Water metabolism disturbances at different stages of primary thyroid failure

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Abstract

The aim of the present study was to study salt and water metabolism in thyroid deficiency.

We performed an oral water loading test (OWL) and a hypertonic 5% saline infusion test (HSI) in 16 patients with overt primary hypothyroidism before replacement treatment (PRE group) and after, in eight patients with subclinical hypothyroidism (SUB group) and in 16 normal individuals (CG group).

In the PRE group, a lower free water clearance was detected in the OWL (P<0·022), with lower plasma osmolality (OWL: P<0·005; HSI: P<0·001) and arginine vasopressin (AVP) (OWL: P<0·001; HSI: P<0·001) than the CG group, across both tests; they normalized with the replacement treatment. The same plasma abnormalities were detected in the SUB group with the HSI. Although the AVP and thirst thresholds did not differ between the groups, the lag between them was lower in the PRE (4·1 ± 3·2 mOsm/kg) and SUB group (2·6 ± 2·1 mOsm/kg) than in the CG group (13·3 ± 9·2 mOsm/kg) (P<0·05). There were no differences in atrial natriuretic hormone (ANH), plasma renin activity (PRA) and plasma aldosterone among the groups.

These results indicate that plasma hypo-osmolality and low levels of AVP are present in primary hypothyroidism, and indeed are already present in the subclinical phase of the disease. An overlap between the thresholds of thirst and AVP seem to play a role in these abnormalities, but ANH, PRA and plasma aldosterone do not appear to contribute.


Introduction

Disturbances in salt and water metabolism, mainly impaired water excretion, have been described in primary hypothyroidism. Severe hyponatremia can appear, especially in the presence of myxedema coma (Moses & Scheinman 1996). However, controversy persists concerning the physiopathological causes and the involvement of hormonal abnormalities, hemodynamic changes, or alterations of the kidney itself.

One hormonal mechanism that has been suggested as a possible explanation of these abnormalities is an altered osmoregulation of arginine vasopressin (AVP) secretion. Levels of this hormone have been reported to be high in some hypothyroid patients, mimicking the state of inappropriate antidiuretic hormone secretion syndrome (SIADH) (Skowsky & Kikuchi 1978, Laczi et al. 1987). However, more recently, plasma AVP has been found to be normal or low in hypothyroid patients (Iwasaki et al. 1990, Barna et al. 1994, Ota et al. 1994). This decrease could influence the sodium and water regulation of patients with hypothyroidism, although its exact contribution remains undefined.

In patients with subclinical hypothyroidism, disturbances in various organs have been described, even in the absence of serum thyroid hormones abnormalities (Surks & Ocampo 1996). However, in-depth studies on their water metabolism are lacking.

The aim of this study was to assess water and salt metabolism and its regulation in patients with overt primary and subclinical hypothyroidism, as well as the changes observed after treatment with thyroid hormones.

Patients, Materials and Methods

Patients

The study was approved by the ethical committee of the hospital and informed consent was obtained from all patients before the beginning of the study. The clinical characteristics of the individuals are detailed in Table 1. The studies were carried out in the following groups.
PRE group These were patients with overt primary hypothyroidism without treatment. Individuals with serum thyrotropin (TSH) levels >10 mU/l, low serum thyroxine (T₄) levels and with clinical symptoms were selected. All the patients presented spontaneous non-iatrogenic hypothyroidism. They had not been treated with thyroid hormones before the study. The etiologic diagnosis was idiopathic thyroid atrophy in eleven and Hashimoto’s thyroiditis in four, in one patient.

SUB group These were patients with subclinical hypothyroidism. Individuals with serum TSH >10 mU/l, normal serum T₄ and tri-iodothyronine (T₃) levels and without recognized symptoms of hypothyroidism were included. In all cases in this group the disease was spontaneous. No patients in this group were taking thyroid hormones before the study. The etiologic diagnosis was idiopathic thyroid atrophy in three and postpartum thyroiditis in one patient.

CG group These were normal individuals who were age (± 5 years)- and sex-matched healthy volunteers recruited for each hypothyroid patient.

