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Thyroid function in patients with proteinuria

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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) $\mu\text{mol/l}$, serum albumin concentration 29 (22 to 35) g/l , and proteinuria 6.6 (3.1 to 10.9) $\text{g/10 mmol creatinine}$. 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.

For comparison we have used data obtained in the Nijmegen Biomedical Study, a population-based study in our hospital.⁵

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.⁵ 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 + (0.0542 x (serum albumin - 46)). Total T₄ and T₃ were measured by means of a Luminometric immunoassay performed on an Architect immunoanalyser (Abbott Diagnostics, Amstelveen, the Netherlands). Within- and between-assay 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 55 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.⁵ Serum and urine creatinine, and albumin, were measured by standard techniques.⁶

Data analysis

Data of the patients were compared with data from an age- and sex-matched control group derived from the Nijmegen Biomedical Study. The Nijmegen Biomedical Study (NBS) is a population-based survey conducted by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the Radboud University Nijmegen Medical Centre. A total of 21,757 age and sex stratified randomly selected inhabitants of the municipality of Nijmegen received an invitation to fill out a postal questionnaire on lifestyle and medical history, and to donate an 8.5 ml blood sample in a serum separator tube and a 10 ml ethylenediaminetetraacetic acid (EDTA) blood sample. The response to the questionnaire was 43% (n=9371). Of the responders, 69% (n=6473) donated blood samples.³ In these blood samples FT₄ and TSH were measured.

For the present study matched controls were selected from the NBS database, in a ratio of one (patient) to five (controls) using age and gender as matching criterion.

Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease (MDRD) formula.⁷ We used the original formula $eGFR(\text{ml}/\text{min}/1.73 \text{ m}^2) = 170 \times$

$(\text{serum creatinine} \times 0.0113)^{-0.999} \times (\text{age})^{-0.176} \times (\text{serum urea} \times 2.8)^{-0.170} \times (\text{serum albumin}/10)^{+0.318} \times 0.762$ (if female) $\times 1.18$ (if black), where serum creatinine in $\mu\text{mol}/\text{l}$, serum urea in mmol/l and serum albumin in g/l .

Statistical analysis was performed using the Mann-Whitney U test for comparison between patients and controls. Pearson's correlation coefficient was used as a parameter for correlation between thyroid parameters and serum albumin concentration or eGFR. For TSH log transformed values were used because of the skewed distribution. P values <0.05 were considered statistically significant.

RESULTS

We studied 200 patients with a renal disease and proteinuria. For comparison we selected 1000 age- and gender-matched controls. Sera of 41 patients and 100 controls were positive for TPOAbs. In view of the well-known relationship between positive anti-TPOAbs and hypothyroidism, we have limited the analysis to TPOAbs-negative patients and controls. Clinical characteristics are presented in table 1. Proteinuria values in our patients were 6.6 (3.1-10.9) g/10 mmol creatinine. Overall TSH was significantly higher in the patients. There were no differences in FT₄ values. In the patients total T₄ concentration was 90 (IQR 78-103) nmol/l and total T₃ concentration 1.99 (IQR 1.72-2.27) nmol/l. These parameters were not measured in our matched

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

	Proteinuria	Proteinuria vs control	Control
Age (years)	52 (40-64)		52 (40-64)
Sex (male/female)	111/48		642/258
Albumin (g/l)	29 (22-35)	p<0.0001	46 (44-48)
Creatinine ($\mu\text{mol}/\text{l}$)	99 (82-134)	p<0.0001	83 (76-92)
TSH (mU/l)	1.81 (1.04-2.81)	p<0.0001	1.34 (0.98-1.87)
FT ₄ (pmol/l)	13.1 (11.4-14.8)		13.1 (11.9-14.5)
Anti-TPO (mU/l)	5.7 (4.2-7.8)	p<0.01	5.1 (4.3-6.1)
Overt hyperthyroidism	0 (0%)		2 (0.2%)
Subclinical hyperthyroidism	1 (0.6%)		0 (0%)
Euthyroid	133 (83.6%)		877 (97.4%)
Overt hypothyroidism	1 (0.6%)		0 (0%)
Subclinical hypothyroidism	18 (11.3%)	p<0.001	16 (1.8%)
Undefined	6 (3.8%)		5 (0.6%)

Data are for TPOAbs-negative subjects. Values are given as median (IQR). Hyperthyroidism was classified as overt if TSH was <0.1 mU/l and FT₄ >22 pmol/l and as subclinical if TSH was <0.1 mU/l and FT₄ ≤22 pmol/l. Hypothyroidism was classified as overt if TSH was >4 mU/l and FT₄ <8.0 pmol/l and as subclinical if TSH was >4 mU/l and FT₄ ≥8 pmol/l. Definitions according to Hoogendoorn *et al.*⁵

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.^{1,4} 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.³ Subclinical hypothyroidism occurred more frequently in our patients and we observed overt hypothyroidism in only one of 159 patients. Figure 1 clearly illustrates that even in patients with the most severe nephrotic syndrome, TSH levels did not often exceed 4 mU/l.

We noted a correlation between total T₄ and T₃ and eGFR. In a recent study Lo *et al.* evaluated thyroid function in relation to renal insufficiency.⁸ These authors noted an increased prevalence of hypothyroidism, as defined by increased TSH levels, in patients with decreased GFR. Unfortunately, FT₄ and proteinuria were not measured by Lo and colleagues. Our data suggest that both proteinuria and GFR influence the activity of the pituitary-thyroid axis. Proteinuria results in loss of thyroid hormones, most probably caused by loss of thyroxin-binding globulin, thus stimulating TSH production.

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.

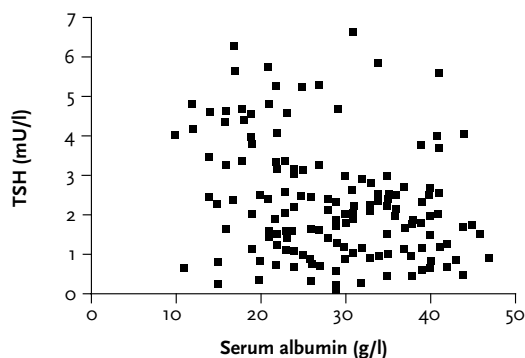
CONCLUSION

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.

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Figure 1. Correlation of thyroid-stimulating hormone and serum albumin concentration in patients with proteinuria



Only patients without anti-TPO antibodies were included in this analysis ($r=-0.21$; $p=0.01$).