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FREE THYROXINE AND TRIIODOTHYRONINE ARE ASSOCIATED WITH RENAL FUNCTION IN NORMOALBUMINURIC EUTHYROID TYPE 1 DIABETIC PATIENTS

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SUMMARY – Both hypothyroidism and hyperthyroidism affect renal function. The aim of this study was to investigate the relationship between parameters of thyroid function (TSH, free triiodothyronine (FT3), and free thyroxine (FT4)) and parameters of renal function in patients with type 1 diabetes (T1DM). The study included 272 T1DM with normoalbuminuria and estimated glomerular filtration rate (eGFR) > 60 ml/min^{-1}1.73m^{-2}, normal thyroid function, and without antihypertensive and antihyperlipidemic therapy. TSH significantly correlated with urinary albumin excretion rate (UAE) ($r=-0.15$, $p<0.05$) and fT3 with serum creatinine ($r=0.12$, $p<0.05$). Furthermore, fT4 significantly correlated with all renal function parameters (serum creatinine, eGFR and UAE ($r=-0.12$, 0.34 and -0.13, respectively, for all $p<0.05$)). Patients in the highest quartile of fT4 had significantly higher eGFR levels compared to those in the lowest quartile (116 vs. 101 ml/min^{-1}1.73m^{-2}, $p<0.001$). In logistic regression analysis, after adjustment for covariates, fT3 and fT4 were significantly associated with worsening of renal function parameters with odds ratios of 0.75 to 1.29. This study, conducted in euthyroid T1DM with normoalbuminuria and eGFR > 60 ml/min^{-1}1.73m^{-2} without therapeutic intervention, suggests that the thyroid function may be connected with renal function parameters even in the euthyroid range.

Key words: *thyroid hormones, type 1 diabetes, renal function, albuminuria*

Introduction

Thyroid hormones play an important role in the metabolism of carbohydrate, lipid, and protein[1]. Thyroid hormones also influence renal development, kidney size, weight, structure, glomerular filtration rate (GFR), water and sodium homeostasis, both during development and in adults[2]. Those effects on renal function, present in the state of hypothyroidism as well as in hyperthyroidism, are well established[2-4]. Most of the renal manifestations of thyroid disorders are reversible with treatment.

It is well known that overt and subclinical hypothyroidism are associated with an increased risk of cardiovascular disorders. Subclinical hypothyroidism is an asymptomatic disorder diagnosed with laboratory findings of small elevation in serum thyrotropin (TSH) level but with normal serum level of free thyroid hormones (free triiodothyronine (FT3) and free

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thyroxine (FT4))[1,5]. Subclinical hypothyroidism has a high prevalence of 4-8% in the general population in western countries[6]. Thyroid dysfunction in patients with type 1 diabetes (T1DM) is relatively common and two- to threefold higher than in the general population[7]. T1DM have a high risk of worsening of renal function up to end-stage renal disease[8]. Subjects with microalbuminuria and impaired GFR also have a high risk of cardiovascular diseases[9]. Thyroid dysfunction has an important influence on the progression of renal disease[2]. The interplay between the thyroid and the kidney may be present in subjects with subclinical hypothyroidism or even in those with normal thyroid function. It has been shown that clinically normal but slightly lower thyroid function or subclinical hypothyroidism are associated with albuminuria and impaired GFR[10-12].

Since the majority of studies investigated the relationship between evident thyroid and renal disorders, there is insufficient knowledge about the relationship between renal and thyroid function in euthyroid T1DM with normoalbuminuria and normal or mildly impaired GFR. Therefore, the aim of this study was to explore the associations between TSH, fT3, and fT4 and parameters of renal function in euthyroid T1DM with normoalbuminuria and estimated GFR > 60 ml/min/1.73m^2.

