Endocrine (2012) 42:139–145
DOI 10.1007/s12020-012-9598-y

ORIGINAL ARTICLE

Insulin sensitivity modifies the relationship between thyroid function and lipid profile in euthyroid type 1 diabetic patients

Tomislav Bulum · Branko Kolarić · Lea Duvnjak

Received: 12 October 2011 / Accepted: 29 December 2011 / Published online: 15 January 2012

Abstract It has been suggested that association between hypothyroidism with dyslipidemia might be present already at the stage of normal thyroid function through altered insulin sensitivity. We analyzed the role of insulin sensitivity as a mediator of thyroid-induced lipid changes in euthyroid type 1 diabetic patients. Study included 304 patients with type 1 diabetes and normal thyroid function. Insulin sensitivity was measured with estimated glucose disposal rate calculated using the equation: eGDR = 24.31 − (12.22 × WHR) − (3.29 × HT) − (0.57 × HbA1c); WHR = waist-to-hip ratio, HT = hypertension. TSH, FT4, FT3, and serum lipids were measured. Correlations and multiple linear regressions analysis were performed to identify relationships between thyroid status and serum lipid parameters after stratifying patients in quartiles of eGDR. After adjustment for age, sex, BMI, duration of diabetes and insulin dose TSH, FT3, and FT4 was not significantly associated with serum lipids in all patients, independently of level of insulin sensitivity. However, after stratifying patients for the degree of insulin sensitivity in subjects in the lowest quartile of insulin sensitivity TSH was independently associated with LDL cholesterol ($\beta = 0.210$, $p = 0.02$). The independent relation of eGDR with TSH and LDL cholesterol suggests that the influence of thyroid function on lipid metabolism might extend into euthyroid range through altered insulin sensitivity.

Keywords Type 1 diabetes · Insulin sensitivity · Thyroid function · Serum lipids · Estimated glucose disposal rate

T. Bulum (✉) · L. Duvnjak
Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, University Hospital Merkur, Dugi dol 4a, Zagreb, Croatia
e-mail: tbulum@idb.hr

B. Kolarić
Medical School, University of Rijeka, Rijeka, Croatia

B. Kolarić
Zagreb County Institute of Public Health, Zagreb, Croatia

L. Duvnjak
Medical School, University of Zagreb, Zagreb, Croatia

Introduction

Thyroid hormones are key regulators of many metabolic processes through their effect on protein, carbohydrate, and lipid metabolism [1]. Those effects might be direct, as well as indirect by modification of other hormones such as insulin or catecholamines [2]. Thyroid hormones also influence on various aspects of lipid metabolism including synthesis, mobilization, and degradation [3]. Overt hypothyroidism (OH) is associated with dyslipidemia and increased atherosclerotic vascular disease [1], as well as subclinical hypothyroidism (SH), an asymptomatic state characterized by normal serum concentrations of free triiodothyronine (FT3) and free thyroxine (FT4) with slightly elevated serum concentrations of thyrotropin (TSH) [1, 3, 4]. Most hypothyroid, as well as patients with SH, showed high serum concentrations of total and low density (LDL) cholesterol [1, 3, 5]. In contrast, high density (HDL) cholesterol and triglycerides levels were found to be higher or similar compared to euthyroid subjects [1, 3, 6]. Besides quantitative lipid changes in OH, qualitative alterations on lipoproteins, such as triglyceride enrichment of the LDL particle and accumulation of remnant lipoproteins can also be found [7, 8].

It has been suggested that OH and SH are an insulin resistant state [9, 10]. Thyroid hormones play a key role in

the regulation and activation of insulin receptor and glucose transporter proteins [11]. Thyroid disorders in terms of OH or SH have also been associated with defective insulin secretion, hyperinsulinemia, altered peripheral glucose disposal, and insulin resistance [9, 13]. Insulin resistance is the central pathophysiological phenomenon of metabolic syndrome [13], and it has been shown that thyroid hormones and TSH are associated with several components of metabolic syndrome in euthyroid subjects [14, 15]. In addition, insulin resistance seems to be a key regulator of dyslipidemia genesis, leading to increases in triglycerides and small dense LDL, and reduction in HDL cholesterol [13]. Although insulin resistance is usually associated with the development of type 2 diabetes, it can also be a feature of patients with type 1 diabetes [16]. In those subjects, insulin resistance is an independent risk factor for the micro- (nephropathy, neuropathy, and retinopathy), macro- (coronary artery disease and peripheral vascular disease) vascular complications, and liver disease [17–21]. Clinically, insulin resistance in type 1 diabetic patients is often recognized by their larger requirements for insulin, but more recently a validated method for estimated glucose disposal rate (eGDR), which has been previously validated by euglycemic-hyperinsulinemic clamp studies, has been developed [22].

