Pediatr Nephrol (1994) 8: 412–415

Pediatric Nephrology

Original article

Thyroid function in children with nephrotic syndrome

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Received December 3, 1993; received in revised form March 9, 1994; accepted March 10, 1994

Abstract. The thyroid function of seven children with untreated nephrotic syndrome who had a normal serum creatinine concentration was compared with that of the same patients in remission and age-matched controls. There was a significant decrease in serum thyroxine (T_4), tri-iodothyronine (T_3) and thyroid-binding globulin (TBG) concentrations in untreated nephrotic children compared with the same patients in remission and age-matched controls. Most values for serum free T_4, free T_3 and thyroid-stimulating hormone (TSH) in the patients with nephrosis were within the normal range. However, the mean serum free T_4 and free T_3 concentrations were significantly ($P < 0.05$) lower in the untreated patients than in the same patients in remission, and the mean serum TSH concentrations were significantly ($P < 0.05$) higher in the untreated patients than in the same patients in remission. There were massive urinary losses of T_4, T_3, TBG, free T_4 and free T_3 in the untreated nephrotic children compared with the same patients in remission and age-matched controls. The daily urinary protein excretion showed a positive correlation with the urinary T_4, T_3, free T_4, free T_3 and TBG excretion. Furthermore, the urinary protein excretion showed a negative correlation with the serum T_4, T_3, free T_4, free T_3 and TBG levels. There was a negative correlation between serum albumin and serum TSH. These findings provide evidence of mild hypothyroidism in children with untreated nephrotic syndrome, partly because of losses of T_4, T_3, free T_4, free T_3 and TBG into the urine.

Key words: Thyroid function – Nephrotic syndrome – Free thyroxine – Free tri-iodothyronine – Urinary thyroid hormones

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Introduction

Serum thyroid-binding globulin (TBG), thyroxine (T_4), tri-iodothyronine (T_3) and thyroid-stimulating hormone (TSH) are usually normal in adults with nephrotic syndrome, despite urinary losses of TBG, T_4 and T_3, and these patients are considered euthyroid [1–3]. However, in children with nephrotic syndrome [4–6] low serum TBG and T_4 concentrations and high serum TSH concentrations were found, because of greater losses of TBG and T_4 in children than in adults. Furthermore, McLean et al. [7] and Warady et al. [8] recommended that thyroid hormone replacement therapy be provided to infants with congenital nephrotic syndrome and evidence of hypothyroidism. Recently, we reported that replacement therapy using desiccated thyroid in a nephrotic boy who showed hypothyroidism and did not respond to glucocorticoids resulted in prompt disappearance of proteinuria in addition to normalization of thyroid function [9].

In this study, we examined whether thyroid function was impaired in children with untreated nephrotic syndrome compared with the same patients in remission and age-matched controls, by measuring serum or urine concentrations of various thyroid hormones, especially free T_4 and free T_3, by a new radioimmunoassay (RIA).

Patients and methods

Patients with nephrotic syndrome hospitalized at the First Department of Paediatrics, Dokkyo University School of Medicine Hospital between June 1990 and December 1992 were included in the study, provided they satisfied the following criteria: (1) oedema; (2) urinary protein excretion greater than 3.5 g/day per 1.73 m^2; (3) serum albumin levels lower than 2.5 g/dl; (4) normal glomerular filtration rate, as defined by a serum creatinine levels lower than 1.0 mg/dl; (5) otherwise healthy with no clinical evidence of other acute or chronic non-thyroidal illness, diabetes mellitus, hypothalamic, pituitary or thyroid disease; (6) not receiving thyroid hormone therapy or any other drugs known to affect thyroid hormone indices, such as glucocorticoids [10], salicylate [11] or heparin [12].

Table 1. Details and routine biochemistry of seven children with nephrotic syndrome in nephrosis (N) and in remission (R)

Patient no.	Age (years)	Sex	Urinary protein (g/24 h per 1.73 m²)		Serum total protein (g/dl)		Serum albumin (g/dl)		Serum total cholesterol (mg/dl)		Serum creatinine (mg/dl)	
			N	R	N	R	N	R	N	R	N	R
1	2	M	20.7	0	3.7	6.5	0.9	4.1	398	178	0.3	0.3
2	7	F	14.1	0	4.3	6.7	1.3	4.2	307	117	0.4	0.5
3	3	F	13.2	0	4.3	6.7	1.4	4.4	322	194	0.4	0.4
4	2	M	10.2	0	5.0	6.4	2.2	4.0	268	180	0.3	0.3
5	8	F	9.9	0	4.3	7.3	1.9	4.0	327	177	0.7	0.7
6	7	M	7.8	0	5.2	6.5	2.2	4.2	382	195	0.5	0.4
7	9	F	6.1	0	5.5	7.2	2.9	4.3	266	136	0.7	0.6
Mean	5.4		11.7*	0	4.6*	6.8	1.8*	4.2	324*	168	0.5	0.5
±SD	3.0		4.8	0	0.6	0.4	0.7	0.1	51	30	0.2	0.2
Controls												
Mean	5.6		0		7.0		4.1		152		0.4	
±SD	2.0		0		0.3		0.2		30		0.2	
P value	NS		<0.01	NS	<0.01	NS	<0.01	NS	<0.01	NS	NS	NS