Subjects, materials, and methods

In this study, we investigated 272 euthyroid T1DM. Type 1 diabetes has been diagnosed according to the age of onset (up to 35 years), insulin treatment, and positive autoantibodies. Normal thyroid function (euthyroidism) implies all thyroid hormones in the reference range (TSH, fT3, and fT4). All patients had no anamnesis of previously renal or thyroid function disorders, nor any other major gland disorders (liver or adrenal gland). Those patients treated with drugs that interfere with renal or thyroid function were excluded from the study. Patients treated with antihypertensive and antihyperlipidemic therapy (particularly those affecting albuminuria like ACE inhibitors and angiotensin II receptor blockers) were also excluded from the study.

Patients collected two 24-h urine samples. The study included patients with normoalbuminuria classified according to mean urinary albumin excretion rate (UAE) <30 mg/24h. Those with microalbuminuria classified according to mean UAE≥30<300 mg/24h as well as those with macroalbuminuria classified according to mean UAE≥300 mg/24h were excluded from the study. Patients with chronic kidney disease classified according to estimated GFR less than 60 ml/min^{-1}1.73m^{-2} calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula were also excluded from the study[13,14]. Patients had normal urine sediment without elements of urinary tract infections. Blood pressure was measured after 10 minutes rest period minimally two times with a mercury sphygmomanometer and expressed in mmHg.

Fasting venous blood samples were collected after an overnight fast for the evaluation of thyroid function (TSH, fT3, and fT4), serum lipids (total, LDL, HDL cholesterol, triglycerides), hemoglobin A1c (HbA1c), and serum creatinine. HbA1c and albumin were evaluated spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Enzymatic colorimetric method (Olympus AU600, Beckman-Coulter, USA) was used to evaluate serum lipids and fasting plasma glucose. Thyroid hormones were evaluated by fluoroimmuno-assay (FIA) (Wallac Oy, Turku, Finland). The reference range for thyroid hormones in our laboratory was: for TSH 0.4-4.0 mU/L, for fT3 2.8-8.2 pmol/L, for fT4 8.4-22.0 pmol/L).

Local ethics committees have approved the study protocol and the study has been conducted according to the Declaration of Helsinki and local institutional guidelines.

Normally distributed values are expressed as means ± SD, while non-normally distributed values are expressed as median with range. Spearman rho test was used to calculate correlations between thyroid and renal parameters with metabolic and anthropometric variables. Kruskal-Wallis test was used to calculate the relation between thyroid and renal function parameters after stratification in quartiles of TSH, fT3, and fT4. Multivariate logistic regression analysis, with and without potential confounders, were used to calculate associations of thyroid function and risk of progression of renal disease. We conducted a statistical analysis with SPSS, version 17.0 for Windows, and a statistical significance level of α=0.05 was chosen.

Results

Table 1 lists the anthropometric and metabolic characteristics of the T1DM. Patients had slightly elevated levels of LDL cholesterol and HbA1, while other metabolic parameters were within the normal range for T1DM. Table 2 lists the association between thyroid hormones and renal function parameters. fT4 was significantly correlated with serum creatinine, UAE, and particularly with eGFR (r=0.34, p<0.001). TSH was significantly correlated with UAE, while fT3 significantly correlated with serum creatinine. In addition, thyroid hormones and renal function parameters are also significantly correlated with several metabolic parameters (duration of diabetes, BMI, age, HbA1c, serum lipids, and blood pressure), especially with HbA1c and HDL cholesterol.

Table 1: Metabolic and clinical characteristics of all patients

Variable	
Gender (m/f)	145/127
Age (years)	34 (18-65)
Diabetes duration (years)	11 (1-42)
BMI (kg/m2)	24 (15-37)
HbA1c (%)	7.3 (4.5-14.2)
SBP (mmHg)	120 (79-180)
DBP (mmHg)	80 (50-110)
TSH (mIU/L)	1.96±0.9
FT3 (pmol/L)	5.4±1.0
FT4 (pmol/L)	14.1±2.5
Total cholesterol (mmol/L)	4.9 (2.6-7.8)
LDL cholesterol (mmol/L)	2.7 (0.6-5.0)
HDL cholesterol (mmol/L)	1.64 (0.7-3.0)
Triglycerides (mmol/L)	0.93 (0.3-4.1)
UAE (mg/24h)	10.9 (1.7-29.8)
Serum creatinine (μmol/L)	72 (41-110)
eGFR (mlmin-11.73m-2)	109 (60-143)