However, it has been observed that TSH and thyroid hormone concentrations have an impact on plasma lipids in euthyroid subjects [23–25]. At least three studies have suggested that the known associations of OH and SH with dyslipidemia may be extended into the normal range of thyroid function through altered insulin sensitivity [15, 26, 27]. A significant influence of insulin sensitivity on the associations of high normal TSH and low normal FT4 with dyslipidemia has been observed in healthy subjects [15, 26, 28]. In euthyroid type 2 diabetic patients, insulin resistance has led to an increased risk of dyslipidemia in patients with higher serum TSH [27].

The objective of this study was to investigate the role of insulin sensitivity as a mediator of thyroid-induced lipid changes in euthyroid type 1 diabetic patients.

Subjects, materials, and methods

This study included 304 euthyroid patients with diabetes mellitus type 1. Type 1 diabetes was defined as an onset of diabetes before the age of 35 years and permanent insulin treatment initiated within 1 year of diagnosis. Euthyroidism was defined as TSH, FT3, and FT4 within the normal reference range while not taking any thyroid medication, and negative finding of thyroid autoantibodies against thyroid peroxidase (TPOAb) or thyroglobulin (TgAb). The study included patients with following characteristics: age of 18–65 years, minimum duration of type 1 diabetes of 1 year, no medical history of disorders of thyroid and adrenal gland function, no medical history of liver, renal, and cardiovascular diseases. Patients were excluded from the study if they took any of the following: lipid-lowering therapy, thyroid hormone therapy, antithyroid drugs, radioiodine treatment, iodine tablets, and medications that might affect thyroid function (amiodarone, lithium, interferon, corticosteroids, dopamine, and other drugs). Those who required medications that might affect glucose metabolism and insulin sensitivity such as glucocorticoids, oral contraceptives as well as patients taking oral glucose-lowering medication, and who had accompanying infectious disease, were also excluded from the study.

All subjects were studied in the morning after an overnight fast. Basic anthropometric measurements were performed on all study subjects, waist-to-hip ratio (WHR) was calculated from the waist circumference (measured on bare skin as the narrowest circumference between the 10th rib and the iliac crest with tailor meter) and hip circumference (at the widest point of the gluteal muscles) and expressed in centimeters (cm), weight was measured by the physician using a balanced-beam scale with light clothing and barefoot and expressed in kilograms (kg), height was measured using a wall mounted stadiometer and expressed in cm, BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 min.

Fasting venous blood samples were collected in the morning between 08:00 and 09:30 h after an overnight fast for the determination of hemoglobin A1c (HbA1c, %), TSH (mIU/L, reference interval 0.4–4.0), FT4 (pmol, reference interval 8.4–22.0), FT3 (pmol/L, reference interval 2.8–8.2), total cholesterol (mmol/L, reference interval <5.0), HDL cholesterol (mmol/L, reference interval >1.0 for men, >1.3 for women), LDL cholesterol (mmol/L, reference interval <3.0), VLDL cholesterol (mmol/L), and triglycerides (mmol/L, reference interval <1.7).

HbA1c was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Cholesterol and triglycerides in serum were measured by an enzymatic colorimetric method after precipitation with polyethylene glycol on an automatic spectrophotometer (Olympus AU600, Beckman-Coulter, USA). TSH, FT3, and FT4 were determined by fluoroimmunoassay (FIA) (Wallac Oy, Turku, Finland).

Measure of insulin sensitivity (eGDR) is calculated using the equation: $24.31 - 12.2 \times (\mathrm{WHR}) - 3.29 \times (\mathrm{HT}) - 0.57 \times (\mathrm{HbA1c})$, where the units are mg kg^{-1} min^{-1}, WHR indicates the waist-to-hip ratio, HT indicates blood pressure, and is expressed as: 0-no, 1-yes. Those on blood pressure medications or with blood pressure

>140/90 mmHg were classified as hypertensive. This equation was derived from a substudy of 24 Epidemiology of Diabetes Complications (EDC) participants (12 men and 12 women drawn from low, middle, and high age-specific tertiles of insulin resistance risk factors in order to represent the spectrum of insulin resistance) who underwent euglycemic-hyperinsulinemic clamp studies [22].