POST group These were patients with primary hypothyroidism, after treatment. The PRE group individuals were studied again after replacement treatment, when serum TSH levels had returned to normal. The time-interval between the first and second study was 14 ± 4.0 months. The mean dose of levothyroxine administered at that moment was 2.2 ± 0.5 µg/kg weight.

Individuals with congestive heart failure or arrhythmia, severe arterial hypertension (systolic >180 and diastolic >100 mmHg), renal failure, diabetes mellitus, diabetes insipidus, SIADH, adrenal insufficiency and hepatic disease were excluded from the study. Patients who at the time of the study were taking thyroid hormones, diuretics, hypotensors, lithium, demeclocycline, glucocorticoids or any other drug that could affect water and sodium homeostasis were also excluded. In menstruating women, studies were preferably made in the follicular phase. There were no significant differences between the groups either in age or in body mass index.

Plasma volume (PV), effective renal plasma blood flow (ERPF) and glomerular filtration rate (GFR) were studied in all patients. Compared with the POST group, all three parameters were lower in the PRE group but not in the SUB group (data published in Villabona et al. 1999).

Methods

On two different non-consecutive days, an oral water loading test and a hypertonic saline infusion test were performed in all subjects. The trials were conducted at outpatient centers, in the morning after an overnight fast and a ban on smoking and alcohol intake of at least 10 h, with a free salt and water diet on the days before the start of all studies. There were no tolerance problems in either test.

Oral water loading test The patient was maintained in a supine position for at least 30 min before time 0, with the head at approximately 30°, throughout the test, standing upright only for micturition. A single arm was cannulated at −15 min, and the oral administration of 20 ml/kg tap water began at time 0 and continued for 30 min. Blood samples were obtained at 30-min intervals for 240 min, and urine samples were obtained hourly. Weight, blood pressure (BP) and heart rate were determined at the beginning and end of the test; in plasma, Na, K, glucose, AVP and osmolality were measured at all times, ANH hourly and renin activity (PRA) and aldosterone at 0 and 240 min. In the urine, Na, K, urea and osmolality were determined every hour.

Hypertonic saline infusion test This test was performed under the same conditions as the oral water loading test. The patient was maintained in a supine position with the head at approximately 30° throughout the infusion period. Both arms were cannulated at −15 min, and the 5% hypertonic saline infusion (3 ml/kg per h) using an infusion pump began at time 0 and continued for 120 min.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PRE (n=16)</th>
<th>POST (n=16)</th>
<th>SUB (n=8)</th>
<th>CG (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>4/12</td>
<td>—</td>
<td>0/8</td>
<td>4/12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.7 ± 14.3</td>
<td>—</td>
<td>38.4 ± 8.1</td>
<td>41.9 ± 16.4</td>
</tr>
<tr>
<td>(range 17–72)</td>
<td></td>
<td></td>
<td>(range 29–54)</td>
<td>(range 18–78)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.7 ± 5.4</td>
<td>—</td>
<td>25.0 ± 2.8</td>
<td>29.8 ± 8.0</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>129.0 ± 90.6</td>
<td>3.8 ± 5.3</td>
<td>13.5 ± 3.5</td>
<td>1.7 ± 0.7</td>
</tr>
<tr>
<td>T₄ (nmol/l)</td>
<td>246 ± 16.9</td>
<td>100.1 ± 22.5</td>
<td>87.1 ± 15.8</td>
<td>99.6 ± 12.1</td>
</tr>
<tr>
<td>FT₃ (nmol/l)</td>
<td>21.5 ± 14.8</td>
<td>95.0 ± 24.2</td>
<td>72.1 ± 14.0</td>
<td>92.6 ± 14.6</td>
</tr>
<tr>
<td>T₃ (nmol/l)</td>
<td>0.84 ± 0.51</td>
<td>1.84 ± 0.3</td>
<td>1.89 ± 0.33</td>
<td>2.08 ± 0.4</td>
</tr>
</tbody>
</table>

The clinical data of those in the POST group were the same as those in the PRE group.
Blood samples were extracted in the contralateral arm at 30-min intervals and urine samples were collected hourly. Weight was determined at the beginning and end of the test and BP and heart rate each 30 min. In plasma, Na, K, glucose, AVP and osmolality were measured at all times, ANH every hour, and renin activity and aldosterone at 0 and 120 min. In the urine, Na, K, urea and urinary osmolarity (UOsm) were measured hourly. Thirst was evaluated every 30 min by asking how many glasses of water the patient would drink at that moment, showing a diagram with drawings of several glasses (maximum eight glasses) (Goldman et al. 1988). The patients were allowed to indicate fractions (e.g. a glass and a half).

