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Original Article

Thyroxine treatment induces upregulation of renin-angiotensin-aldosterone system due to decreasing effective plasma volume in patients with primary myxoedema

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Abstract

Background. In experimental animals and humans, hypothyroidism is associated with fluid retention and generalized oedema, increased antidiuretic hormone (ADH), decreased atrial natriuretic hormone (ANH), and decreased renin-angiotensin-aldosterone system (RAAS), which subsequently can be corrected by thyroid hormone replacement. The purpose of this study was to determine the effect of thyroxine therapy on RAAS and neurohormones affecting water and electrolyte metabolism and the reason for these changes in patients with primary myxoedema.

Methods. We measured changes in the plasma renin activity (PRA), serum aldosterone (Aldo), ADH, ANH levels, serum and 24 h urinary electrolytes and osmolalities, and cardiac function in 22 female patients with primary myxoedema before and after correction of hypothyroidism. We also evaluated age-, sex-, and BMI-matched 15 healthy control subjects (Cont).

Results. It took an average of 4.3 months (range, 3–9 months) to normalize thyroid function. The mean reductions of body weight and estimated plasma volume were 1.8 ± 1.0 kg ($P=0.002$) and 8.5% ($P<0.001$), respectively. In addition, serum Na^+ and osmolality and the haematocrit were significantly elevated after correction of hypothyroidism ($P<0.01$ and $P<0.001$, respectively). Increased F_ENa and C_{OSM} ($P<0.05$) levels in patients with hypothyroidism (Ho) compared with those in Cont did not change after thyroxine therapy (Eu). However, C_{H_2O}, U_EK, F_EK, and TTKG levels as well as creatinine clearance (Ccr) were markedly increased in Eu compared with Ho and Cont ($P<0.01$, respectively). Increased plasma ADH concentration and decreased plasma ANH concentration were normalized compared to Cont after thyroxine therapy ($P<0.001$ and $P<0.01$, respectively). Low PRA and serum Aldo concentration in Ho were significantly increased in Eu ($P<0.001$ and $P<0.01$, respectively). In addition, increased left ventricular mass index and decreased cardiac output in Ho were normalized compared to Cont after thyroxine therapy ($P<0.01$, respectively)

Conclusions. These findings suggest that the exaggerated upregulation of RAAS after correction of hypothyroidism in patients with primary myxoedema is associated with an increase in Ccr and a decrease in plasma volume resulting from water diuresis, natriuresis, osmotic diuresis and inappropriate changes in plasma ADH and ANH levels. The improved renal function coincided with an amelioration of cardiac function. These changes seem to be an adaptive response for preventing excessive plasma volume and weight loss after thyroxine therapy.

Keywords: antidiuretic hormone; atrial natriuretic hormone; glomerular filtration rate; myxoedema; renin-angiotensin-aldosterone; thyroxine

Introduction

Hypothyroidism, particularly severe primary myxoedema, produces marked changes of cardiovascular, renal haemodynamic and tubular reabsorptional responses [1]. Hypothyroidism is also associated with fluid retention and generalized oedema, which are corrected by thyroid hormone therapy. Impaired free water excretion, oedema and hyponatremia in patients with myxoedema were attributed to antidiuretic

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hormone (ADH)-dependent or ADH-independent mechanisms [2]. Previous studies have shown that the major cause of impaired water excretion of hypothyroidism is an alteration in renal perfusion and glomerular filtration rate (GFR) secondary to systemic effects of thyroid hormone deficiency on cardiac output and peripheral vascular resistance [3,4]. Hypothyroid patients often have generalized vascular constriction and increased systemic resistance, but little is known about its cause. Furthermore, several studies demonstrated that hypothyroidism is associated with cardiac fibrosis and interstitial oedema resulting in cardiac dilatation and decreased cardiac output with normal cardiac filling pressure [5,6]. It was also shown that hypothyroidism was associated with decreased basal concentrations of circulating atrial natriuretic peptide (ANH), which can be elevated in response to an increase in atrial pressure and paralleled natriuresis during saline volume expansion. Though the role of ANH deficiency in hypothyroidism is unknown, subnormal ANH levels are the result of thyroid deficiency itself [2,7].

