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ORIGINAL ARTICLE

Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes

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Abstract Thyroid hormones have generally been found normal in diabetic patients. The question of whether variation within the euthyroid range influences insulin sensitivity in type 2 diabetes remains to be established. To investigate this, a meal was given to four groups: 17 healthy volunteers (controls), 22 first-degree relatives of type 2 diabetic subjects (relatives), 15 subjects with impaired glucose tolerance (IGT), and 24 subjects with overt type 2 diabetes (DM). Blood was drawn for 360 min for measurements of glucose and insulin. Plasma-free-T4(FT4) and plasma-free-T3(FT3) levels were measured. Fasting and postprandial insulin resistance was assessed by HOMA-IR and ISI indices, respectively. FT4 levels were found to be lower in controls (13.73 $\pm$ 0.48 pmol/l) than relatives, IGT, and DM (15.33 $\pm$ 0.52, 16.13 $\pm$ 0.65, and 17.7 $\pm$ 0.85 pmol/l, respectively, $P = 0.007$). FT3 levels were lower in controls (3.68 $\pm$ 0.09 pmol/l) than in relatives, IGT, and DM (4.35 $\pm$ 0.1, 4.8 $\pm$ 0.067, and 4.87 $\pm$ 0.11 pmol/l, respectively, $P = 0.001$). HOMA-IR was positively associated with FT4 and FT3 levels (β-co-efficient = 1.876 $\pm$ 0.476, $P = 0.001$; and 0.406 $\pm$ 0.090, $P = 0.001$, respectively). ISI was negatively associated with FT4 and FT3 levels (β-co-efficient = -0.051 ± 0.009, $P = 0.001$ and -0.009 ± 0.002, $P = 0.001$, respectively). In conclusion, increases of thyroid hormone levels within the normal range associate positively with insulin resistance. These data suggest that thyroid hormones may be part of the pathogenetic mechanism to explain metabolic derangement early in the development of type 2 diabetes.

Keywords Insulin resistance · Thyroid hormones · Type 2 diabetes

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Introduction

Insulin resistance is a prominent feature in type 2 diabetes, but the pathophysiologic mechanisms are obscure. Thyroid hormones are important determinants of glucose homeostasis [1, 2]. In contrast to the general notion that insulin is the primary hormone responsible for glycemic control, there is ample molecular biological evidence that the synergistic effects of T3 and insulin determine the pathways of glucose and lipid metabolism [1]. Current knowledge on the role of thyroid hormones on insulin secretion and action comes mainly from studies performed during experimental [3] or spontaneous hyperthyroidism [4] or hypothyroidism [5]. However, recent studies indicate that even in euthyroid individuals, fluctuations of plasma thyroid hormones within the physiological range correlate with changes in insulin secretion [6] and insulin sensitivity [7].

In euthyroid patients with type 2 diabetes, correlation of plasma levels of thyroid hormones and insulin sensitivity has never been done. In a recent study, the interaction

between thyroid function (assessed by TSH measurements) and insulin sensitivity (assessed by HOMA Index), was found to be an important contributor to diabetic dyslipidemia [8].

This study was performed in euthyroid subjects in the early stages of type 2 diabetes, to investigate the association of plasma thyroid hormone levels with both fasting and postprandial sensitivity of glucose metabolism to insulin, after the administration of a standard mixed meal. The meal creates a metabolic environment that permits the interaction of insulin and substrates to be investigated under conditions as close to physiological as possible [4, 5].

Materials and methods

Four groups were examined: healthy control subjects (Controls, HbA1c 3.8 ± 0.12%), first-degree relatives of subjects with type 2 diabetes (parents and siblings) (Relatives, HbA1c 4.3 ± 0.18%) with normal glucose tolerance, subjects with impaired glucose tolerance (IGT, HbA1c 5 ± 0.16%) and subjects with overt type 2 diabetes (DM, HbA1c 6.2 ± 0.3%) (normal range for HbA1c 3.5–5.5%). Subjects' characteristics are shown in Table 1. All type 2 diabetic subjects had a known duration of diabetes of 2–5 years, and only those who diet-controlled were included in the study. The study was approved by the hospital ethics committee, and subjects gave informed consent.