The study protocol complies with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethics committees.

All statistical analyses were performed with the SAS statistical program, version 9.1.3 (SAS Institute, Cary, NC, USA). Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values. To investigate the relationships between thyroid function, serum lipids and insulin sensitivity, data were stratified in quartiles of eGDR. Differences between groups for normally distributed variables were tested using ANOVA and non-parametric data with the Kruskal–Wallis test. Pearson's correlation coefficients were used to calculate correlations between normally distributed values and Spearman's rank correlation coefficients were used for non-normally distributed values. Multiple linear regression analysis was performed to identify relationships between thyroid status and serum lipid parameters depending on the level of insulin sensitivity, after adjusting for age, sex, BMI, duration of diabetes, and insulin dose. A p value of <0.05 ($p < 0.05$) was considered statistically significant.

Results

The characteristics of the study subjects are listed in Table 1. Mean/median values of BMI, WHR, systolic and diastolic blood pressure, total, LDL, HDL cholesterol, and triglycerides were within the normal range for patients with diabetes. Relationship between clinical and metabolic characteristics of patients among those in the second, third, and fourth quartiles of eGDR compared to those in quartile 1 are presented in Table 2. Stratifying clinical and metabolic characteristics for the degree of insulin sensitivity, trends across quartiles of eGDR for sex, age, duration of diabetes, BMI, daily insulin dose, TSH, total, LDL, HDL, VLDL cholesterol, and triglycerides were statistically significant (all $p < 0.05$). The magnitude of these associations was strongest for sex, age, BMI, daily insulin dose, and serum lipids (all $p < 0.001$). The four patients groups did not differ regarding levels of FT3 and FT4.

Correlations of TSH and thyroid hormones with serum lipids are presented in Table 3. After stratifying patients for the degree of insulin sensitivity (quartiles of eGDR) in those who were considered to be more insulin resistant (the lowest quartile of insulin sensitivity), TSH was positively correlated with all lipids parameters except HDL cholesterol. Correlation between TSH and LDL cholesterol were statistically significant ($r = 0.225$, $p = 0.04$). In contrast, in patients with higher insulin sensitivity (third quartile of eGDR) TSH was significantly positively correlated with HDL cholesterol ($r = 0.239$, $p = 0.03$). FT3 was in a significant negative correlation with HDL cholesterol independently of the level of insulin sensitivity ($r = -0.162$, $p = 0.005$), as well as in subjects with higher insulin sensitivity (third quartile of eGDR) ($r = -0.282$, $p = 0.01$). Correlations between FT4 and total, LDL and HDL cholesterol were opposite in subjects depending on level of insulin sensitivity, and only significant between FT4 and HDL cholesterol in subjects in second quartile of eGDR ($r = -0.278$, $p = 0.01$).

Table 1 Clinical and metabolic characteristics of all patients

Variable	
Sex (m/f)	166/138
Age (years)	38 ± 11
Duration of diabetes (years)	15 ± 10
BMI (kg/m^2)	24 (15–37)
WHR	0.82 ± 0.07
HbA1c (%)	7.08 (4.4–14.2)
Daily insulin dose (IU/day)	41 (8–96)
SBP (mmHg)	122 (90–180)
DBP (mmHg)	80 (50–110)
e-GDR (mg kg^{-1} min^{-1})	9.72 (3.9–12.7)
TSH (mIU/L)	1.92 ± 0.9
FT3 (pmol/L)	5.4 ± 0.9
FT4 (pmol/L)	13.5 ± 2.4
Total cholesterol (mmol/L)	4.9 (2.5–8.0)
LDL cholesterol (mmol/L)	2.7 (0.6–5.8)
HDL cholesterol (mmol/L)	1.66 (0.7–3.6)
VLDL cholesterol (mmol/L)	0.41 (0.2–1.9)
Triglycerides (mmol/L)	0.91 (0.3–5.0)