Renal alterations in hypothyroidism include decreased GFR and renal plasma flow as well as increased fractional excretion of sodium (F_ENa). The increased F_ENa has been associated with decreased proximal tubular reabsorption [8,9]. It is well known that hypothyroid patients and experimental rats have impaired ability to conserve sodium during rigid sodium restriction and that plasma ANH is decreased [7]. Hypothyroid rats have decreased plasma renin activity (PRA) and plasma angiotensin (AT) and aldosterone (Aldo) concentrations. Similarly, patients with hypothyroidism often have low PRA and plasma Aldo concentration [10]. Decreased sodium transport and water retention might be induced as a result of these hormonal changes. In experimental rats, the abnormalities were corrected quickly after treatment [11]. However, the changes of renin-angiotensin-aldosterone (RAAS) and neurohormones and the cause of these changes after correction of hypothyroidism in patients with primary myxoedema has not been clarified well. For this purpose, we investigated the effect of thyroxine therapy on RAAS and neurohormones affecting water and electrolytic metabolism in patients with primary myxoedema.

Methods

Patients

We studied 22 young female patients with primary myxoedema (Ho) and 15 young healthy female control subjects (Cont) suitably matched for age, weight, and body mass index (BMI) (Table 1). The mean age of study patients was 30.6 years and that of healthy control subjects 30.4 years. All patients presented with classical symptoms and signs of thyroid deficiency (range: 1–49 months), including increased tiredness, sleep disturbance with a depressed mood, constipation, decreased exercise tolerance, and cold, dry, and rough skin with non-pitting oedema. Hypothyroidism was confirmed in all patients by the determination of low serum T_4, low serum T_3, markedly elevated TSH, and low ^{123}I uptake. Other causes of hypothyroidism were excluded by appropriate clinical and radiological studies. The patients were studied during in-hospital stay. They were recruited over a 4-year period. No subjects received any medications and had not been treated for hypothyroidism before. Informed written consent was obtained prior to the study.

Treatment protocol

Patients' characteristics were obtained at the time of diagnosis of primary myxoedema. In patients with myxoedema, the study protocol was performed before thyroxine replacement therapy. Subjects were placed on a diet containing 60 g protein, 150 mEq Na^+, and 60 mEq K^+ per day for the entire study [12]. After 7 days of controlled diet, the subjects were admitted for 3 days and 2 nights where confirmation of Na^+ balance was achieved with urinary Na^+, K^+, and creatinine monitoring throughout the study. On the second day, the neurohormonal responses and serum electrolytes as well as 24 h urinary output and electrolytes were measured. During the study period (range: 3–9 months), patients with primary myxoedema received various doses of oral thyroxine (0.05–0.15 mg daily). The thyroxine doses were adjusted every month in order to achieve and maintain euthyroidism (Eu) (i.e. normalization of TSH and T_4 levels). In all patients the dosage remained stable for at least 3 months. The mean dose of thyroxine at the euthyroid state was 0.12 ± 0.03 mg/day. Four months after normalization of TSH, T_3 and T_4levels, each subject underwent reconfirmation of TSH levels and follow-up studies were initiated at the time which the same study protocol was performed. The 15 normal healthy subjects were on 7-day controlled diet and their plasma neurohormones, urinary excretion of Na^+, K^+, and creatinine were comparable to those of the patients.