BMI - body mass index, SPB - systolic blood pressure, DBP - diastolic blood pressure, FT3 - free T3, FT4 - free T4, UAE - urinary albumin excretion rate, eGFR - estimated glomerular filtration rate

Table 3 lists relationships between renal function parameters of patients stratified in the 2nd, 3rd, and 4th quartiles of TSH, fT3, and fT4 compared to patients in quartile 1. After stratification of renal function parameters, a statistically significant relationship was only observed across quartiles of fT4 for eGFR (p<0.001) and almost significant across quartiles of fT3 for serum creatinine (p=0.06).

Table 4 presents multivariate logistic regression analysis where fT4 was significantly associated with eGFR and UAE after adjustment for age and sex, while fT3 was significantly associated with serum creatinine (p≤0.03), with odds ratios of 0.75 to 1.29 (Table 4, Model A). After adjustment for age, sex, duration of diabetes, HbA1c and BMI odds ratio did not significantly change and remained significant, particu-

Table 2: Correlation analysis between thyroid and renal function parameters with metabolic parameters

Variable	TSH	fT3	fT4	creatinine	eGFR	UAE
Age	-0.01	-0.06	-0.13*	0.03	-0.58*	0.09
Duration of diab.	-0.01	-0.01	-0.08	0.01	-0.33*	0.15*
BMI	0.10	0.05	-0.08	0.16*	-0.13*	0.01
HBA1c	-0.25*	-0.04	0.13*	-0.13*	0.16*	0.02
Total cholesterol	0.01	0.07	0.08	-0.01	-0.18*	0.01
LDL cholesterol	-0.04	-0.01	0.13*	0.08	-0.18*	0.03
HDL cholesterol	0.13*	-0.19*	-0.19*	-0.13*	-0.22*	-0.10
Triglycerides	-0.11	0.04	0.14*	0.04	0.04	0.09
Systolic BP	0.01	-0.01	0.05	0.05	-0.02	0.11
Diastolic BP	-0.01	-0.04	-0.07	0.05	-0.01	0.22*
Serum creatinine	-0.01	0.12*	-0.12*			
eGFR	-0.06	0.06	0.34*			
UAE	-0.15*	-0.01	-0.13*			

BMI - body mass index, HbA1c - hemoglobin A1c, UAE - albumin excretion rate, eGFR - estimated glomerular filtration rate, *P<0.05

Table 3: Correlation coefficients (r) of thyroid hormones with renal function parameters

		1st quartile	2nd quartile	3rd quartile	4th quartile	P
	Group					
creatinine (μmol/L)	1	71 (42-110)	73 (41-105)	74 (43-110)	69 (44-105)	0.4
	2	74 (47-110)	74 (44-105)	71 (40-108)	68 (41-102)	0.06
	3	73 (44-96)	73 (42-108)	67 (41-110)	71 (41-108)	0.09
eGFR ($mlmin^{-1}1.73m^{-2}$)	1	114 (66-142)	108 (71-143)	109 (60-135)	107 (69-130)	0.5
	2	105 (66-142)	109 (71-130)	109 (60-129)	109 (78-143)	0.5
	3	101 (69-129)	102 (60-142)	112 (66-143)	116 (72-137)	<0.001
UAE (mg/24h)	1	12.9 (2.2-29.8)	11.0 (2.1-28.7)	10.7 (1.7-28.7)	10.1 (3.7-28.3)	0.1
	2	12.0 (2.4-29.8)	10.7 (1.7-29.8)	10.5 (2.1-28.5)	11.9 (2.8-28.7)	0.7
	3	12.8 (3.4-29.5)	12.6 (1.7-29.8)	10.6 (2.1-29.8)	9.9 (2.1-28.7)	0.1

Group 1: TSH (≤1.29 mU/L, 1.30-1.86, 1.87-2.57, and ≥2.58 mU/L for quartiles); Group 2: fT3 (≤4.7 pmol/L, 4.8-5.3, 5.4-6.1, and ≥6.2 pmol/L for quartiles); Group 3: fT4 (≤12.3 pmol/L, 12.4-13.8, 13.9-15.6, and ≥15.7 pmol/L for quartiles).
*P<0.05.