BMI body mass index, *WHR* waist-to-hip ratio, *SPB* systolic blood pressure, *DBP* diastolic blood pressure; *FT3* free T3, *FT4* free T4, *eGDR* estimated glucose disposal rate

To investigate the relation between TSH with insulin sensitivity and serum lipids data were also stratified in different groups of TSH level [0.4–1.6 (130 patients), 1.61–2.8 (106 patients), and 2.81–4.0 mIU/L (68 patients)]. However, trends across different groups of TSH levels were not statistically significant for eGDR, total, LDL, HDL, VLDL cholesterol, and triglycerides (data not shown). In addition, correlation between TSH, FT3, FT4, and eGDR, as well as with individual components of insulin resistance, were statistically significant only for FT3 with WHR ($r = 0.133$, $p = 0.01$).

Multiple linear regression models, adjusted for age, sex, duration of diabetes, BMI and insulin dose, were used to

Table 2 Comparison of clinical and metabolic characteristics of patients depending on level of insulin sensitivity (quartiles of eGDR)

	First quartile ($n = 76$) (eGDR < 7.81)	Second quartile ($n = 77$) (7.81–9.72)	Third quartile ($n = 75$) (9.73–10.8)	Fourth quartile ($n = 76$) (eGDR > 10.8)	p
Sex (m/f)	51/25	50/27	43/32	22/54	<0.001
Age (years)	44 ± 11	35 ± 11	36 ± 9	35 ± 10	<0.001
Duration of diabetes (years)	19 ± 9	15 ± 10	14 ± 8	14 ± 10	0.01
BMI (kg/m^2)	26 (18–34)	24 (17–37)	24 (19–33)	23 (15–29)	<0.001
Daily insulin dose (IU/day)	48 (22–96)	46 (17–88)	40 (14–71)	34 (8–65)	<0.001
TSH (mIU/L)	2.0 ± 1.0	1.6 ± 0.7	2.0 ± 0.9	2.0 ± 0.8	0.009
FT3 (pmol/L)	5.4 ± 1.0	5.5 ± 1.0	5.4 ± 1.0	5.4 ± 0.8	0.8
FT4 (pmol/L)	13.5 ± 2.7	13.5 ± 2.2	13.5 ± 2.1	13.6 ± 2.4	0.9
Total cholesterol (mmol/L)	5.61 (3.3–8.0)	4.85 (2.5–6.6)	4.75 (3.3–6.5)	4.83 (3.1–6.7)	<0.001
LDL cholesterol (mmol/L)	3.21 (1.4–5.8)	2.73 (1.0–4.2)	2.67 (0.6–3.9)	2.58 (1.4–4.3)	<0.001
HDL cholesterol (mmol/L)	1.69 (0.8–3.1)	1.47 (0.7–3.6)	1.67 (0.9–3.6)	1.80 (0.7–2.8)	<0.001
VLDL cholesterol (mmol/L)	0.49 (0.2–1.9)	0.50 (0.2–1.4)	0.36 (0.2–1.1)	0.33 (0.2–0.9)	<0.001
Triglycerides (mmol/L)	1.08 (0.4–4.1)	1.10 (0.4–5.0)	0.80 (0.4–2.3)	0.72 (0.3–2.0)	<0.001

BMI body mass index, *WHR* waist-to-hip ratio, *SPB* systolic blood pressure, *DBP* diastolic blood pressure, *FT3* free T3, *FT4* free T4, *eGDR* estimated glucose disposal rate

Table 3 Spearman correlation coefficients (r) of TSH and free thyroid hormones with serum lipids concentrations

	Group	Total chol. r	LDL r	HDL r	VLDL r	Triglycerides r
TSH	1	0.044	0.015	0.059	−0.035	−0.036
	2	0.184	0.225*	−0.097	0.139	0.126
	3	0.044	0.073	0.048	0.018	0.024
	4	−0.120	−0.114	0.239*	−0.123	−0.129
	5	0.064	0.100	0.039	−0.002	−0.004
FT3	1	−0.054	0.008	−0.162*	0.039	0.037
	2	−0.067	−0.089	−0.148	0.153	0.148
	3	0.013	0.121	−0.063	−0.124	−0.130
	4	−0.100	0.021	−0.282*	0.100	0.092
	5	−0.045	0.028	−0.156	−0.033	−0.030
FT4	1	−0.002	0.039	−0.061	−0.005	−0.002
	2	−0.063	−0.030	−0.017	−0.098	−0.085
	3	−0.101	0.042	−0.278*	0.139	0.143
	4	0.141	0.140	−0.113	0.018	0.020
	5	0.070	0.047	0.101	−0.007	−0.003