Parameters of clinical, biochemical and neurohormonal mediators

Blood cell count was determined by Coulter and serum creatinine (Cr), blood urea nitrogen (BUN), and electrolytes using an autoanalyser (Hitachi, Tokyo, Japan) at the beginning and at the end of the study (after normalization of thyroid test). The 24-h urine samples were used for estimating creatinine clearance (Ccr), fractional excretion of sodium (F_ENa), fractional excretion of potassium (F_EK), free water clearance (C_{H2O}) and osmolar clearance (C_{OSM}). Thyroid hormones were determined by radioimmunoassay (RIA). At the start of and after the T_4 therapy, the samples were obtained between 8 and 9 a.m. A cannula was inserted into a forearm vein in all patients for blood sampling. Patients were placed in supine position for at least 45 min before obtaining blood pressure (BP), pulse rates and blood sampling. BP and pulse rates were measured twice within an interval of 5 min with mercury sphygmomanometer. Blood samples were collected in pre-chilled tubes, which were immediately centrifuged at 4°C. PRA, serum Aldo, ADH, and ANH were also measured by RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). At least 2 measurements of each hormone were averaged.

Plasma volume (EPV) was estimated based on haematocrit (Hct) and body weight (wt):

$$EPV=[0.065 \times wt\ (kg)] \times [1 - Hct]\ [13].$$

Echocardiographic studies for cardiac output and left ventricular mass index

Echocardiographic studies were also performed for evaluation of cardiac output (CO) and left ventricular mass index (LVMi) at the beginning and the end of the study. All measurements and recordings were performed in accordance with the recommendation of the American Society of Echocardiography using average values of three measures. CO was calculated as the product of LV volume and heart rate; the cardiac output index (COi) relates this value to the body surface area and is expressed as $l/min/m^2$. LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), the interventricular septal thickness (IVST), and LV posterior wall thickness (LVPWT) were calculated according to Penn's corrected formula [14]

$$LVM\ (g) = 0.8\{1.04\times[(LVEDD + IVST + LVPWT)^3 - (LVEDD)^3]\} + 0.6$$

Statistical analyses

The values were expressed as means ± standard deviation. When variables were normally distributed, the data were analysed by means of the paired *t*-test in patients treated with thyroxine hormone before and after the study and by the unpaired *t*-test comparing myxoedema patients to healthy control subjects. When variables were not normally distributed, the data were analysed by means of the Wilcoxon matched-pairs signed-rank test in patients with myxoedema and the Mann-Whitney signed-rank test when comparing myxoedema patients to healthy control subjects. Significance was defined as a value of $P < 0.05$.

Results

Entry characteristics and follow-up in clinical parameters and thyroid hormone profile

Clinical parameters and evolution of thyroid hormones in patients with myxoedema and Cont are shown in Table 1 and Figure 1. At the time of diagnosis of primary myxoedema, all patients had markedly elevated serum TSH concentrations and low T_4 and T_3 concentrations. The administration of thyroxine produced a statistically significant decrease in serum TSH (from 71.95 ± 35.56 to 2.3 ± 4.06 μU/ml, $P < 0.001$) and increase in serum T_4 (from 3.11 ± 0.96 to 9.33 ± 2.54 μg/dl, $P < 0.001$) and T_3 concentrations (from 0.48 ± 0.13 to 1.30 ± 0.46 ng/dl, $P < 0.01$) (Figure 1). As shown in Table 1, there were significant decreases in body weight ($P < 0.01$), BMI ($P < 0.05$), and plasma volume ($P < 0.001$) as a result of treatment with thyroxine. There was no significant difference in body weight, BMI, EPV, and thyroid hormone levels between Eu and Cont.

Haemodynamic data and results of laboratory tests before and after achievement of Eu are shown in Table 2. At the time of diagnosis of primary myxoedema, most patients had heart rates less than 70 beats/min (sinus rhythm). In contrast, heart rate was more than 80 beats/min after initiation of thyroxine treatment. Blood pressure, however, remained unchanged after correction of hypothyroidism. Increased serum creatinine levels at the time of diagnosis decreased significantly ($P < 0.01$), whereas previously decreased serum Na^+ and osmolality (Osm) levels increased significantly after thyroxine therapy ($P < 0.01$ and $P < 0.05$, respectively). Haemoglobin and Hct values increased significantly after correction of hypothyroidism ($P < 0.001$).

