

Effect of treatment of overt hypothyroidism on insulin resistance

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Abstract

AIM: To investigate the impact of hypothyroidism and thyroxine therapy on insulin sensitivity in patients with overt hypothyroidism.

METHODS: The study included twenty seven overtly hypothyroid and fifteen healthy euthyroid South Western Asian females. Both groups had matching age and body mass index. Physiological and pathological conditions as well as medications that may alter thyroid function, glucose homeostasis or serum lipids were ruled out. Serum thyrotropin (TSH), free tetraiodothyronine (FT4), free triiodothyronine (FT3), fasting insulin (FI), fasting plasma glucose (FPG), total cholesterol and triglycerides were measured before and six months after initiating thyroxine therapy for hypothyroid patients and once for the control group. Insulin resistance (IR) was estimated using homeostasis model assessment (HOMA-IR) and Body mass index (BMI) was calculated.

RESULTS: Both study groups, hypothyroid patients and euthyroid control subjects, had matching age and body mass index (P -value 0.444, 0.607 respectively). No significant difference was found between the hypothyroid patients and the euthyroid control group re-

garding fasting plasma glucose, fasting insulin, insulin resistance, total cholesterol and triglycerides (P -values 0.432, 0.621, 0.883, 0.586, 0.05 respectively). In the hypothyroid patients, triglycerides showed direct correlation to TSH and inverse correlation to FT3. Similarly total cholesterol inversely correlated to FT3 but its direct correlation to TSH did not reach statistical significance. After thyroxine replacement and reaching an euthyroid state as confirmed by clinical and laboratory data, there was no significant change in fasting plasma glucose, insulin resistance or triglyceride level (P -value 0.216, 0.204, 0.175 respectively) while total cholesterol significantly decreased (P -value 0.043) and fasting insulin significantly increased (P -value 0.047).

CONCLUSION: Hypothyroidism has no impact on insulin sensitivity. Correction of hypothyroidism is not associated with a significant change of insulin sensitivity or triglycerides, but with a significant reduction of total cholesterol.

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Key words: Hypothyroidism; Female; Thyroxine; Insulin resistance; Triglycerides; Cholesterol

Core tip: Thyroid dysfunction is the second most common endocrine disorder after diabetes mellitus. Both diseases are strong associated. Hypothyroidism is claimed to cause insulin resistance. Some available reports are in agreement and others are against this suggestion. In our study, we did not find a significant effect of hypothyroidism or thyroxine replacement on insulin resistance as calculated by insulin resistance was estimated using homeostasis model assessment. Thyroxine therapy leads to a significant reduction of total cholesterol but it does not change triglycerides. This may partially explain the association between hypothyroidism and dyslipidaemia as well as cardiovascular risk.

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INTRODUCTION

Thyroid dysfunction and diabetes mellitus (DM) are the two most common endocrine disorders. Both disorders appear to be closely linked^[1]. A recent meta-analysis that was conducted on available data in 10920 patients with DM revealed a mean frequency of thyroid disease of 11% with no difference between type 1 DM and type 2 DM. The prevalence in women was consistently more than two-folds that in men^[2].

It has also been postulated that insulin secretion is regulated by the thyroid hormone^[3,4] and diabetes risk is related to thyroid hormone levels^[5,6]. The initial event of glucose-stimulated insulin secretion is glucose sensing. The glucose transporter 2 (GLUT2) and glucokinase (GK) are key molecules which affect various processes of glucose sensing in pancreatic β -cells^[7]. Impairment in glucose sensing contributes to pancreatic β -cell dysfunction. Therefore, it is necessary to maintain adequate expression levels of GLUT2 and GK to ensure normal β -cell function^[8]. Triiodothyronine (T₃) can modulate the expression of GLUT2 and GK mRNAs and proteins in pancreatic islets^[9] and liver^[10].

