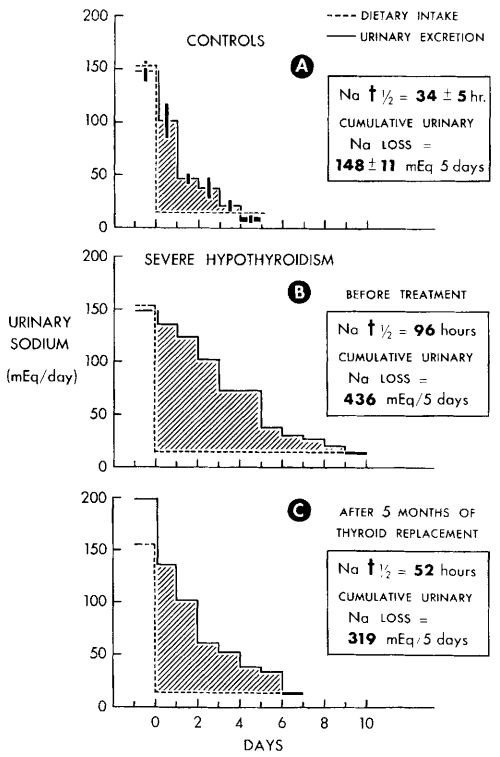

FIG. 1. Renal Response to dietary Na restriction in 4 control subjects (A) and in patient 6 with severe hypothyroidism, before treatment (B) and after 5 mo of modest thyroid hormone replacement (desiccated thyroid 60 mg daily) (C). The shaded area represents urinary Na loss in excess of dietary intake. The vertical bars on (A) represent 1 ± SE of the mean of daily sodium excretion in the control subjects.

control subjects (142 ± 1 mEq/liter) ($P < 0.02$) (Table II). Following Na restriction, serum Na concentration remained unchanged in the hypothyroid subjects; while in the control patients a mean decrease of 5.3 ± 2.0 mEq/liter was observed.

Prior to salt restriction, the patients with hypothyroidism as a group had a significantly lower mean endogenous creatinine clearance (68 ± 11 ml/min) than control subjects (115 ± 6 ml/min) ($P < 0.02$) (Table II) with only one of the 6 hypothyroid patients (Patient 2) having a creatinine clearance within the range of the controls. Creatinine clearances did not change significantly in either group following salt restriction.

Urinary potassium excretion in the 2 groups was not significantly different, either before or after Na deprivation (Table II), nor was a difference observed in mean serum potassium concentrations before or after salt restriction in the hypothyroid (4.3 ± 0.2 and 4.3 ± 0.1 mEq/liter, respectively) or control patients (4.3 ± 0.1 and 4.4 ± 0.1 mEq liter, respectively).

Discussion. The results of the present study indicate that the ability of patients with mild to moderate hypothyroidism to adapt to dietary salt restriction is indistinguishable from that of euthyroid subjects. Neither the time required to reduce Na excretion by 50% (Na $t_{½}$) nor the cumulative Na loss with salt deprivation differed significantly in the 4 patients with mild to moderate hypothyroidism as compared to the control subjects.

In contrast, the responses of the 2 patients with laboratory and clinical evidence of severe myxedema were clearly abnormal. Both demonstrated a slow exponential decline in urinary Na following salt restriction, requiring 81 and 96 hr to reduce Na excretion by 50% as compared to a mean of 34 hr in the control subjects and in the patients with mild to moderate hypothyroidism. While Na $t_{½}$ has been shown to increase modestly with age the values demonstrated here in the 2 severely hypothyroid patients exceed by severalfold those found in euthyroid subjects of comparable age.[4] This marked prolongation of the interval required to effect appropriate Na conservation resulted in cumulative urinary Na losses in these 2 patients that were 2–3 times greater than in the control and less severely affected hypothyroid patients. In the one patient restudied after partial correction of the myxedematous state the ability to conserve Na was improved, though still grossly impaired.

Although the decreased serum Na in pa-

[4] Epstein, M. and Hollenberg, N. K. found a significant correlation between Na $t_{1/2}$ and age (F value = 15.9; $P < 0.0005$) in a group of 84 normal subjects during their adaptation to dietary Na deprivation (10 mEq/day) (personal communication).

tients with myxedema is generally attributed to their impaired capacity to excrete water (6, 7, 17, 18), it may be that a defect in renal sodium conservation contributes to the development of hyponatremia in patients with severe myxedema and coma (18, 19) and in those reported to exhibit the syndrome of inappropriate secretion of ADH (20, 21). This consideration may be particularly relevant in those patients undergoing salt restriction or extrarenal sodium losses with excessive fluid replacement.

The data reported here confirm the well-documented decreases in glomerular filtration rate (4–7) in hypothyroidism. The glomerular filtration rate as estimated in this study by the endogenous creatinine clearance was reduced in 5 of the 6 patients with hypothyroidism. It is apparent that the ability to conserve sodium was not related to the degree of reduction of glomerular filtration, since hypothyroid patients with similar creatinine clearances had normal (patients 1 and 4) or abnormal (patient 6) ability for sodium conservation (Table II). Likewise, age does not appear to be a factor in the subnormal response, since myxedema patients above 60 years of age had both normal (patient 4) and abnormal (patients 5 and 6) responses.

Since the filtered load of sodium is decreased, the consistent impairment in salt conservation is most reasonably attributed to decreased renal tubular sodium reabsorption. This limitation in sodium reabsorption apparently is not a consequence of mineralocorticoid deficiency since Luetscher and associates (22) have calculated normal plasma levels of aldosterone in hypothyroidism despite somewhat depressed secretory rates. Furthermore, we have demonstrated previously that even supraphysiological doses of mineralocorticoid result in a lesser sodium reabsorptive response in hypothyroid patients than in normals. Mineralocorticoid administration also fails to prevent the marked salt wasting observed in experimental hypothyroidism (10, 12).

The demonstration here and in previous clinical (9) and animal (10–13) studies of an abnormality in renal tubular sodium reabsorption in hypothyroidism suggests a possible role for thyroid hormone in the processes involved in normal renal tubular sodium handling. More direct evidence in support of such a possibility is provided by the demonstration that thyroid hormone affects active sodium transport and cell membrane permeability to sodium in several experimental systems (23–24).

Summary. The renal response to dietary Na restriction after initial equilibration on a liberal salt intake was studied under carefully controlled conditions in 6 patients with myxedema and four euthyroid control subjects. In 4 patients with mild to moderate hypothyroidism, the time required to reduce Na excretion by 50% (Na $t_{½}$) and the cumulative urinary Na losses were comparable to those of the euthyroid controls. In 2 patients with clinically severe myxedema, however, renal Na conservation was clearly abnormal, with delayed achievement of sodium balance, prolonged Na $t_{½}$ and increased cumulative sodium losses. Improvement in the ability to conserve Na was demonstrated upon restudy of one patient after partial correction of his myxedematous state. Available evidence suggests that the basis for the impairment in sodium conservation in hypothyroidism is a decrease in renal tubular sodium reabsorption.

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