Group 1: all patients (304); Group 2: eGDR < 7.81 mg kg^{-1} min^{-1} (76 patients); Group 3: eGDR 7.81–9.72 mg kg^{-1} min^{-1} (77 patients); Group 4: eGDR 9.73–10.8 mg kg^{-1} min^{-1} (75 patients); Group 5: eGDR > 10.8 mg kg^{-1} min^{-1} (76 patients); * $p < 0.05$

determine whether the associations of TSH, FT3, and FT4 with serum lipids were modified by level of insulin sensitivity (Table 4). The association of TSH and LDL cholesterol ($\beta = 0.210$, 95% CI = 0.02–0.39, $p = 0.02$) appeared to be significantly modified in patients in the lowest quartile of insulin sensitivity, and almost significant for the association of TSH with total cholesterol ($\beta = 0.197$, 95% CI = −0.09 to 0.40, $p = 0.06$). In patients with higher insulin sensitivity (second, third, and fourth quartiles of eGDR) associations of TSH, FT3, and FT4 with serum lipids were not significant after multivariate adjustment for a broad spectrum of metabolic risk factors.

Discussion

Thyroid disease and diabetes mellitus are the two most common endocrine disorders in everyday practice. Their strong association with insulin sensitivity might have

Table 4 Multiple linear regression coefficients (β), adjusted for age, sex, duration of diabetes, body mass index and insulin dose, for the effects of thyroid function and insulin sensitivity on serum lipid parameters

	Group	Total cholesterol β	LDL β	HDL β	VLDL β	Triglycerides β
TSH	1	0.044	0.025	0.026	−0.005	0.007
	2	0.197	0.210*	−0.049	0.037	0.077
	3	0.007	−0.071	0.076	0.001	0.145
	4	−0.083	−0.108	0.043	−0.016	−0.037
	5	0.091	0.107	−0.021	0.006	0.013
FT3	1	0.022	0.027	−0.024	0.015	0.032
	2	0.043	−0.037	−0.000	0.083	0.178
	3	0.127	0.128	0.027	−0.028	−0.057
	4	−0.053	−0.018	−0.069	0.019	0.040
	5	−0.029	0.028	−0.060	0.002	0.007
FT4	1	0.005	0.015	−0.006	−0.001	0.002
	2	−0.011	−0.002	−0.004	0.000	0.004
	3	−0.010	0.016	−0.034	0.007	0.052
	4	0.061	0.060	−0.001	0.000	0.001
	5	−0.002	0.000	0.002	−0.005	−0.011

Group 1: all patients (304); Group 2: eGDR < 7.81 mg kg^{-1} min^{-1} (76 patients); Group 3: eGDR 7.81–9.72 mg kg^{-1} min^{-1} (77 patients); Group 4: eGDR 9.73–10.8 mg kg^{-1} min^{-1} (75 patients); Group 5: eGDR > 10.8 mg kg^{-1} min^{-1} (76 patients); * $p < 0.05$

important clinical implications [12, 29]. Insulin resistance as a key component of the metabolic syndrome leads to dyslipidemia [13]. On the other side, both OH and SH, known to be associated with the development of dyslipidemia, represent an insulin resistant state [1, 7–9, 11, 31]. The correlation between thyroid hormones and insulin resistance has been proven in diabetic patients but also in subjects with normal glucose tolerance [14, 15, 27, 28]. Even subtle decrease in the level of thyroid hormones within the normal range has been shown to inversely correlate with insulin resistance [15, 28].

The significant relationship between insulin sensitivity, thyroid function, and lipid profile has been documented in healthy subjects and type 2 diabetic patients with normal thyroid function [15, 26–28]. Chubb et al. [27] demonstrated significant associations between TSH and serum total, HDL cholesterol and triglycerides in euthyroid insulin-resistant type 2 diabetic patients. The influence of insulin sensitivity on thyroid function and lipid profile was not previously investigated in euthyroid type 1 diabetic patients. Our data gave evidence that insulin sensitivity could modify the relationship between thyroid function and lipid profile in type 1 diabetic patients with normal thyroid function. In all patients, after adjustment for age, sex, BMI, duration of diabetes and insulin dose, TSH, FT3, and FT4 level was not significantly associated with serum lipids. However, after stratifying patients for the degree of insulin sensitivity, in insulin-resistant type 1 diabetic patients TSH was independently associated with LDL cholesterol ($\beta = 0.210$, $p = 0.02$), and almost with total cholesterol ($\beta = 0.197$, $p = 0.06$).