In order to divide subjects into groups, all subjects with a fasting plasma glucose value lower than 126 mg/dl underwent an oral glucose tolerance test (OGTT),before the meal tolerance test. Subjects with a fasting value of more than 126 mg/dl (checked twice), and/or an HbA1c value of more than 6.2%, were classified as having diabetes and did not undergo an OGTT. The results indicated normal/IGT/diabetes, as classified according to the ADA criteria: (1) fasting plasma glucose <110 mg/dl and 2-h postchallenge glucose <140 mg/dl indicated the control and relatives group, (2) fasting plasma glucose 110–126 mg/dl and 2-h postchallenge glucose 140–200 mg/dl indicated the IGT group, (3) fasting plasma glucose >126 mg/dl and 2-h'postchallenge glucose >200 mg/dl indicated the group with diabetes.

The subjects were admitted to the hospital at 0700 h after an overnight fast, and had the radial artery catheterized. A meal (730 kcal, 50% carbohydrate, 38% starch, 40% fat, and 10% protein, consisting of bread, cheese, tomato, cucumber, olive oil, orange juice, and apple) was given at least one hour after catheter insertion and consumed within 20 min. All experiments were undertaken in a temperature-controlled room at 23 C. Blood samples were drawn from the radial artery for measurements of insulin (Linco Research, St. Charles, MO) and glucose (Yellow Springs Instruments, Yellow Springs, OH) before the meal and at 30–60 min intervals for 360 min thereafter. Baseline samples were also obtained for measurements of free thyroxin (FT4), free 3′-iodo-thyronine (FT3) (Brahms RIA FT3 Kit, Hennigsdorf Germany) and thyroid stimulating hormone (TSH) (Brahms RIA FT3 Kit, Hennigsdorf Germany). Euthyroidism was defined as FT4 (reference range 11–24 pmol/l) and FT3 (reference range 3.4–7.2 pmol/l) levels within the normal range. After collection of blood, the tubes were put into ice; spinning, separation of plasma, and freezing at −20°C was always less than 30 min from collection.

Insulin sensitivity in the fasting state was measured by homeostasis model assessment [9] and in the postprandial state by Gutt index (insulin sensitivity index, ISI [10]).

Statistical analysis

Data are presented as mean ± SEM. Generalized linear models, having FT3, FT4 levels, HOMA-IR, and ISI, as outcomes and a categories' variable that indicates the

Table 1 Subjects' characteristics

	Controls	Relatives	IGT	DM	$P_{overall}$
No of subjects	17	22	15	24	–
Men/Women	9/8	10/12	8/7	13/11	0.939
Age (years)	43.3 ± 1.78	42.2 ± 2	44 ± 2.52	49 ± 2.34	0.105
BMI (kg/m^2)	23.1 ± 0.63	23.9 ± 0.53	24.9 ± 0.8	24.9 ± 0.56	0.180
Free T3 (pmol/l)	3.68 ± 0.09	4.35 ± 0.1	4.8 ± 0.067	4.87 ± 0.11	0.001
Free T4 (pmol/l)	13.73 ± 0.48	15.33 ± 0.52	16.13 ± 0.6	17.7 ± 0.85	0.007
HOMA index	0.91 ± 0.07	1.3 ± 0.11	1.98 ± 0.11	2 ± 0.17	<0.001
ISI (mg l^2/mmol mU min)	101.2 ± 7.8	76.5 ± 6.4	44.4 ± 1.46	35.5 ± 3.16	<0.001

Data are expressed as means ± SEM, and *P* values represent overall comparison (AVOVA), after adjustment for possible covariates (age, sex, and BMI). Relatives: 1st degree relatives of diabetic patients with a normal glucose tolerance test, *IGT* subjects with impaired glucose tolerance, *DM* subjects with overt type 2 diabetes

group studied, were performed. Between groups, comparisons were performed using post hoc tests through Bonferroni correction rule. The latter was applied to test for the group effect on the investigated variables at specific time points. As more than three groups had to be compared and the results could be unexpected, the authors used the post-hoc procedure to test their statistical significance.