**Analytical measurements** Plasma and urine sodium, potassium, glucose, urea and creatinine were determined with a Hitachi 911 Automatic Autoanalyzer (Boehringer Mannheim Immunodiagnostics, Mannheim, Germany). Plasma and urinary osmolalities were determined by the freezing point depression method (Advanced Cryomatic® Osmometer 3C2; Advanced Instruments, Needham Heights, MA, USA). These determinations were used in the calculation of the free water clearance using standard formula. Plasma effective osmolality was also calculated by the formula: 2×(plasma Na+plasma K)+plasma glucose (all in mmol/l). The TSH, as well as T4, T3 and thyroxine-binding capacity (TBK) were determined with an enzyme-linked immunosorbent assay method (Boehringer Mannheim Immuno-diagnostics). With the T4 and TBK values, the free thyroxine index (FT4I) was calculated. PRA was determined using competitive radioimmunoassay (RIA) (Incstar, Stillwater, MN, USA). Plasma aldosterone was determined by competitive RIA (Sorin, Saluggia, Italy).

For determination of AVP, the samples were deposited in chilled heparinized tubes and centrifuged at 4°C, 2500 g for 15 min. The supernatant was maintained in ice until extraction, which was completed within 6 h. The extraction was done with ethanol 98%. The determination was performed using RIA (Bühlmann, Schönenbuch, Switzerland). The between-assay coefficient of variation of the method was 14·1%. The minimal detectable levels were 0·15 pmol/l. For ANH, the extracted blood was deposited in a chilled tube containing trasylol (400 µl) and EDTA (15 mg). The sample was placed in ice until its centrifugation at 4°C, 2500 g for 15 min. The resulting supernatant was frozen to ≤−20°C until analysis was performed. The sample was extracted in C18 columns. The determination was performed by RIA (Nichols Institute, San Juan Capistrano, CA, USA). The between-assay coefficient of variation of the method was 16·6%, and the minimal detectable levels were 15 pg/ml.

**Statistical analysis** The means in the variables with normal distribution were compared by a Student’s t-test of paired data, in the case of the PRE and the POST groups, and with one-way ANOVA when more than two groups were studied, with Scheffé’s and Bonferroni’s *a posteriori* contrasts to determine the differences group by group. In the variables with non-normal distribution, the Kruskal–Wallis test was applied. In the variables in which evolution at different points of the tests was of interest, an ANOVA of repeated measures was applied, directly if the distribution was normal, or after neparian logarithm or squared root transformation if it was not. In variables in which a significant difference was found, each point was studied by a one-way ANOVA test. The differences between groups at each point were studied with Scheffé and Bonferroni tests. The comparisons of continuous quantitative variables were performed by correlation test, with Pearson’s or Spearman’s coefficient as appropriate. In the case of AVP and thirst, correlation with plasma osmolality was determined in each person, using the individual thresholds and slopes to determine the mean and standard deviation of the group. For the correlation test with thyroid hormones, the base values of plasma osmolality, plasma AVP, plasma ANH, PRA and plasma aldosterone were calculated as the pool of the water loading and saline infusion test values. The area under the curve (AUC) was calculated with the trapezoidal method. The increase of one variable was calculated as the maximum – base/base, and the decrease as base – minimum/base. For all the tests, a difference of *P*<0·05 was considered significant. All results are expressed in the text as the mean±S.D. unless otherwise indicated. For the statistical analysis, undetectable values of AVP were considered at 0·1 pmol/l.

**Results**

**Oral water loading test**

The percentage of water excreted at the end of the test, compared with that ingested at the beginning, did not differ significantly between groups (PRE: 108·01±26·8%; SUB: 139·37±33·4%; CG: 122·69±24·4%; POST: 118·55±27·0%). None of the individuals presented an excretion at the end of the test of less than 80% of the ingested volume.