Echocardiographic studies were performed to evaluate cardiac function and cardiac mass in response to thyroxine treatment (Table 2). Decreased COi and increased LVMi at the start of thyroxine treatment were normalized, compared with Cont after the correction of Ho ($P < 0.01$, respectively).

Renal response to thyroxine treatment

Ccr in Eu was significantly increased after treatment with thyroxine compared with Ho and Cont ($P < 0.01$) (Table 3). Increased F_ENa and C_{OSM} levels in patients with Ho, compared with Cont ($P < 0.05$, respectively), remained unchanged after correction of hypothyroidism. However, Ccr, U_KV, F_EK, C_{H2O} and TTKG levels were markedly increased in Eu compared with Ho and Cont ($P < 0.01$). After correction of hypothyroidism, patients showed excessive generation of

Table 1. Changes in clinical parameters in the patients treated with thyroxine and healthy control subjects

	Myxoedema		Control	*P* value
	Pre-treatment	Post-treatment		
Age (years)	30.6 ± 4.1		30.4 ± 2.7	NS
Body weight (kg)	58.0 ± 8.1*	56.28 ± 8.0	56.56 ± 5.9	< 0.01
BMI	22.65 ± 3.15*	21.87 ± 3.14	21.77 ± 3.02	< 0.05
Effective plasma volume (ml)	2460 ± 360*	2311 ± 356	2354 ± 489	< 0.001

Data are mean ± SD. *Compared with post-treatment or control.

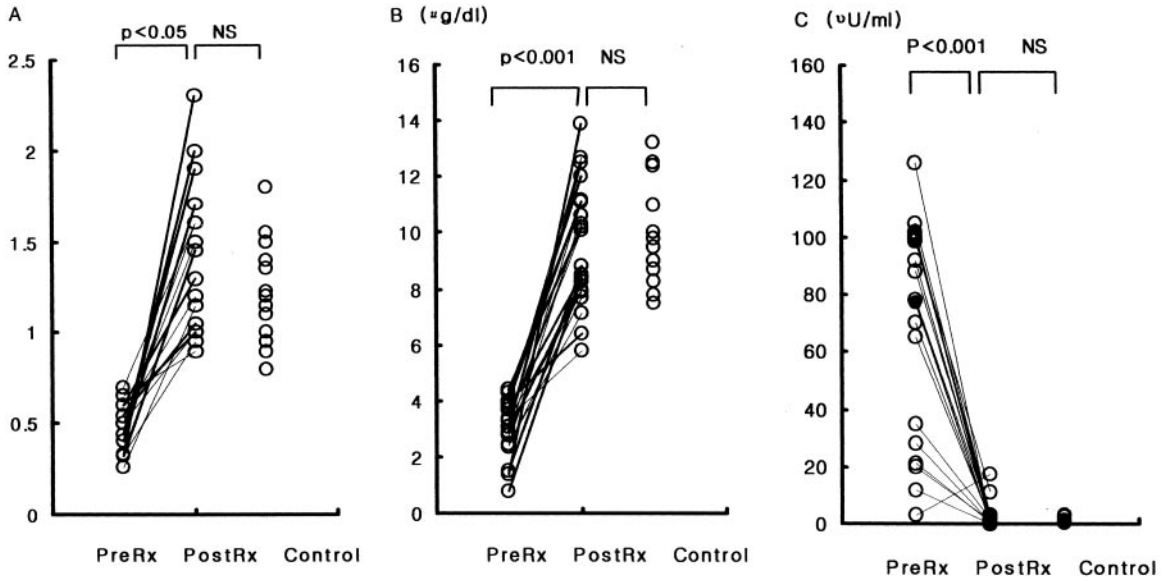

Fig. 1. Changes in thyroid hormonal profile in the patients treated with thyroxine and healthy control subjects. (**A**) plasma T3, (**B**) plasma T4, and (**C**) plasma TSH. PreRx, pre-treatment; PostRx, post-treatment; NS, non-specific.

