The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/70604

Please be advised that this information was generated on 2017-07-12 and may be subject to change.
Thyroid function in patients with proteinuria


Departments of 1Nephrology, 2Endocrinology, 3Epidemiology and Biostatistics, and 4Chemical Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-361 40 48, fax: +31(0)24-361 89 42, e-mail: r.gilles@nucmed.umn.nl

ABSTRACT

Background: Patients with proteinuria may suffer from substantial losses of functional proteins such as hormones and hormone-binding proteins. A limited number of studies have reported urinary losses of thyroid hormones and thyroxin-binding globulin. Overt hypothyroidism attributable to these urinary losses has been described. However, the impact of proteinuria on thyroid function parameters has not been studied in a large patient cohort.

Methods: We evaluated thyroid function parameters in patients with proteinuria who are negative to thyroxine peroxidase antibodies (TPOAbs). Values of free thyroxin and thyroid-stimulating hormone (TSH) were compared with data from age- and gender-matched controls derived from the Nijmegen Biomedical Study, a population-based survey conducted in our hospital.

Results: We evaluated 159 patients. There were 111 males and 48 females. Median (IQR) age was 52 (40 to 62) years, serum creatinine concentration 99 (82 to 134) µmol/l, serum albumin concentration 29 (22 to 35) g/l, and proteinuria 6.6 (3.1 to 10.9) g/10 mmol creatinine. Median TSH was significantly higher in the patients than the controls (1.81 mU/l vs 1.34 mU/l, p<0.0001). In the patients, TSH was negatively correlated with serum albumin (r=-0.21; p<0.01). Subclinical hypothyroidism was six times more frequent in the patients (11.3 vs 1.8%, p<0.001); however, overt hypothyroidism was observed in only one patient.

Conclusion: Patients with proteinuria have higher TSH levels, consistent with urinary loss of thyroid hormones. However, these urinary losses do not result in overt, clinically relevant, hypothyroidism. The role of subclinical hypothyroidism in these patients needs further evaluation.

KEYWORDS
Hypothyroidism, proteinuria, thyroid hormones

INTRODUCTION

Proteinuria is a hallmark of renal diseases. Severe proteinuria results in the nephrotic syndrome, which is characterised by proteinuria, hypoalbuminaemia, oedema and hyperlipidaemia. Albumin is the most abundant protein in serum and urine. In patients with a nephrotic syndrome urinary losses of albumin are not fully compensated by the increased hepatic production, with hypoalbuminaemia as a consequence. In patients with proteinuria many other proteins beside albumin are lost in the urine. Among these are hormones and hormone-binding proteins. Several studies have documented urinary loss of thyroid hormones and thyroxin-binding globulin (TBG) in patients with proteinuria.1-4 The clinical relevance of this is unknown. The abovementioned studies included a limited number of patients (in total 49 patients in four studies). In one study overt hypothyroidism was noted in two patients that resolved after remission of the nephrotic syndrome.3

In patients with the nephrotic syndrome, loss of thyroid hormones may lead to low free thyroid hormone levels unless production is increased under the influence of thyroid-stimulating hormone (TSH). Furthermore, loss of albumin and TBG may reduce the binding capacity for thyroid hormones, resulting in a decrease in total triiodothyronine (T3) and thyroxin (T4) concentrations.

Thus far no study has systematically evaluated thyroid hormone status in patients with proteinuria. We have analysed thyroid function in a large cohort of patients with proteinuria. We have compared data obtained in the Nijmegen Biomedical Study, a population-based study in our hospital.

SUBJECTS AND METHODS

In our centre patients with proteinuria are evaluated using a standard protocol.6 In brief, patients are seen after an overnight fast. Blood pressure and bodyweight are measured and serum and urine samples are collected.
for measurement of creatinine and albumin. In addition aliquots of serum are stored at -70°C.

For the current study we thawed frozen samples obtained from 200 consecutive patients studied in the period 2001-2004.

**Laboratory methods**

In the serum of the patients, TSH, T4, free thyroxin (FT4), T3 and thyroxine peroxidase antibodies (TPOAbs) were measured. TSH, FT4 and TPOAbs were measured as described. For the measurement of FT4 an incubation buffer was used without a physiological concentration of chloride. Since chloride primarily affects T4 binding to albumin, a slight artefact (a decrease of 10 g/l in serum albumin causes apparent increase of FT4 by about 0.5 pmol/l) results that is normally negligible, but must be taken into account with moderate to severe hypoalbuminaemia. To correct for this in vitro artefact we used the following formula: corrected FT4 = FT4 ÷ (serum albumin - 46). Total T4 and T3 were measured by means of a Luminometric immunoassay performed on an Architect immunoanalysers (Abbott Diagnostics, Amstelveen, the Netherlands). Within- and between-assy CVs were: for T4 3.8 and 6.5% at a level of 46 nmol/l, 3.6 and 5.1% at 108 nmol/l and 4.2 and 10.8 at 194 nmol/l respectively; for T3 3.5 and 5.4% at 1.05 nmol/l, 2.8 and 4.3% at 1.68 nmol/l and 2.5 and 3.3% at 6.0 nmol/l. The reference range for T4 is 15 to 155 nmol/l and for T3 1.2 to 2.9 nmol/l. For TPOAbs we used a cut-off value of <12 kU/l to define TPOAbs-negative patients as described. Serum and urine creatinine, and albumin, were measured by standard techniques.