The response of the free water clearance (C H2O) to the water loading differed between the four groups (*P*=0·022, ANOVA) (Fig. 1A). The C H2O at 120 min was significantly lower in the PRE group (329·44±201·77 ml/h) than in the POST group (510·24±165·12 ml/h) (*P*<0·017, paired *t*-test). Conversely, at 240 min it was significantly lower in the POST group (6·63±67·11 ml/h) than in the PRE group (96·28±111·37 ml/h) (*P*<0·017, paired *t*-test). The AUC of C H2O throughout the 240 min of the test showed significant intergroup differences. In the PRE group (39·4±11·7 liters/h per min) and the POST group (46·9±11·3 liters/h per min) the AUC was significantly lower than in the CG group (64·4±11·0 liters/h per min) (*P*<0·05, one-way ANOVA). The AUC of the SUB
group (44·9 ± 16·3 liters/h per min) was also lower than that in the CG group, but without reaching significance. The base UOsm and its decrease was similar in all groups (Fig. 1B).

There were significant differences in the plasma osmolality response to the oral water loading in the four groups (P<0·005, ANOVA) (Fig. 2A). Beforehand and throughout the test the PRE group showed a lower plasma osmolality than the CG group, the difference being significant (P<0·05) at most points. The plasma osmolality in the SUB and POST groups showed levels between those of the PRE and the CG groups, and presented no significant differences, except between the POST and the CG groups at 60 min.

The evolution of plasma AVP showed significant differences between the four groups (P<0·001, ANOVA) (Fig. 2B). All levels in the PRE group were lower than those of the CG group, the difference being significant at
Figure 2 (A) Plasma levels of osmolality (POsm), (B) AVP and (C) ANH throughout the oral water loading test. PRE (●), SUB (◆), CG (▼) and POST (■). Values are means ± S.E.M. *P<0.05 compared with CG group; §P<0.05 compared with POST group.
most points \((P<0.05)\). In the POST group, plasma AVP was higher, beforehand and throughout the test, than in the other three groups; the differences between the PRE and the POST groups in this variable were significant at each point \((P<0.05)\). In the SUB group, plasma AVP levels were similar to those of the CG group although slightly lower, without significant differences either with respect to this group or to the PRE group. Plasma ANH during the oral water loading test was similar in the four groups (Fig. 2C).

In this test, the PRA and plasma aldosterone was found to be similar in the four groups, without significant differences in the base, end or decline (Table 2).

**Table 2** PRA and aldosterone in water and salt loading tests. Values are means ± S.D.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRE ((n=16))</th>
<th>SUB ((n=8))</th>
<th>CG ((n=16))</th>
<th>POST ((n=16))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral water loading</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base PRA (µkat/l per h)</td>
<td>31.45 ± 26.27</td>
<td>27.22 ± 20.83</td>
<td>33.21 ± 53.09</td>
<td>25.86 ± 21.37</td>
</tr>
<tr>
<td>Final PRA (µkat/l per h)</td>
<td>26.4 ± 25.72</td>
<td>20.93 ± 17.94</td>
<td>27.99 ± 43.99</td>
<td>19.3 ± 21.19</td>
</tr>
<tr>
<td>PRA decrement (%)</td>
<td>12.7 ± 45.4</td>
<td>30.93 ± 21.4</td>
<td>19.74 ± 33.3</td>
<td>34.86 ± 25.5</td>
</tr>
<tr>
<td>Base plasma aldosterone (nmol/l)</td>
<td>0.33 ± 0.11</td>
<td>0.43 ± 0.43</td>
<td>0.6 ± 0.6</td>
<td>0.30 ± 0.17</td>
</tr>
<tr>
<td>Final plasma aldosterone (nmol/l)</td>
<td>0.16 ± 0.09</td>
<td>0.15 ± 0.12</td>
<td>0.17 ± 0.17</td>
<td>0.19 ± 0.14</td>
</tr>
<tr>
<td>Plasma aldosterone decrement (%)</td>
<td>52.69 ± 15.0</td>
<td>58.5 ± 37.1</td>
<td>56.87 ± 31.6</td>
<td>37.31 ± 19.9</td>
</tr>
</tbody>
</table>

**Hypertonic saline infusion**

With the hypertonic saline infusion there were no significant differences between the four groups in the response of the urinary volume, base UOsm, final UOsm, UOsm increase, total urinary sodium excretion, osmolar clearance or in \(C_{H_2O}\) (Table 3).