Thyroid hormones are involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes of serum lipids [1, 7, 8, 30]. OH and SH are associated with dyslipidemia, affecting mainly total and LDL cholesterol value [1, 3]. An accumulation of LDL cholesterol due to a reduction in the number of hepatic and peripheral LDL receptors resulting in decreased clearance of LDL is considered as the primary mechanism for hypercholesterolemia in OH and SH [5]. Our results indicate that insulin sensitivity might have influence on these pathophysiological mechanisms already at the euthyroid state. Subjects with low insulin sensitivity show an increased hepatic cholesterol synthesis, with overproduction of VLDL cholesterol, the precursor particles of LDL cholesterol [31]. However, in subjects with low insulin sensitivity the composition of LDL seems to be modified by depletion in cholesterol content of LDL particle and increasing concentrations of small dense LDL particles [13, 32]. The more atherogenic small dense LDL particles have lower affinity for the LDL receptor, causing a delay in their clearance [33]. Insulin resistance associated dyslipidemia with predominance of small LDL particles could possibly explain higher LDL cholesterol concentrations in subjects with high normal TSH level and partially reduced LDL receptor number.

In comparison with the study performed in type 2 diabetic patients [27], our patients showed significantly lower

levels of total, LDL cholesterol and triglycerides as well as higher levels of protective HDL cholesterol. Our results and subjects characteristics are comparable with the study of Bakker et al. [26], who found significant positive associations of TSH with total and LDL cholesterol in euthyroid insulin resistant subjects without diabetes. In our study, insulin resistance was not measured using the gold standard, euglycemic-hyperinsulinemic clamp method, which represents a potential limitation. Insulin sensitivity was determined using eGDR, a method based on clinical parameters that include hypertension, HbA1c, and WHR. It shows a close correlation with the clamp method and was previously used to determine the extent of insulin resistance in type 1 diabetes [19, 22, 34].

We did not find a significant correlation between TSH, thyroid hormones, and insulin resistance or its components, except between FT3 and WHR. Moreover, after stratifying patients in different groups of TSH level, trends across different groups were not statistically significant for eGDR and serum lipids. It is evident that the complex interaction between insulin sensitivity, thyroid status, and lipid profile will remain unclarified in clinical trials. More studies need to be done in order to understand mechanisms underlying insulin resistance and thyroid function in type 1 diabetes. However, evidence that in insulin resistant patients with type 1 diabetes TSH level within the normal limits causing lipid disorder point on earlier therapeutic intervention.

Our findings suggest that in type 1 diabetic patients, with documented lower insulin sensitivity, the lowest TSH concentrations within the reference range should be aimed. Such a view is supported by experimental data showing that in insulin resistant patients with type 2 diabetes an estimated 10-year cardiovascular risk at a TSH level of 1 mIU/L was almost half of that at a TSH level of 7 mIU/L [27]. Although thyroid hormones therapy in SH is still a matter of debate, it could represent a valuable adjunct to lipid-lowering therapy in dyslipidemic diabetic patients with reduced insulin sensitivity [35, 36]. Moreover, the majority of studies suggest a normalization of LDL cholesterol levels after thyroxine substitution therapy in SH [1, 6, 37, 38].

Our results on a large number of type 1 diabetic patients prove that the influence of altered insulin sensitivity on thyroid function and lipid metabolism extends into euthyroid range. Whether the detection of increased TSH level within the normal range in insulin-resistant type 1 diabetic patients has predictive value for development of dyslipidemia and increased cardiovascular risk needs to be assessed in further follow-up studies.

Conflicts of interest None.