**Table 1. Baseline characteristics and thyroid hormone status of patients and controls**

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Proteinuria vs control</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 (40-64) 111/48</td>
<td>52 (40-64) 642/258</td>
</tr>
<tr>
<td>Sex (male/ female)</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>29 (22-35) 99 (82-134)</td>
<td>45 (44-48) 83 (76-92)</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>1.81 (1.04-2.81) 5.7 (4.2-7.8)</td>
<td>p&lt;0.0001 1.34 (0.98-1.87) 5.1 (4.3-6.1)</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>13.1 (11.4-14.8) 7.8 (4.2-7.8)</td>
<td>p&lt;0.01 13.1 (11.9-14.5) 5.1 (4.3-6.1)</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>111/48</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Anti-TPO (mU/l)</td>
<td>0 (0%) 1 (0.6%) 18 (11.3%) 6 (3.8%)</td>
<td>2 (0.2%) 0 (0%) 16 (1.8%) 5 (0.6%)</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>133 (83.6%)</td>
<td>877 (97.4%)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>1 (0.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>3 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>18 (11.3%)</td>
<td>16 (1.8%)</td>
</tr>
<tr>
<td>Hypothyroidism Unundefined</td>
<td>6 (3.8%)</td>
<td>5 (0.6%)</td>
</tr>
</tbody>
</table>

Data are for TPOAbs-negative subjects. Values are given as median (IQR). Hypothyroidism was classified as overt if TSH was <0.1 mU/l and FT4 >2.5 pmol/l and as subclinical if TSH was <0.1 mU/l and FT4 2.5-4.2 pmol/l. Hyperthyroidism was classified as overt if TSH was >4 mU/l and FT4 >4.4 pmol/l and as subclinical if TSH was >2.4 mU/l and FT4 2.3-3.8 pmol/l. Definitions according to Hoogendoorn et al.

Gilles, et al. Thyroid function in patients with proteinuria.
control population of the Nijmegen Biomedical Study. For comparison, normal values as used in our laboratory are 55 to 155 nmol/l for total T4 and 1.2 to 2.9 nmol/l for total T3. Subclinical hypothyroidism was six times more frequent in the patients than in the controls (table 1). Of note, overt hypothyroidism was observed in only one patient. In the patients TSH was negatively correlated with serum albumin (r=-0.21; p<0.001; figure 1). TSH was not correlated with eGFR (r=0.05). Total T4 correlated with eGFR (r=0.16, p<0.05), not with serum albumin concentration (r=0.125). FT4 did not correlate with eGFR (r=-0.09). We observed significant correlations between T3 and eGFR (r=0.26; p<0.01) and T3 and serum albumin (r=0.36; p<0.001).

**DISCUSSION**

Our study demonstrates that abnormalities in thyroid function occur in patients with proteinuria. Specifically, TSH levels were higher in patients with proteinuric renal diseases when compared with age- and sex-matched controls. These data are consistent with the reports of urinary losses of thyroid hormones in patients with proteinuria. Apparently, these urinary losses of thyroid hormones in patients with proteinuria result in a stimulation of TSH production. The role of proteinuria is confirmed by the significant and negative correlation between TSH and serum albumin.

Although one study described the development of overt hypothyroidism in patients with a nephrotic syndrome, the prevalence of this complication has remained unclear. Our patients and we observed overt hypothyroidism in only one patient. In view of the well-known relation between TPOAbs and hypothyroidism, we excluded TPOAbs-positive patients and controls from the final data analysis. However, even when considering all patients, overt hypothyroidism was observed in only one patient. The prevalence of TPOAbs positivity was similar in patients and controls. There is one caveat. Since TPOAbs could have been lost in the urine, the usual criteria for discerning between TPOAbs-positive and -negative persons might not fully apply to patients with proteinuria. Of note, there was no correlation between TPOAbs titre and serum albumin.

**CONCLUSION**

Our study shows that TSH is elevated in patients with proteinuria. However, the clinical relevance of this finding is limited since overt hypothyroidism was present in less than 1% of the patients.

**REFERENCES**