Hypertonic saline infusion produced the expected increase in plasma osmolality in the four groups, although there were significant differences between them \((P<0.001, \text{ANOVA})\) (Fig. 3A). As with the water loading, plasma osmolality was significantly lower in the PRE group than in the CG group throughout the test \((P<0.05)\). The POST group maintained levels of plasma osmolality similar to those of the CG and higher than the PRE groups, significantly so in the base times and at 30 and 60 min \((P<0.05)\). In the SUB group, evolution of the plasma osmolality was similar to that of the PRE group, and significantly lower than the CG group at most points \((P<0.05)\). The peaks of plasma osmolality also differed significantly in the four groups \((P<0.002, \text{one-way ANOVA})\); it was lower in the PRE \((305.12 ± 5.0 \text{ mOsm/kg})\) and SUB groups \((306.46 ± 4.66 \text{ mOsm/kg})\), than in the CG group \((313.46 ± 6.69 \text{ mOsm/kg})\) \((P<0.05)\). There were no significant differences between the POST group \((310.37 ± 5.61 \text{ mOsm/kg})\) and the others. The base plasma osmolality showed a positive correlation with \(T_4\) \((r=0.49, P<0.001), FT_1\) \((r=0.54, P<0.001)\) and \(T_3\) \((r=0.45, P<0.001)\). The peak plasma osmolality showed a positive correlation with \(T_4\) \((r=0.49, P<0.001), FT_1\) \((r=0.52, P<0.001)\) and \(T_3\) \((r=0.42, P<0.003)\). The plasma osmolality increase showed no significant differences in the four groups \((PRE: 5.1 ± 1.5; SUB: 5.8 ± 1.2; CG: 5.9 ± 1.3; POST: 5.2 ± 1.3%)\). The saline infusion stimulated plasma AVP in all individuals, but there were significant differences between
Figure 3 (A) Plasma levels of osmolality (POsm), (B) AVP and (C) ANH throughout the hypertonic saline infusion. PRE (◇), SUB (☆), CG (▼) and POST (■). Values are means ± S.E.M. *P<0.05 compared with CG group; §P<0.05 compared with POST group.
the four groups ($P<0.001$, ANOVA) (Fig. 3B). The PRE group showed significantly lower plasma AVP levels than the CG group throughout the test. In the POST group, plasma AVP levels were similar to those of the CG and significantly higher than in the PRE group ($P<0.05$). Plasma AVP levels in the SUB group were similar to those of the PRE group, and lower than the CG group, significantly so at several points ($P<0.05$). Significant differences were also detected in the peak of plasma AVP reached, which was lower in the PRE (2.03 ± 0.93 pmol/l) than in the CG group (3.77 ± 1.46 pmol/l) ($P<0.014$, one-way ANOVA). The peak of plasma AVP in the SUB group (3.31 ± 1.82 pmol/l) and in the POST group (3.59 ± 1.17 pmol/l) did not show significant differences with regard to the others. Base plasma AVP showed a positive correlation with $T_4$ ($r=0.62$, $P<0.001$), $FT_4I$ ($r=0.49$, $P<0.001$) and $T_3$ ($r=0.55$, $P<0.001$). The peak of plasma AVP showed a positive correlation with $T_4$ ($r=0.50$, $P<0.001$), $FT_4I$ ($r=0.47$, $P<0.001$) and $T_3$ ($r=0.38$, $P<0.02$).

The saline infusion stimulated plasma ANH similarly in the four groups (Fig. 3C). There were no significant differences between the four groups in the base, final and decrease values of PRA and plasma aldosterone (Table 2). Base plasma aldosterone showed a significant correlation with $T_4$ ($r=0.44$, $P<0.001$) and $T_3$ ($r=0.49$, $P<0.001$).

In the individuals whose thirst was also tested, a regression study of plasma osmolality and plasma AVP showed that the osmotic threshold and the sensitivity of plasma AVP did not differ significantly between the groups (Table 4).

In all patients, the saline infusion stimulated the sensation of thirst, with a similar threshold in the four groups (Table 4). The sensitivity to thirst was different in each of the four groups ($P<0.041$, one-way ANOVA), although no group was found to be clearly different from the others.