References

1. Peppa M., Betsi G., Dimitriadis G. Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. J. Lipids (2011). doi:10.1155/2011/575840
2. B. Kim, Thyroid hormone as a determinant of energy expenditure and the basal metabolic state. Thyroid **18**, 141–144 (2008)
3. X. Zhu, S.Y. Cheng, New insights into regulation of lipid metabolism by thyroid hormone. Curr. Opin. Endocrinol. Diabetes Obes. **17**, 408–413 (2010)
4. A.E. Hak, H.A. Pols, T.J. Visser, H.A. Drexhage, A. Hofman, J.C. Witteman, Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann. Intern. Med. **132**, 270–278 (2000)
5. L.H. Duntas, Thyroid disease and lipids. Thyroid **12**, 287–293 (2002)
6. S. Miura, H. Iitaka, H. Yoshimura, S. Kitahama, N. Fukasawa, Y. Kawakami, S. Sakurai, M. Urabe, Y. Sakatsume, K. Ito, J. Ishii, Disturbed lipid metabolism in patients with subclinical hypothyroidism: effect of L-thyroxine therapy. Intern. Med. **33**, 413–417 (1994)
7. G. Brenta, G. Berg, P. Arias, V. Zago, M. Schnitman, M. Luz Muzzio, I. Sinay, L. Schreier, Lipoprotein alterations, hepatic lipase activity, and insulin sensitivity in subclinical hypothyroidism: response to L-T_4 treatment. Thyroid **17**, 453–460 (2007)
8. G. Brenta, G. Berg, V. Zago, M. Luz Muzzio, M. Schnitman, I. Sinay, P. Arias, L. Schreier, Proatherogenic mechanisms in subclinical hypothyroidism: hepatic lipase activity in relation to the VLDL remnant IDL. Thyroid **18**, 1233–1236 (2008)
9. A. Maratou, D.J. Hadjidakis, A. Kollias, K. Tsegka, M. Peppa, M. Alevizaki, P. Mitrou, V. Lambadiari, E. Boutati, D. Nikzas, N. Tountas, T. Economopoulos, S.A. Raptis, G. Dimitriadis, Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur. J. Endocrinol. **160**, 785–790 (2009)
10. C. Rochon, I. Tauveron, C. Dejax, P. Benoit, P. Capittan, A. Fabricio, C. Berry, C. Champredon, P. Thieblot, J. Grizard, Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. Clin. Sci. **104**, 7–15 (2003)
11. F. Amati, J.J. Dube, F. Stefanovic-Racic, F.G. Toledo, B.H. Goodpaster, Improvements in insulin sensitivity are blunted by subclinical hypothyroidism. Med. Sci. Sports Exerc. **41**, 265–269 (2009)
12. Peppa M., Koliaki C., Nikolopoulos P., Raptis S.A. Skeletal muscle insulin resistance in endocrine disease. J. Biomed. Biotechnol. (2010). doi:10.1155/2010/527850
13. R.H. Eckel, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome. Lancet **365**, 1415–1428 (2005)
14. H.K. Kumar, R.K. Yadav, J. Prajapati, C.V. Reddy, M. Raghunath, K.D. Modi, Association between thyroid hormones, insulin resistance, and metabolic syndrome. Saudi Med. J. **30**, 179–183 (2009)
15. A. Roos, S.J. Bakker, T.P. Links, R.O. Gans, B.H. Wolffenbuttel, Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J. Clin. Endocrinol. Metab. **92**, 491–496 (2007)
16. R.A. DeFronzo, R. Hendler, D. Simonson, Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes **31**, 795–801 (1982)
17. F.I. Martin, J.L. Hopper, The relationship of acute insulin sensitivity to the progression of vascular disease in long-term type 1 (insulin-dependent) diabetes mellitus. Diabetologia **30**, 149–153 (1987)