To date, only a few studies have investigated the effect of hypothyroidism and its recovery by thyroid hormone treatment on glucose metabolism and lipid profile, and the results have been controversial. Some researchers elucidated lower insulin sensitivity in patients with overt hypothyroidism which improved after thyroxine treatment^[11,12]. Subclinical hypothyroidism was also encountered as a cause of insulin resistance and its related dyslipidaemia in patients with rheumatoid arthritis^[13]. Contrary to that, Brenta *et al*^[14] did not find significant differences in insulin sensitivity or lipid profile before and after thyroxine replacement in subclinical hypothyroidism.

In the light of existing data, we decided to study the impact of hypothyroidism on insulin sensitivity in overtly hypothyroid patients and to investigate the possible effect of thyroxine replacement on insulin sensitivity, triglycerides and total cholesterol in those populations.

MATERIALS AND METHODS

This study was approved by the Research and Ethics Committee of Asir Central Hospital and written informed consents were acquired from all participants.

Forty-two South Western Asian females were recruited from the endocrine clinic in a tertiary care hospital in southern region of Saudi Arabia, during January 2010 and December 2011. They included twenty seven patients with overt hypothyroidism and fifteen healthy euthyroid control women with matching age and body mass index

(BMI). Full history taking and clinical examination were done for all participants. The inclusion criteria were: adult, premenopausal females, who were newly diagnosed with overt hypothyroidism. Exclusion criteria were diabetes, polycystic ovarian disease, liver disorders, renal disorders, congestive cardiac failure or any other systemic illness. In addition, pregnancy and lactation, intake of oral contraceptive pills, statins and other medications that may alter thyroid functions, glucose homeostasis or serum lipids also accounted for exclusion from the study.

After an overnight fasting, blood samples were collected from all participants for measuring biochemical parameters. Thyroid profile (TSH, FT4 and FT3), fasting insulin, fasting plasma glucose, total cholesterol and triglycerides were measured, before and six months after initiating thyroxine therapy and reaching an euthyroid state for hypothyroid patients. These parameters were measured once for the euthyroid control group.

Insulin resistance (IR) was estimated using HOMA-IR, $IR = FPG \text{ in milli-gram per deciliter} \times FI \text{ in micro-international unit per milli-litre} / 405^{[15,16]}$. BMI was calculated by dividing weight of the patient in kilograms by square the height of the patient in meters^[17].

Thyroid profile and insulin level were estimated by Advia centaur auto-analyzer Siemens using chemiluminescent technology. Fasting plasma glucose and triglycerides were measured by bichromatic technique while cholesterol was measured by polychromatic technique. Normal ranges for all parameters: TSH: 0.27-4.2 μ IU/mL, FT4: 12-22 pmol/L, FT3: 3.9-6.8 pmol/L, FI: 2.6-37.6 μ IU/mL, total cholesterol: 50-200 mg/dL, triglycerides: 30-150 mg/dL^[18-22].

Statistical analysis

Collected data were analyzed using the Statistical Package for Social Sciences (SPSS ver. 19). Descriptive statistics (*i.e.*, mean and standard deviation) were applied. Pearson's Correlation Coefficients (*r*) between study variables were calculated. Significant *P*-values were considered at < 0.05 .

RESULTS

Our study population consisted of 42 females; 27 patients with overt hypothyroidism and 15 euthyroid healthy participants. The two groups had matching age and body mass index (33.12 ± 10.4 vs 35.67 ± 9.1 , $P = 0.44$, 31.11 ± 6.78 vs 32.24 ± 6.68 , $P = 0.61$ respectively). Fasting insulin, FPG, IR, total cholesterol and triglycerides did not show significant difference in hypothyroid patients as compared to the euthyroid group (*P*-values 0.432, 0.621, 0.883, 0.586, 0.05 respectively) as shown in Table 1.

In the hypothyroid state, Triglycerides directly correlated to TSH and inversely to FT3 (*P*-value 0.009, 0.001 respectively). Total cholesterol inversely correlated to FT3 (*P*-value 0.029) and was directly proportionate to TSH although this relation did not reach statistical significance (*P*-value = 0.327) as shown in Table 2.