A significant difference was found between the PRE group and the CG group ($P<0.017$, t-test).

Comparison of the thirst and AVP thresholds showed that in all four groups the secretion of plasma AVP began at lower plasma osmolality levels than the thirst sensation. The separation between the thresholds (Table 4) showed differences between the four groups ($P<0.0186$, one-way ANOVA). The only significant difference was between the SUB group and the CG group. When the PRE and CG groups were studied by t-test, the difference between thresholds was also significantly lower in the PRE group ($P<0.04$).

### Discussion

In our study, there were no significant differences in the four groups in terms of percentage of excreted water, and none of the patients fulfilled the criteria for inappropriate secretion of ADH after administration of oral water loading. However, $C_{142O}$ presented alterations in the PRE and SUB groups: quantitative (lower AUC) and qualitative (slower increase). This behavior was not due to an impairment in gastrointestinal water absorption, since plasma osmolality was low at the beginning of the test, and PRA and aldosterone were inhibited. These findings coincided with a lower plasma osmolality in these patients, which tended to normalize after replacement treatment. There was no complete loss of osmoregulation of AVP, since it was stimulated with the saline infusion and suppressed with the water loading. However, throughout both tests, plasma AVP was always significantly lower in the hypothyroid patients than in the control group. Base and stimulated plasma ANH concentrations showed no differences between the groups. In addition, our results suggested the integrity of the PRA–aldosterone axis.

The studies of plasma AVP in hypothyroid patients show a wide variety of results. Some authors have found high plasma AVP and postulate the role of this hormone in the development of hyponatremia of hypothyroidism (Skowysky & Kikuchi 1978, Lacci et al. 1987). Others have found that plasma AVP is normal or even suppressed (Iwaski et al. 1990, Vargas et al. 1991, Arnaout et al. 1992, Ota et al. 1994). Probably the discrepancies are due to the different characteristics of the individuals studied, principally the duration and severity of the hypothyroidism, which may cause an increase in plasma AVP by raising non-osmotic stimuli. These stimuli may be due to a fall in cardiac output and/or the blood volume, caused by the disease itself or by additional alterations (Skowysky & Kikuchi 1978). Our series was homogeneous in that we included only patients with recently diagnosed and untreated hypothyroidism, of mild or moderate severity, and in whom all drugs and clinical entities that might have influenced salt and water metabolism were ruled out.

Our results are in accordance with those of the authors who report plasma AVP to be normal or suppressed. The possibility that the alterations in water excretion and decreased plasma osmolality found in hypothyroid patients are due to an inappropriately high secretion of AVP seems improbable. Other possible explanations could be an increase in the sensitivity to AVP, although some experimental studies in rats suggest, in fact, that there is a resistance to its action (Seif et al. 1979, Kim et al. 1987). Another possibility is the action of other AVP-independent mechanisms at the level of the renal tubule, such as the decrease of urine flow at the distal tubule (DeRubertis et al. 1971, Emmanouel et al. 1974, Lacci et al. 1987) or both morphological (Davis et al. 1983) or functional (Michael et al. 1976, Garg & Tisher 1985, Kim et al. 1987) abnormalities of the distal tubule in hypothyroidism. It has been suggested that in some hyponatremia cases with characteristics of inappropriate secretion of ADH and with decreased AVP, there may be an increase in a non-filleted substance with an action similar to AVP (Robertson et al. 1982, Kern et al. 1986).

The levels of AVP are lower in hypothyroid patients in spite of a lower plasma volume.

In patients with hypothyroidism, plasma ANH concentrations have been reported to be low (Kohno et al. 1987, Zimmerman et al. 1987, Woolf & Moult 1988, Widecka et al. 1990, Barna et al. et al. 1994, Ota et al. 1994) or normal (Ladenson et al. 1987, Rolandi et al. 1992). After thyroid replacement these concentrations have increased in some reports (Kohno et al. 1987, Zimmerman et al. 1987, Woolf & Moult 1988, Rolandi et al. 1992, Bernstein et al. 1997) but not in others (Weissel et al. 1986, Ladenson et al. 1987). One of the possible explanations for these discrepancies may lie in the comparability of the groups, since in most studies the mean age of the hypothyroid patients is higher than that of the control group. In our study the age of the hypothyroid patients and that of the controls was totally comparable. The principal cause of the discrepancies may be differences in the severity of the hypothyroidism, with significant differences only in the patients with serious deficit, as suggested by Kohno et al. (1987).