Table 2. Clinical, biochemical and haematological profile in the patients treated with thyroxine and healthy control subjects

	Myxoedema		Control	*P* value
	Pre-treatment	Post-treatment		
Systolic BP (mmHg)	114.5±13.1	118.7±11.0	116.9±12.1	NS
Diastolic BP (mmHg)	71.9±11.3	74.1±8.9	72.3±10.4	NS
Heart rate (beats/min)	71.9±11.3	80.1±10.6**	72.4±10.4	<0.001
Serum Cr (mg/dl)	0.79±0.13	0.67±0.13**	0.82±0.12	<0.01
Na (mEq/l)	136.5±3.1*	141.7±1.9	142.0±2.0	<0.01
K (mEq/l)	4.17±0.32	4.15±0.33	4.15±0.40	NS
Osm (mmol/kg)	286.5±7.3*	291.2±8.1	291.7±8.2	<0.05
Hb (g/l)	11.8±1.1*	12.6±0.7	12.8±1.3	<0.001
Hct (%)	34.9±2.8*	37.0±1.9	37.3±2.1	<0.001
COi (l/min/m^2)	2.77±0.31*	3.00±0.42	3.12±0.21	<0.01
LVMi (g)	135±25*	125±22	123±35	<0.01

*Compared with post-treatment or control; **compared with pre-treatment or control.

Table 3. Renal response to thyroxine treatment in patients with primary myxoedema and healthy control subjects

	Myxoedema		Control	*P* value
	Pre-treatment	Post-treatment		
Ccr	96.5±19.1	118.3±28.6**	102.4±10.1	<0.01
$U_{Na}V$ (mEq/day)	153.2±17.2	151.5±21.2	152.3±14.2	NS
U_KV (mEq/day)	59.8±18.9	74.2±22.9**	49.4±20.4	<0.05
FENa (%)	1.62±0.41*	1.30±0.37*	0.62±0.43	<0.01
FEK (%)	9.68±3.29	12.35±5.51**	8.24±4.10	<0.05
TTKG	4.74±1.48	7.13±2.04**	3.92±1.11	<0.01
C_{H2O} (ml/min)	−1.03±0.56	0.89±0.27**	−0.49±0.36	<0.01
C_{OSM} (ml/min)	3.04±0.76*	3.12±0.70*	2.16±0.69	<0.01

*Compared with control; **compared with pre-treatment or control.

free water, natriuresis, kaliuresis, and elevated TTKG compared with Cont ($P<0.01$).

Neurohormonal effects of thyroxine treatment

Increased plasma ADH and decreased plasma ANH concentrations in Ho, compared with Cont (ADH, 3.21 ± 0.44 pg/ml and ANH, 3.86 ± 5.44 pg/ml, respectively), were normalized after correction of hypothyroidism (ADH from 8.34 ± 4.90 to 3.18 ± 0.52 pg/ml, $P<0.001$ and ANH from 1.15 ± 3.26 to 3.56 ± 5.50 pg/ml, $P<0.01$, respectively) (Figure 2). PRA and plasma Aldo concentrations in Ho were normal compared with Cont (PRA, 1.55 ± 1.11 ng/ml/day and Aldo, 119.01 ± 91.1 pg/ml, respectively), but were increased markedly in Eu after thyroxine treatment (PRA from 1.05 ± 0.79 to 8.44 ± 25.77 ng/ml/day, $P<0.01$ and Aldo from 93.23 ± 85.22 to 215.88 ± 92.44 pg/ml, $P<0.001$, respectively) (Figure 2).