* $P < 0.05$ nephrosis vs. remission

There were seven patients with steroid-responsive idiopathic nephrotic syndrome (4 girls, 3 boys, mean age 5.4±3.0 years, range 2–9 years). Renal biopsy was performed in two of these who showed minimal change lessions. The serum creatinine was between 0.3 and 0.7 (0.5±0.2) mg/dl and the urinary excretion of protein between 6.1 and 20.7 (11.7±4.8) g/day per 1.73 m² (Table 1). The age- and gender-matched control group consisted of nine children without thyroid dysfunction and nephrotic syndrome (5 girls, 4 boys) hospitalized between June 1990 and December 1992 (mean age 5.6±2.0 years); five had microhaematuria, two bronchitis and two tonsillitis. The urinary protein concentration was measured by the sulphosalicylic acid method. Serum total protein, total cholesterol and creatinine were measured with an autoanalyser (Hitachi 710, Tokyo, Japan). Serum albumin was measured by cellulose acetate electrophoresis. Table 1 shows further details of the patients and controls.

T_4, T_3, free T_4, free T_3 and TBG concentrations in serum and urine and the serum TSH concentration were measured in children with untreated nephrotic syndrome, the same patients in complete remission 1 month after cessation of various treatments and age-matched controls. Serum and urine T_4 concentrations were measured by a fluorescence polarization immunoassay (Abott Laboratories, Ill., USA). Serum and urine T_3 concentrations were measured by RIA (Dainabot, Tokyo, Japan). Serum and urine free T_4 concentrations were measured with a new two-step RIA (Ria-gnost, Behring, Marburg, Germany). The results of two-step free T_4 RIAs, such as Ria-gnost, are the least associated with serum concentrations of albumin or TBG [13, 14]. Serum and urine free T_3 concentrations were measured by a new one-step RIA (Ria-gnost, Behring). Results obtained with the Ria-gnost free T_3 kit agree more closely with equilibrium dialysis results than those obtained with the Amerlex-M kit, which is influenced by albumin or TBG [14, 15]. The serum TSH concentration was measured by enzyme immunoassay (Dainabot, Tokyo, Japan). Serum and urine TBG concentrations were measured by RIA (Eiken, Tokyo, Japan).

Results are expressed as mean and standard deviation. The Wilcoxon test was used for statistical analysis of paired data from the same patients with untreated nephrotic syndrome and in complete remission. The Mann-Whitney test was used for statistical analysis of unpaired data from patients with nephrotic syndrome and controls. A *P* value of less than 0.05 was considered significant.

Results

Table 2 shows the serum concentrations of various indicators of thyroid function. There was a significant decrease in the mean serum T_4, T_3 and TBG concentrations in untreated nephrotic children compared with the same patients in remission and age-matched controls. Serum free T_4 was below two standard deviations of the mean of the controls in one of the seven patients, but the mean value of serum free T_4 in nephrosis was significantly ($P < 0.05$) lower than in the same patient in remission. Serum free T_3 was below two standard deviations of the mean of the controls in one of the seven patients, but the mean value of serum free T_3 in nephrosis was significantly lower than in the patients in remission or in controls. The mean serum TSH concentration in the patients with nephrosis was significantly higher than in the patients in remission or in the age-matched controls.

Table 3 shows the urinary concentrations of thyroid hormones and TBG. There were massive urinary losses of T_4, T_3, free T_4, free T_3 and TBG in untreated nephrotic children. The mean urinary T_4, T_3, free T_4, free T_3 and TBG concentrations in the patients with nephrosis were significantly higher than in patients in remission or the controls. The daily urinary protein excretion showed a significant positive correlation with the urinary excretion of T_4 ($r = 0.87$, $P < 0.01$), T_3 ($r = 0.96$, $P < 0.01$), free T_4 ($r = 0.86$, $P < 0.01$), free T_3 ($r = 0.78$, $P < 0.05$) and TBG ($r = 0.77$, $P < 0.05$).