The duration of the hypothyroidism could also influence the plasma ANH levels of these patients, although Widecka et al. (1990) found differences after only a short period of levothyroxine withdrawal. In our study, as in all those in which the hypothyroid patients have been diagnosed recently and have not received treatment, the real duration of the disease is unknown. Given the variability of the results in the different studies, as well as the overlap of the plasma levels in the groups, it seems unlikely that ANH plays an important role in water disorders in hypothyroidism.

We detected no abnormalities in the urinary excretion parameters in the patients with subclinical hypothyroidism, either in the oral water loading or in the saline infusion tests. However, we found lower plasma osmolality and AVP than in the control group, similar to that seen in patients with clinical primary hypothyroidism, especially in the saline infusion test, in which the levels of plasma osmolality and those of plasma AVP of the SUB group were very similar to those of PRE group, and significantly lower than the CG group. No abnormalities were found in plasma ANH, PRA or plasma aldosterone. The PV, ERPF and GFR in this group were normal (Villabona et al. 1999). To our knowledge, no other studies have been undertaken specifically to assess this aspect in subclinical hypothyroidism. In the study of Cooper et al. (1984) in 17 women with subclinical hypothyroidism, although the levels of water excretion after water loading were relatively low, there was no variation pre- and post-normalization of TSH with levothyroxine. Our results suggest that, in spite of the theoretical abnormality of the thyroid hormones, there are abnormalities in plasma sodium and AVP in subclinical hypothyroidism, similar to those detected in patients with primary hypothyroidism, as described in other systems (Surks & Ocampo 1996). The real clinical implication remains unclear, and more accurate studies in these subjects are required, analysing their basal situation as well as their response to the replacement treatment.

As regards thirst, in our study no differences were detected in the thirst thresholds of the groups (Table 4). The PRE slope indicated a lower sensitivity than the CG. One interesting point is the difference between the thresholds of AVP secretion and of thirst. In our control group, the threshold of plasma AVP (279.4 ± 11.0 mOsm/kg) was lower than the thirst threshold (292.7 ± 4.5 mOsm/kg), with an average difference of

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At 13.3 ± 9.2 mOsm/kg. This coincides with some authors, like Robertson et al. (1982), who also find a thirst threshold higher than the AVP threshold and with a similar difference. However, other authors (Thompson et al. 1986) report that the thresholds are similar. The difference between the osmotic thresholds of AVP and thirst varied significantly in all four groups. It was significantly lower in the PRE and the SUB groups than in the CG. Thus, the thresholds seem to be closer than normal in the PRE group. This smaller difference between thresholds already appears in subclinical hypothyroidism and disappears after replacement treatment. Only a few studies have evaluated thirst in hypothyroidism. In a review, Fitzsimons (1972) describes the increase in water intake in rats with antithyroid treatment, although the author doubts whether it can be considered a direct effect of the thirst mechanism or an effect of the increase in atrial natriuretic peptide (ANP) responsiveness in patients with hypothyroidism. Atrial natriuretic peptide (ANP) responsiveness in patients with euthyroidism, and hypothyroidism: studies in man and rat. J Clin Endocrin Metab 51: 148–152.

In summary, primary thyroid hypofunction is accompanied by impairment in water excretion and a tendency towards plasma hypo-osmolality, even in early phases such as subclinical hypothyroidism. These disturbances could be due to a direct action of the decrease of the thyroid hormones on the renal dilution mechanisms, since hemodynamic factors do not seem to be determinant, nor is there an increase in plasma AVP. The narrowing of the gap between plasma AVP and thirst osmotic thresholds could contribute to these disturbances. With this trend towards plasma hypo-osmolality, it is conceivable that hyponatremia may appear, due to excessive water administration, or to an increase in plasma AVP secondary to a substantial decrease in the effective volemia or of the cardiac output. Plasma ANH and the renin–aldosterone axis do not appear to play a determinant role in the water and sodium disturbances in this disease.

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References


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