Discussion

Recent *in vivo* and *in vitro* studies identified an interaction between hypothyroidism and RAAS

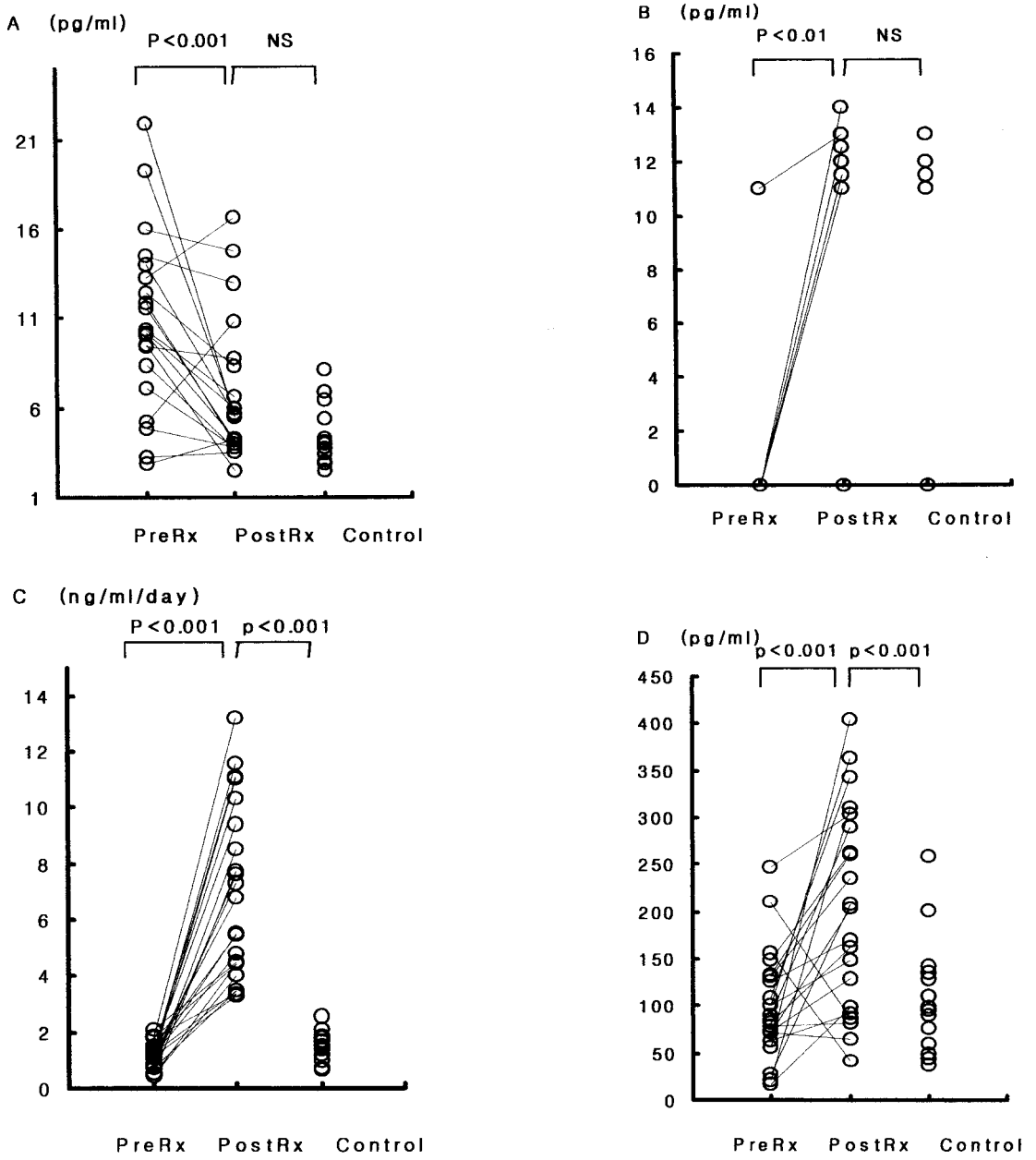

Fig. 2. Neurohormonal changes in primary myxoedema patients treated with thyroxine and healthy control subjects. (**A**) ADH, (**B**) ANH, (**C**) PRA, and (**D**) Aldo. In ANH measurement, values below minimum sensitivity (<10 pg/ml) were assigned a value of zero for calculation of mean values.