Table 1 Laboratory and anthropometric parameters in hypothyroid patients versus euthyroid subjects

Parameter	Hypothyroid (mean \pm SD)	Euthyroid (mean \pm SD)	P-value
Age (yr)	33.2 \pm 10.4	35.7 \pm 9.1	0.444
BMI	31.1 \pm 6.8	32.2 \pm 6.7	0.607
TSH	22.4 \pm 36.2	2.9 \pm 1.5	0.010
FT4	11.2 \pm 4.0	13.7 \pm 2.1	0.013
FT3	4.4 \pm 1.0	4.5 \pm 0.5	0.557
FPG	93.5 \pm 14.7	89.8 \pm 13.9	0.432
FI	10.6 \pm 8.1	11.8 \pm 6.3	0.621
IR	2.5 \pm 2.1	2.6 \pm 1.5	0.883
TG	144.8 \pm 85.4	97.9 \pm 36.1	0.050
TCH	195.0 \pm 37.9	189.0 \pm 29.9	0.586

BMI: Body mass index; TSH: Thyrotropin; FPG: Fasting plasma glucose; FI: Fasting insulin; IR: Insulin resistance; FT4: Free tetraiodothyronine; FT3: Free triiodothyronine; TG: Triglycerides; TCH: Total cholesterol.

Table 2 Correlation between different variables before thyroxine replacement

		TSH	FT4	FT3
TG	<i>r</i>	0.496	-0.321	-0.585
	<i>P</i>	0.009	0.102	0.001
TCH	<i>r</i>	0.196	-0.176	-0.420
	<i>P</i>	0.327	0.380	0.029

TSH: Thyrotropin; FT4: Free tetraiodothyronine; FT3: Free triiodothyronine; TG: Triglycerides; TCH: Total cholesterol; R: Relative coefficient.

After thyroxine replacement and attaining euthyroid state, there was no significant change in FPG or IR as compared to that before starting treatment (P -value = 0.216, 0.204 respectively) while FI significantly increased (P = 0.047). There was no significant change in triglycerides (P -value 0.175) meanwhile total cholesterol significantly decreased (P -value 0.043) as shown in Table 3.

DISCUSSION

The association between hypothyroidism and diabetes mellitus had raised great interest in studying the mechanism of this association. Many studies targeted the influence of hypothyroidism on insulin sensitivity as the main underlying pathophysiology of this relation. Despite the many studies, results are conflicting with several studies reporting that hypothyroidism is a state of increased insulin resistance^[11,23].

In our study, there was no significant difference between the hypothyroid patients and the euthyroid healthy group regarding fasting insulin, FPG and insulin resistance. This is consistent with results of a study conducted by Giménez-Palop *et al*^[24] on 17 hypothyroid women compared to 20 euthyroid control women.

Similarly, Owecki *et al*^[25] did not find a significant difference in insulin sensitivity between hypothyroid patients and euthyroid participants.

Neither FPG nor insulin resistance as calculated by HOMA-IR significantly changed after thyroxine replace-

Table 3 Comparison between different variables before and after thyroxine replacement

Variable	Before treatment (mean \pm SD)	After treatment (mean \pm SD)	P-value
BMI	31.1 \pm 6.8	31.4 \pm 7.2	0.485
TSH	22.4 \pm 36.2	3.0 \pm 1.9	0.010
FT4	11.2 \pm 4.0	14.5 \pm 2.6	0.001
FT3	4.4 \pm 1.0	4.7 \pm 0.7	0.037
FPG	93.5 \pm 14.7	90.2 \pm 12.2	0.216
FI	10.6 \pm 8.1	13.6 \pm 7.3	0.047
IR	2.5 \pm 2.1	3.0 \pm 1.9	0.204
TG	144.8 \pm 85.4	128.1 \pm 64.8	0.175

BMI: Body mass index; TSH: Thyrotropin; FPG: Fasting plasma glucose; FI: Fasting insulin; IR: Insulin resistance; FT4: Free tetraiodothyronine; FT3: Free triiodothyronine; TG: Triglycerides; TCH: total cholesterol.

ment and reaching an euthyroid state as per clinical and laboratory evidence. There was a significant increase in the fasting insulin as compared to the pretreatment level but this was not statistically significant when compared to the euthyroid control (13.55 ± 7.25 vs 11.82 ± 6.31 , P = 0.445) and it did not affect the overall calculated insulin resistance. This is again in agreement with results demonstrated by Giménez-Palop *et al*^[26] although the increase in insulin levels in his study did not reach a statistical significance.