The daily urinary protein excretion showed a significant negative correlation with the serum T_4 ($r = -0.86$, $P < 0.01$), T_3 ($r = -0.97$, $P < 0.01$), free T_4 ($r = -0.91$, $P < 0.01$), free T_3 ($r = -0.94$, $P < 0.01$) and TBG ($r = -0.93$, $P < 0.01$). The patient with the lowest values of serum free T_4 and free T_3 was also the patient with the greatest protein excretion. Serum albumin showed a significant negative correlation with the urinary excretion of T_4 ($r = -0.93$, $P < 0.01$), T_3 ($r = -0.88$, $P < 0.01$), free T_4 ($r = -0.78$, $P < 0.05$), free T_3 ($r = -0.82$, $P < 0.01$) and TBG ($r = -0.88$, $P < 0.01$), and serum TSH ($r = -0.70$, $P < 0.05$). Serum albumin showed a significant positive correlation with serum T_4 ($r = 0.86$, $P < 0.01$), T_3 ($r = 0.95$, $P < 0.01$), free T_4 ($r = 0.84$, $P < 0.01$), free T_3 ($r = 0.92$, $P < 0.01$) and TBG ($r = 0.86$, $P < 0.01$).

The serum concentrations of T_4, T_3, free T_4 and free T_3 showed significant ($P < 0.05$) negative correlations with

Table 2. Serum concentrations of thyroid hormones in seven children with nephrotic syndrome in nephrosis and in remission

Patient no.	T_4 (μg/dl)		Free T_4 (ng/dl)		T_3 (ng/ml)		Free T_3 (pg/ml)		TSH (μIU/ml)		TBG (μg/ml)	
	N	R	N	R	N	R	N	R	N	R	N	R
1	3.2	7.3	0.65	1.48	0.2	1.1	2.1	3.6	2.4	0.9	9.0	18.0
2	5.6	7.3	0.95	1.50	0.7	1.8	2.5	3.3	1.6	0.8	14.0	21.0
3	4.4	6.7	1.08	1.17	0.7	1.3	2.8	3.2	2.6	0.8	16.0	19.0
4	4.2	7.8	0.90	1.22	0.7	1.7	2.6	4.3	2.0	0.9	13.0	21.0
5	6.3	8.7	1.00	1.29	0.8	1.5	2.7	4.1	2.8	1.4	17.0	22.0
6	4.4	6.4	1.20	1.60	0.8	1.1	2.8	3.1	1.7	0.7	16.0	23.0
7	6.5	6.5	1.10	1.22	1.2	1.4	3.3	4.3	2.5	0.5	17.0	20.0
Mean	4.9*	7.2	0.98*	1.35	0.7*	1.4	2.7*	3.7	2.2*	0.9	14.6*	20.6
±SD	1.2	0.8	0.18	0.17	0.3	0.3	0.4	0.5	0.5	0.3	3.0	1.7
Controls												
Mean	8.6		1.21		1.4		3.3		0.6		22.1	
±SD	1.2		0.25		0.2		0.4		0.2		3.5	
P	<0.01	NS	NS	NS	<0.01	NS	<0.01	NS	<0.01	NS	<0.01	NS

T_4, Thyroxine; T_3, tri-iodothyronine; TSH, thyroid-stimulating hormone; TBG, thyroid-binding globulin; * $P < 0.05$ nephrosis vs. remission

Table 3. Urinary concentrations of thyroid hormones in seven children with nephrotic syndrome in nephrosis and in remission

Patient no.	T_4 (μg/24 h per 1.73 m²)		Free T_4 (ng/24 h per 1.73 m²)		T_3 (μg/24 h per 1.73 m²)		Free T_3 (ng/24 h per 1.73 m²)		TBG (mg/24 h per 1.73 m²)	
	N	R	N	R	N	R	N	R	N	R
1	28.0	1.9	69.4	8.4	6.30	0.80	27.9	11.4	6.2	0
2	33.2	1.7	56.3	5.5	4.33	0.71	35.8	8.5	6.4	0
3	27.3	2.1	17.9	6.7	3.33	0.67	17.0	10.5	7.6	0
4	9.5	1.3	39.6	10.4	2.12	0.69	22.0	9.1	6.0	0
5	18.1	0.8	19.5	12.0	2.23	1.10	27.2	13.5	9.0	0
6	21.2	1.7	30.4	4.6	2.22	0.39	22.5	9.3	5.9	0
7	8.8	1.5	16.3	7.1	1.39	0.69	14.4	10.6	1.7	0
Mean	20.9*	1.6	35.6*	7.8	3.13*	0.72	23.8*	10.4	6.1*	0
±SD	9.4	0.4	20.7	2.6	1.69	0.21	7.2	1.7	2.2	0
Controls										
Mean	1.4		6.5		0.62		9.6		0	
±SD	0.5		3.0		0.30		2.1		0	
P value	<0.01	NS	<0.01	NS	<0.01	NS	<0.01	NS	<0.01	NS

* $P < 0.05$ nephrosis vs. remission

the urinary concentrations of T_4 ($r = -0.71$), T_3 ($r = -0.91$), free T_4 ($r = -0.84$) and free T_3 ($r = -0.84$), respectively.