Table 4: Multivariate logistic regression analysis of TSH, fT3 and fT4 with the risk of worsening of renal function parameters

Independent variable			
	Group	Model A	Model B
TSH	1	0.86 (0.66-1.12)	0.78 (0.59-1.03)
	2	1.21 (0.83-1.51)	0.99 (0.72-1.36)
	3	0.79 (0.60-1.03)	0.80 (0.60-1.05)
fT3	1	1.29 (1.02-1.63)*	1.27 (1.00-1.61)*
	2	0.94 (0.72-1.21)	0.91 (0.70-1.19)
	3	1.09 (0.87-1.37)	1.09 (0.87-1.38)
fT4	1	0.95 (0.86-1.05)	0.97 (0.88-1.07)
	2	0.75 (0.66-0.85)*	0.76 (0.67-0.87)*
	3	0.90 (0.82-1.00)*	0.90 (0.81-0.99)*

Group 1: serum creatinine; Group 2: estimated glomerular filtration rate; Group 3: urinary albumin excretion rate.
Model A adjusted for gender and age; model B further adjusted for diabetes duration, BMI and HbA1c.
*P < 0.05.

larly in respect for fT4 and eGFR (p<0.001) (Table 4, Model B).

Discussion

Diabetes mellitus and thyroid disorders are two major endocrine disorders. T1DM has a high risk of worsening renal function and developing end-stage renal disease, while thyroid dysfunction also has an important role in renal insufficiency[2,8]. However, it has been demonstrated that low thyroid function is associated with GFR even in the euthyroid state of healthy subjects. In support of these data, we documented that in this cross-sectional study, including normoalbuminuric T1DM, that low normal thyroid function measured with fT4 and fT3 were associated with reduced eGFR and higher UAE.

The significant relationship between thyroid disorders, also in their subclinical form, and renal function has been observed in subjects without diabetes as well as in those with type 2 diabetes[2-4,6,11,12,15]. In addition, subclinical and overt hypothyroidism is common in

patients with reduced renal function (estimated GFR≤60 ml/min^{-1}1.73m^{-2}), and it is supposed that hypothyroidism might contribute to the development of renal disease[16,17]. Moreover, low fT3 is connected with inflammatory processes, endothelial dysfunction, and increased mortality in euthyroid patients with nephropathy[18,19]. In this study, we observed an independent and strong association between low normal fT4 and fT3 and lower eGFR. It is well documented that subclinical hypothyroidism is associated with reduced GFR[4,12,16,20].

Moreover, T4 treatment of subclinical and overt hypothyroidism resulted in an increase of GFR[4,12,21,22]. The most obvious explanation relating to thyroid hormone therapy and GFR is that T4 treatment increases renal blood flow, resulting in an increase in GFR[23]. Moreover, the relationship between thyroid function and increase in renal circulation has been documented even in clinically normal thyroid function[24]. In contrast, reduced cardiac output in overt or subclinical hypothyroidism may result in reduced renal blood flow and reduced GFR[2,25]. Our results are in line with these findings and indicate that low normal thyroid function measured with fT3 and fT4 is associated with GFR even in the euthyroid range. Although we estimated GFR with creatinine-based formula, studies that have measured glomerular filtration with gold standard methods also documented associations between low thyroid function and reduced GFR[22,23]. Moreover, although previously validated in patients with diabetes, the cystatin C-based formula is not optimal to estimate GFR in patients with thyroid disorders[26,27].