Referring to our study and studies in agreement with our findings, we can say that the association between hypothyroidism and T2DM may be attributed to a complex interplay^[26]. It may depend on the severity of hypothyroidism^[27]. There may be direct genetic links between thyroid diseases and T2DM as suggested by few studies. These studies suggest that homozygosity of polymorphism of the deiodinase type 2 (DIO2) gene, Thr92Ala is associated with an increased risk of T2DM^[28]. Thyroid hormones may also affect glucose and lipid homeostasis *via* central effects at the level of the hypothalamus^[29].

Hypothyroidism is known to be associated with normal or high levels of triglycerides^[30-32]. In our study, triglycerides in the hypothyroid patients did not differ significantly from the euthyroid control with direct proportion to TSH and inverse proportion to FT3^[33]. Triglycerides did not significantly change after thyroxine replacement. This is in agreement with reports of several studies, which showed that triglycerides might be normalized or remain unchanged after treatment, suggesting a more complex cause of dyslipidaemia in hypothyroidism^[34-43].

Total cholesterol inversely correlated to FT3 in the hypothyroid patients with a significant decrease after thyroxine therapy. This is consistent with results obtained by Melpomeni *et al* who found that restoration of an euthyroid state in hypothyroid patients was associated with a significant reduction in total cholesterol^[33,43]. Our findings are also consistent with those demonstrated in several other studies^[35,37-41,44].

The presence of some variations among different studies regarding the association between hypothyroidism and disturbed lipid profile may be explained by the variable effects of hypothyroidism on lipids according to the

severity of hypothyroidism in the studied groups of patients as evidenced by Sunanda *et al*^[45]. Sunanda *et al*^[45] studied the lipid profile in hypothyroid patients with different degrees of hypothyroidism and concluded that the effect of hypothyroidism on the serum lipids is more marked in patients with higher TSH levels.

So, the association between hypothyroidism and cardiovascular risk^[45,46] may be attributed to the dyslipidaemic effect of hypothyroidism, underlying genetic factor or there may be another complex underlying mechanism that deserves further studies.

In conclusion, our study suggests that hypothyroidism has no impact on insulin sensitivity in overtly hypothyroid females of South Western Asian ethnicity. Thyroxine therapy does not cause significant change in insulin sensitivity in this ethnic group. So, other mechanisms that may explain the strong association between hypothyroidism and T2DM may exist. Although total cholesterol and triglycerides are not significantly higher in hypothyroid patients, thyroxine treatment leads to a significant reduction in total cholesterol without a significant effect on triglycerides. This may partially explain the association between hypothyroidism and cardiovascular risk.

COMMENTS

Background

Diabetes mellitus and hypothyroidism are the most common endocrine disorders. A strong association between both conditions exists. It was claimed that hypothyroidism increases the risk of developing diabetes mellitus through increased insulin resistance but studies in this field demonstrated conflicting data.

Research frontiers

Recent evidences suggest that hypothyroidism is associated with dyslipidaemia and increased cardiovascular risk.

Innovations and breakthroughs

The results presented herein show that in South Western Asian females, neither overt hypothyroidism nor thyroxine replacement has an effect on insulin resistance. Thyroxine therapy leads to a significant reduction in total cholesterol.

Applications

The authors study indicates that the increased risk of diabetes mellitus in hypothyroid patients cannot be attributed to increased insulin resistance. So, investigating other mechanisms that may be involved is highly encouraged. Thyroxine therapy leads to a significant reduction in total cholesterol but it does not affect triglycerides. This partially explains the association between hypothyroidism and increased cardiovascular risk.

Peer review

This is an interesting article about the effect of overt hypothyroidism and thyroxine therapy on insulin resistance and lipid profile in a specific ethnic population.

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