Linear regression analysis evaluated the association between FT4 and FT3 levels with HOMA and Gutt indices before and after correcting for potential confounders (age, gender, and BMI etc.). These results are presented as b-coefficient ± SEM. SPSS 16.0 statistical software was used for all calculations. All the subjects were non-smokers.

Results

Subject characteristics

HOMA index in controls was lower than that in relatives, IGT, and DM subjects ($P_{overall} < 0.001$) after adjustment for confounders (P for age, sex, and BMI: 0.617, 0.339, and 0.154, respectively). ISI in controls was higher compared to that in relatives, IGT, and DM subjects ($P_{overall} < 0.001$) after adjustment for covariates (P for age, sex, and BMI: 0.659, 0.259, and 0.088, respectively) (Table 1).

FT4 levels were lower in controls than those in relatives, IGT and DM subjects ($P_{overall} = 0.007$), after adjustment for covariates (P for age, sex, and BMI: 0.889, 0.222, and 0.051, respectively). FT3 levels were also lower in controls than those in relatives, IGT, and DM subjects ($P_{overall} < 0.001$), after adjustment for covariates (P for age, sex, and BMI: 0.436, 0.116, and 0.178, respectively) (Table 1).

TSH levels were within the normal range (0.4–4 μU/ml). There was no subclinical hypothyroidism or hyperthyroidism. TSH levels were not different between groups (Controls 1.94 ± 0.175, Relatives 1.707 ± 0.118, IGT subjects 1.58 ± 0.148, DM subjects 1.716 ± 0.147 μU/ml, $P = 0.468$).

Associations among thyroid hormone levels and insulin sensitivity

The authors found a significant positive relationship of HOMA index with FT4 levels (β co-efficient 1.876 ± 0.476, $P = 0.001$), after adjusting for covariates (P for age, sex, and BMI: 0.712, 0.427, and 0.092, respectively). ISI was negatively associated with FT4 (β co-efficient = −0.051 ± 0.009, $P = 0.001$) after adjusting for covariates (P for age, sex, and BMI: 0.925, 0.399, and 0.187, respectively) (Fig. 1).

HOMA index was positively associated with FT3 levels (β co-efficient = 0.406 ± 0.090, $P = 0.001$) after adjusting for covariates (P for age, sex, and BMI: 0.342, 0.449, and 0.180, respectively). ISI was negatively associated with FT3 (β co-efficient = −0.009 ± 0.002, $P = 0.001$)