Previous studies documented that TSH is independently connected with albuminuria in patients with type 2 diabetes and subclinical hypothyroidism and that proteinuria often precedes the reduction in GFR in hypothyroidism[11,28]. In our study, we have observed a significant association between low normal fT4 and albuminuria in euthyroid normoalbuminuric T1DM. Patients with subclinical hypothyroidism have endothelial dysfunction characterized by reduced endothelium-dependent vasodilatation, which improved with thyroid hormone therapy[29,30]. Moreover, endothelial dysfunction exists already in euthyroidism in subjects with Hashimoto thyroiditis, the most common thyroid disorder in T1DM[31]. Albuminuria is also a marker of chronic complications of diabetes, particularly diabetic nephropathy, but also a marker of increased cardiovascular risk[32,33]. At baseline, endothelial dysfunction is a significant and independent risk factor for progression and higher UAE in initially normoalbuminuric T1DM[34]. Moreover, endothelium-mediated vasodilatation is significantly impaired in diabetic subjects with microalbuminuria, but not in those with normoalbuminuria[35,36]. Therefore, low normal fT4 may be connected with the development of albuminuria and diabetic nephropathy via vascular endothelial dysfunction.

There are several potential limitations in the present study. First, this was a cross-sectional study and interpretation of the causal relation between thyroid function and the risk of renal disease progression is limited. Second, we measured GFR with a creatinine-based formula, which is, although indirect and not a gold standard method for assessment of glomerular filtration, practical for this number of patients. Third, we measured renal and thyroid function parameters on two consecutive days instead of in a more extended period of time.

In conclusion, our results imply that low-normal thyroid function in the clinically euthyroid range is associated with renal disease progression in T1DM with normoalbuminuria and estimated GFR > 60 ml/min^{-1}1.73m^{-2}. The study included patients without antihypertensive and antihyperlipidemic therapy. Further prospective studies are needed to explore whether the detection of low-normal thyroid function in normoalbuminuric T1DM is associated with the progression of renal disease.

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Sažetak

SLOBODNI TIROKSIN I TRIJODTIRONIN SU POVEZANI S BUBREŽNOM FUNKCIJOM U NORMOALBUMINURIČNIH EUTIREOIDNIH BOLESNIKA S ŠEĆERNOM BOLEŠĆU TIPA 1

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Hipotireoza kao i hipertireoza utječu na bubrežnu funkciju. U ovoj studiji istraživali smo povezanost između TSH, slobodnog trijodtironina (sT3) i slobodnog tiroksina (sT4) s parametrima bubrežne funkcije u normoalbuminuričnih bolesnika sa tipom 1 šećerne bolesti (ŠB1). Studija je uključila 272 bolesnika sa ŠB1 i normalnom funkcijom štitnjače te prije terapije statinima, ACE-inhibitorima ili blokatorima receptora angiotenzina 2. Studija je uključila bolesnike s glomerularnom filtracijom (GF) > 60 $mlmin^{-1}1.73m^{-2}$. sT4 je statistički značajno korelirao s serumskim kreatininom, GF i albuminurijom (r=-0.12, 0.34 i -0.13, za sve p<0.05), TSH je statistički značajno korelirao s albuminurijom (r=-0.15, p<0.05) a sT3 s serumskim kreatininom (r=0.12, p<0.05). Razina GF bila je značajno viša u ispitanika u najvišoj kvartili sT4 u usporedbi s onim u najnižoj kvartili (116 prema 101 ml min^{-1} $1.73m^{-2}$, p<0.001). U logističkoj regresiji, nakon prilagodbe za dob, spol, indeks tjelesne težine, trajanje šećerne bolesti i HbA1c, sT3 i sT4 bili su statistički značajno povezani s rizikom od pogoršanja bubrežne funkcije u naših bolesnika s omjerom izgleda (odds ratios) između 0.75 i 1.29. Ova studija, provedena na eutireotičnim normoalbuminuričnim bolesnicima s ŠB1 bez terapijskih intervencija, ukazala je da je utjecaj funkcije štitnjače na parametre bubrežne funkcije prisutan već i u stanju eutireoze.

Ključne riječi: *šećerna bolest tipa 1, hormoni štitnjače, bubrežna funkcija, albuminuria*