[7,8,10]. Although previous studies reported the changes of RAAS in hypothyroid state, this is the first study to examine the effect of thyroxine therapy on RAAS in patients with primary myxoedema. In this study, clinical and neurohormonal evaluation showed that oedema-forming weight gain, impaired C_{H2O}, elevated ADH concentrations, decreased ANH concentrations and reduced GFR, compared to euthyroidism as determined by creatinine clearance, were normalized after correction of hypothyroidism. EPV estimated from body weight and Hct decreased significantly in the euthyroid state, compared with hypothyroid state. Furthermore, thyroxine administration to myxoedema patients was associated with ongoing natriuresis and elevated kaliuresis and TTKG. In addition, patients exhibited an upregulation of renin-aldosterone response to thyroxine therapy. Of interest, we also found a thyroxine effect on the heart, i.e. an increase in cardiac output and a decrease in left ventricular mass index, which may have contributed to the observed changes of plasma ANH and ADH.

Hypothyroidism is associated with significant changes in renal function in patients with myxoedema and in experimental animals following thyroidectomy or drug-induced hypothyroidism. Commonly reported renal alterations in hypothyroidism include a decrease in GFR and renal plasma flow, and a decrease in tubular sodium reabsorption (i.e. an increase in F_ENa). A major factor limiting GFR in myxoedema is a reduction of renal blood flow to as low as half that with normal function, probably as a consequence of low cardiac output, which can be corrected by thyroid hormone therapy [15]. In this study, a possible explanation for the elevated Ccr is the correction of reduced GFR and renal blood flow as well as the decrease in cardiac output [3–6].

It is also well known that in hypothyroidism, increased sodium excretion is associated with decreased proximal tubular sodium reabsorption and decreased Na^+-K^+ pump activity in collecting tubules [8,9,16]. Recently, Allon *et al.* [17] reported that the mechanism responsible for renal tubular abnormalities in sodium and water excretion in hypothyroid patients was a consequence of the associated decrease in renal function. Furthermore, they also showed that maximal urinary flow and C_{H2O} were similarly reduced in hypothyroid patients [17]. In this study, as demonstrated previously, patients in the hypothyroid state had a significant decrease in GFR, impaired C_{H2O}, and increased sodium and osmolar clearances (C_{OSM}). Among these abnormalities, C_{H2O} increased in parallel with GFR after thyroxine therapy. However, elevated natriuresis and C_{OSM} persisted after correction of hypothyroidism. The exact mechanism of ongoing natriuresis and osmotic diuresis in patients with euthyroid state is unknown. It is possible that the rise in GFR due to improved cardiac function and increased ANH, compared with hypothyroid status, as well as thyroxine replacement itself and the ensuing medullary washout, which is a consequence of Ho, might be of importance [18]. However, additional prospective studies are needed to delineate further the relationship between thyroxine and renal tubular function.

To date, the pathophysiology and pathogenesis of impaired water excretion and hyponatremia in severe hypothyroidism are still not entirely clear. In several reports, the complication of this disorder was attributed to ADH-dependent and ADH-independent mechanisms [2,3]. Normally, thyroid hormone suppresses ADH secretion by a central mechanism and enhances delivery of tubular fluid to the distal diluting segments presumably by augmenting GFR [19]. Especially in hypothyroidism, abnormal water excretion is a result of nonosmotic factors stimulating ADH release, such as cardiac fibrosis and interstitial oedema resulting in cardiac dilatation and decreased cardiac output, and of intrarenal factors, such as diminished GFR or increased proximal reabsorption which lead to decreased distal fluid delivery to the diluting segment of the nephron [20]. In this study, the increase in ADH in hypothyroidism is consistent with previous studies in humans. Elevated ADH concentrations decreased after thyroxine therapy, in accordance with the observed increase in GFR and serum Osm and the decrease in LV mass. The absence of a correlation between plasma ADH concentrations and serum Osm or EPV in our study further supports a functional link between nonosmotic factors and plasma ADH concentrations (data not shown). There is also evidence in support of the theory that thyroxine itself plays a role in the decrease of plasma ADH after thyroxine treatment [20].