18. J. Yip, M.B. Mattock, A. Morocutti, M. Sethi, R. Trevisan, G. Viberti, Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. Lancet **342**, 883–887 (1993)
19. E.S. Kilpatrick, A.S. Rigby, S.L. Atkin, Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes. Double diabetes in the Diabetes Control and Complications Trial. Diabetes Care **30**, 707–712 (2007)
20. T.M. Davis, D.G. Bruce, W.A. Davis, Prevalence and prognostic implications of the metabolic syndrome in community-based patients with type 1 diabetes: The Fremantle Diabetes Study. Diab. Res. Clin. Prac. **78**, 412–417 (2007)
21. T. Bulum, B. Kolarić, L. Duvnjak, M. Duvnjak, Nonalcoholic fatty liver disease markers are associated with insulin resistance in type 1 diabetes. Dig. Dis. Sci. **56**, 3655–3663 (2011)
22. K.V. Williams, J.R. Erbey, D. Becker, S. Arsianian, T.J. Orchard, Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes **49**, 626–632 (2000)
23. E. Bruckert, P. Giral, R. Chadarevian, G. Turpin, Low free-thyroxine levels are a risk factor for subclinical atherosclerosis in euthyroid hyperlipidemic patients. J. Cardiovasc. Risk **6**, 327–331 (1999)
24. B.O. Asvold, L.J. Vatten, T.I. Nilsen, T. Bjoro, The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur. J. Endocrinol. **156**, 181–186 (2007)
25. G.J. Canaris, N.R. Manowitz, G. Mayor, E.C. Ridgway, The Colorado thyroid disease prevalence study. Arch. Intern. Med. **160**, 526–534 (2000)
26. S.J. Bakker, J.C. Ter Maaten, C. Popp-Snijder, J.P. Slaets, R.J. Heine, R.O. Gans, The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J. Clin. Endocrinol. Metab. **86**, 1206–1211 (2001)
27. S.A. Chubb, W.A. Davis, T.M. Davis, Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations: The Fremantle Diabetes Study. J. Clin. Endocrinol. Metab. **90**, 5317–5320 (2005)
28. J.M. Fernandez-Real, A. Lopez-Bermejo, A. Castro, R. Casamitjana, W. Ricart, Thyroid function in intrinsically linked to insulin sensitivity and endothelium-dependent vasodilatation in healthy euthyroid subjects. J. Clin. Endocrinol. Metab. **91**, 3337–3343 (2006)
29. L.H. Duntas, J. Orgiazzi, G. Brabant, The interface between thyroid and diabetes mellitus. Clin. Endocrinol. **75**, 1–9 (2011)
30. T. Tzotzas, G.E. Krassas, T. Konstantinidis, M. Bougoulia, Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid **10**, 803–808 (2000)
31. H.N. Ginsberg, Diabetic dyslipidemia: basic mechanisms underlying the common hypertriglyceridemia and low HDL cholesterol levels. Diabetes **45**, S27–S30 (1996)
32. B.V. Howard, Insulin resistance and lipid metabolism. Am. J. Cardiol. **84**, 28J–32J (1999)
33. N.F. Galeano, R. Milne, Y.L. Marcel, M.T. Walsh, E. Levy, T.D. Ngu'yen, A. Gleeson, Y. Arad, L. Witte, M. Al-Haideri, S.C. Rumsey, R.J. Deckelbaum, Apoprotein B structure and receptor recognition of triglyceride-rich low density lipoprotein (LDL) is modified in small LDL but not in triglyceride-rich LDL of normal size. J. Biol. Chem. **269**, 511–519 (1994)
34. G.M. Reaven, Role of insulin resistance in human disease. Diabetes **37**, 1595–1607 (1988)
35. N. Rotondi, W.P. den Elzen, D.C. Bauer, A.R. Cappola, S. Razvi, J.P. Walsh, B.O. Asvold, G. Iervasi, M. Imaizumi, T.H. Collet, A. Bremner, P. Maisonneuve, J.A. Sgarbi, K.T. Khaw, M.P. Vanderpump, A.B. Newman, J. Cornuz, J.A. Franklyn, R.G. Westendorp, E. Vittinghoff, J. Gussekloo, Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA **304**, 1365–1374 (2010)
36. G. Michalopoulou, M. Alevizaki, G. Piperingos, D. Mitsibounas, E. Mantzos, P. Adamopoulos, D.A. Koutras, High serum cholesterol levels in persons with "high-normal" TSH levels: should one extend the definition of subclinical hypothyroidism? Eur. J. Endocrinol. **138**, 141–145 (1998)
37. M.D. Danese, P.W. Ladenson, C.L. Meinert, N.R. Powe, Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J. Clin. Endocrinol. Metab. **85**, 2993–3001 (2000)
38. C. Meier, J.J. Staub, C.B. Roth, M. Guglielmetti, M. Kunz, A.R. Miserez, J. Drewe, P. Huber, R. Herzog, B. Müller, TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J. Clin. Endocrinol. Metab. **86**, 4860–4866 (2001)