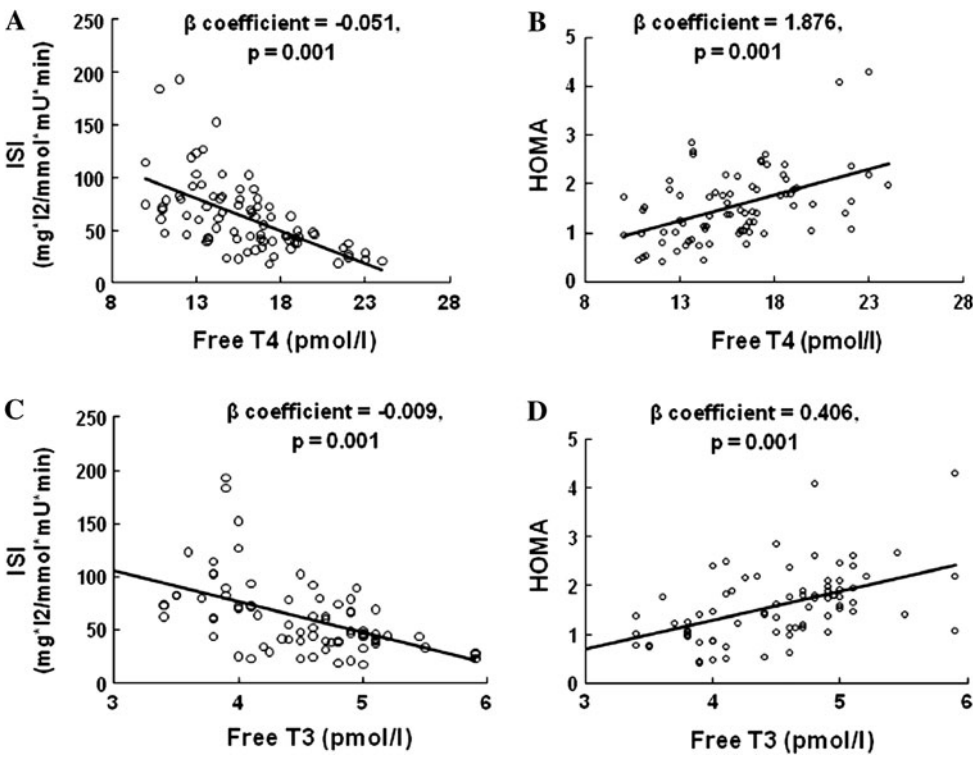

Fig. 1 Association between plasma Free T4 and Free T3 concentrations and ISI (**a**, **c**) and HOMA index (**b**, **d**) in subjects in the early stages of type 2 diabetes

after adjustment for covariates (*P* for age, sex, and BMI: 0.403, 0.422, and 0.240, respectively) (Fig. 1).

Discussion

This study shows that, in subjects in the early stages of type 2 diabetes, as glucose metabolism worsens and even before the development of overt hyperglycemia, there is an increase in plasma thyroid hormone levels within normal range; these changes in thyroid hormones are positively associated with indices of insulin resistance. These data suggest that, in the early stages of type 2 diabetes, thyroid hormones may contribute to the development of insulin resistance in both fasting and postprandial state.

Thyroid hormones antagonize insulin action [1]. Increases in plasma thyroid hormone levels (as for example in hyperthyroidism) impair the ability of insulin to suppress hepatic glucose production and to increase glucose uptake in muscle [2, 3]. Interestingly, even subtle increases in the levels of thyroid hormones within the physiological range (as in subclinical hyperthyroidism) have been shown to induce insulin resistance [11, 12].

The results of this study seem to disagree with data in the literature showing that, in subjects with diabetes, plasma T3 levels are in the low rather than high physiological range [13–15]; however, these studies have not separated patients with diabetes according to the level of glycemic control. This apparent discrepancy can be explained by systematic observations showing that, in euthyroid subjects with type 2 diabetes, plasma T3 levels correlate inversely with fasting plasma glucose levels [16] and glycosylated hemoglobin [17]: when diabetes was uncontrolled and glycosylated hemoglobin was high (>12%), plasma T3 levels were low; in contrast, when diabetes was well controlled and glycosylated hemoglobin was low (around 6%), plasma T3 levels increased by three-fold, and these values were even higher than respective values in euthyroid controls [17]. Indeed, as has been shown in patients with type 1 diabetes, T3 in plasma quickly decreases within a few hours after withdrawal of insulin and with the ensuing metabolic derangement [18]. In this study, patients who had poor or long-standing diabetes were not included. Consequently, it could be assumed that thyroid hormone levels may be more important in the early development of insulin resistance, as seen in relatives of subjects with type 2 diabetes, subjects with impaired glucose tolerance, and patients with diet-controlled diabetes.

It is well established that both hyperthyroidism and hypothyroidism are associated with insulin resistance [3–5]. Recently, a study has been published showing that insulin resistance also exists in subclinical hypothyroidism and is comparable to that of clinical hypothyroidism [19]. Recently, two studies, as well as a study by the authors' group showed that subclinical hyperthyroidism is also an insulin resistant state with a decrease in peripheral glucose uptake [11, 20, 21]. Thus, a possible hypothesis could be that there is a range in thyroid hormone values at which insulin sensitivity is optimal, and out of which metabolic disturbances may occur. The responsible mechanisms for the latter may be the same that apply in clinical hyperthyroidism, that is insulin resistance in the liver (increased gluconeogenesis) as well as in peripheral tissues (mainly skeletal muscle).

The associations that the authors found were highly significant. However, it should be pointed out that this study was cross sectional, and so its ability to infer causality is limited and the suggestion remains speculative.

In conclusion, it has been shown that, in the early stages of type 2 diabetes, increases in plasma thyroid hormone levels within the normal range are positively associated with indices of insulin resistance. These data suggest that, in the early stages of type 2 diabetes, thyroid hormones may contribute to the development of insulin resistance in both fasting and postprandial states.

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Conflict of interest The authors declare that "no financial conflict of interest exists".

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