A decrease of EPV in healthy subjects leads to an increase of heart rate and haemoconcentration, activates the RAAS, releases plasma epinephrine and ADH, and decreases plasma ANH level [12]. In this study, patients showed such changes, as excepted for inappropriate ADH and ANH changes. The decrease in plasma ADH and the relatively normal plasma ANH levels compared with healthy control subjects are not in agreement with the findings indicating a decrease in effective circulating volume after correction of myxoedema. The mechanism of these inappropriate plasma ADH and ANH changes is not known. However, such changes can be expected if the thyroid function improves [19,20]. It is well known that thyroid hormones suppress ADH secretion by a central mechanism [20] and increase the secretion of ANH by an improvement of cardiac structure [5,6]. Recent reports have suggested that this paradoxical finding may be associated with cardiac fibrosis and interstitial oedema resulting in cardiac dilatation and decreased cardiac output in hypothyroid patients [5,6]. Other studies also demonstrated that hypothyroidism and hyperthyroidism were associated, respectively, with decreased and increased basal concentrations of circulating ANH, which increased in response to thyroxine and decreased in response to methimazole [7]. Therefore, subnormal ANH levels in hypothyroidism would be the direct result of thyroid hormone deficiency. Therefore, both the improvement of cardiac

structure and the supplement of thyroxine itself may play a significant role in the elevation of plasma ANH. In our study, this notion is supported by the finding of a significantly improved cardiac function and decreased left ventricular mass after thyroxine replacement. Moreover, it is well known that ANH is involved in the upregulation of salt excretion [17]. Increased circulating ANH levels in our patients after thyroxine therapy may play another role in the ongoing elevated natriuresis, at least during the observation period in euthyroid state.

The RAAS plays an important role in the regulation of extracellular volume (ECF) and arterial pressure. In normal conditions, the activity of the RAAS varies inversely with sodium and water balance. Impaired water excretion leads to low PRA and low Aldo concentrations as seen in our patients relative to their euthyroid state [21]. Furthermore, other reports showed that patients with hypothyroidism had a hormonal pattern reminiscent of 'low renin hypertension'. Such anomaly was corrected when the patients became euthyroid on thyroxine therapy. Similar to a previous report [21], our patients had evidence of volume expansion prior to the treatment, i.e. decreased PRA and Aldo together with increased EPV relative to their euthyroid state. In healthy subjects, Davies *et al.* [22] showed that a 17% PV reduction over 14 min contributed to a corresponding mean increase of PRA by 73%. Robertson *et al.* [23] also demonstrated changes of RAAS in hypothyroidism of short duration, i.e. one month after thyroxine therapy, with a 1.7-fold increase in PRA and a 1.6-fold increase in Aldo. Our patients had their PRA and plasma Aldo levels increased by 8-fold and 2.3-fold, respectively, after thyroxine therapy. These findings suggest that the marked increase in RAAS in our myxoedema patients after correction of hypothyroidism might be related to a prolonged decrease in plasma volume.

The TTKG is known as the best indirect index of the renal response to Aldo activity [24]. In our myxoedema patients, TTKG as an indirect functional assay of renal tubular Aldo activity was also well matched with serum Aldo concentrations. Markedly increased renal K excretion in our patients after thyroxine therapy might be due to increased plasma Aldo, increased delivery of sodium to the collecting duct, increased fluid flow to distal tubule, and increased excretion of osmolytes [25].

In conclusion, our findings suggest that the exaggerated upregulation of the RAAS after correction of hypothyroidism in patients with primary myxoedema is associated with the observed decrease in EPV resulting from natriuresis, osmotic diuresis and inadequate changes in plasma ADH and ANH levels, which coincide with improved renal and cardiac function. This change seems to be an adaptive response for the prevention of excessive EPV and weight loss after thyroxine therapy. The changes of plasma ADH and ANH may be primarily associated not with the observed decrease in PV but with the improvement of cardiac structure and myxoedema itself due to thyroxine treatment.

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