Discussion

Serum TBG, T_4, free T_4 and TSH concentrations remain normal in adults with nephrotic syndrome despite urinary losses of TBG and T_4, and these patients are considered euthyroid [1–3, 16]. However, in children with nephrotic syndrome [4–6, 9], low serum TBG, T_4 and free T_4 concentrations and a high serum TSH concentration were demonstrated, because of the extraordinarily high urinary losses of TBG and T_4. This difference could be explained by the fact that urinary protein loss in adults with nephrotic syndrome, expressed relative to weight, is usually considerably less than in children. For example, assuming an average weight of 60 kg for adults in the previous study [3], protein loss was up to 118 mg/kg per day, which was less than the 295–865 mg/kg per day range noted in patients with congenital nephrotic syndrome [7]. Careful examination of each adult with nephrotic syndrome revealed that adult patients with extremely high urinary losses of protein had low serum TBG, T_4 and free T_4 concentrations and a high serum TSH concentration [1]. In our study, serum TBG and T_4 concentrations were low, serum free T_4 values were in the low normal range and serum TSH values were in the high normal range. The urinary protein values in our patients were higher than in adults with nephrotic syndrome [1–3, 16], but lower than in patients with the congenital nephrotic syndrome [9].

In adults with nephrotic syndrome, a significant positive correlation between the degree of proteinuria and urinary T_4 or T_3 and a significant negative correlation between the degree of proteinuria and serum T_4, T_3 or TBG have been reported [2]. We measured the free T_4 and free T_3 concentrations in the urine and serum simultaneously. This is the first report of the measurement of urinary concentra-

tions of free T_4 and free T_3 in nephrosis employing the new RIA. Proteinuria showed a significant positive correlation with urinary free T_4 and free T_3 concentrations and urinary T_4, T_3 and TBG concentrations, a significant negative correlation with serum free T_4 and free T_3 concentrations and serum T_4, T_3 and TBG concentrations. These findings suggest that hypothyroidism in severe nephrosis is caused partly by marked losses of T_4, T_3, free T_4 and free T_3 into the urine.

Fonseca et al. [17] recently reported that the mean serum free T_3 concentration measured by the Amerlex kit in adults with nephrotic syndrome with detectable urinary T_4 was significantly lower than in patients with undetectable urinary T_4. However, when using the Amerlex kit, the serum free T_3 concentration is influenced by albumin, which is markedly decreased in patients with low albumin [14, 15, 18]. Therefore, the Amerlex free T_3 kit cannot be expected to produce valid results when the concentration of albumin in the serum is abnormally low, as in the nephrotic syndrome. DeLuca et al. [4] reported that serum free T_3 concentrations measured by RIAs after column adsorption chromatography of the sera were normal in all children with nephrotic syndrome. Our data showed that the serum free T_3 concentration in untreated nephrotic children was within the normal range, except in one patient, but the mean value was significantly lower than in these patients in remission or in controls. We measured free T_3 using the Ria-gnost kit, which is influenced very little by albumin or TBG [14, 15].

Recently, McLean et al. [7] and Warady et al. [8] provided thyroid hormone replacement therapy for infants with congenital nephrotic syndrome with severe prolonged proteinuria and evidence of hypothyroidism. We also provided replacement therapy using desiccated thyroid for a nephrotic boy with severe proteinuria between 14.9 and 30.4 g/day per 1.73 m^2 (from 377 to 840 mg/kg per day) for 3 weeks due to resistance to glucocorticoid therapy and evidence of hypothyroidism. His proteinuria disappeared promptly and his thyroid function normalized [9]. Furthermore, animal experiments have revealed that glucocorticoid receptors are reduced in the hypothyroid state [19] and T_4 increases the glucocorticoid binding capacity [20]. Therefore, we recommend that serum thyroid hormone concentrations be measured in children with nephrotic syndrome and severe proteinuria persisting for more than 3 weeks despite glucocorticoid therapy, and that thyroid hormone replacement therapy, in addition to glucocorticoids, be provided to children with nephrotic syndrome and evidence of moderate or severe hypothyroidism.

In summary, this study provides evidence of mild hypothyroidism even in children with nephrotic syndrome who have moderate proteinuria, partly because of losses of T_4, T_3, free T_4, free T_3 and TBG into the urine.

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