Original Research Article

Prevalence of metabolic syndrome in euthyroid patients in Perambalur District

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Abstract

**Background:** Euthyroid diseases are frequently observed in clinical practice. They comprise both functional abnormalities such as overproduction and underproduction of thyroid hormone as a consequence of intrinsic thyroid diseases, as well as the development of structural abnormalities like goiter, adenoma or carcinoma. In community surveys, prevalence rates of elevated TSH levels – indicating impaired thyroid hormone secretion – range from 4–10% while prevalence rates of decreased TSH levels – indicating thyroid hormone overproduction – range from 0.7–1.5 %.

**Aim of this study:** To assess the thyroid function, in euthyroid subjects, is associated with components of the metabolic syndrome parameters.

**Materials and methods:** The study was conducted in the Department of Biochemistry at Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur District, Trichy. Total of 100 cases was included in the study homeostasis model assessment for insulin resistance (HOMA-IR) metabolic syndrome was defined according to the national cholesterol education program’s adult treatment panel III criteria.

**Results:** The T4 (FT4) was significantly associated with total cholesterol (standardized beta (β) = -0.059; P = 0.014), low-density lipoprotein cholesterol (β = -0.068; P = 0.004), high-density lipoprotein cholesterol (β = 0.100; P < 0.001), and triglycerides (β = -0.102; P < 0.001). Both FT4 and TSH were significantly associated with HOMA-IR (β = -0.133; P < 0.001 and β = 0.055; P = 0.024, respectively). Median HOMA-IR increased from 1.42 in the highest tertile of FT4 to 1.66 in the lowest tertile of FT4. FT4 was significantly related to four of five components of the metabolic syndrome (abdominal obesity, triglycerides, high-density lipoprotein cholesterol, and blood pressure), independent of insulin resistance.
Conclusions: We have demonstrated an association between FT4 levels within the normal reference range and lipids, in accordance with the earlier observed association between (sub) clinical hypothyroidism and hyperlipidemia. Moreover, low normal FT4 levels were significantly associated with.

Key words
Euthyroid patients, Dyslipidemia, Cardiovascular Disease, Insulin Resistance.

Introduction
The thyroid is an endocrine gland, found in the neck and producing thyroid hormones. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) strongly influence energy metabolism, temperature regulation, and body heat production. They also play an important role in skeletal muscle and cardiac contraction, memory, and sleep [1]. The synthesis of thyroid hormone is dependent on factors like the nutritional availability of iodine and is predominantly regulated by thyrotropin (thyroid stimulating hormone, TSH), a hormone secreted by the pituitary gland. Free synthesis and secretion of TSH are stimulated by hypothalamic TSH-releasing hormone (TRH) and inhibited through negative feedback by thyroid hormone itself [2]. Thyroid dysfunction, prominently subclinical hypothyroidism has been observed more frequently in metabolic syndrome patients than the general population. Both metabolic syndrome and hypothyroidism are independent risk factors for cardiovascular diseases (CVD) [3]. Presence of both conditions may be compounded to increase the risk for CVD and considerable overlap occurs in the pathogenic mechanisms of atherosclerotic cardiovascular disease by metabolic syndrome and hypothyroidism. There are reports about higher thyroid stimulating hormone (TSH) level in metabolic syndrome patients than in healthy ones, and high prevalence of metabolic syndrome in subjects with TSH level higher than normal as compared to those with normal TSH level. However, the association between thyroid dysfunction and components of metabolic syndrome is still debatable [4].

Materials and methods
The study was conducted in the Department of Biochemistry at Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, District, Trichy. Total of 100 cases was included in the study homeostasis model assessment for insulin resistance (HOMA-IR) metabolic syndrome was defined according to the national cholesterol education program’s adult treatment panel III criteria. Serum samples were stored at -20 °C until analysis. Serum TSH was assessed using a microparticle enzyme immunoassay FT4, FT3, and insulin concentrations were also assessed using a microparticle enzyme immunoassay. Serum TGs were measured enzymatically. Serum total cholesterol and plasma glucose were assessed using Kodak Ektachem dry chemistry HDL-C was measured with a homogenous method. In this assay system, HDL and apolipoprotein (Apo) B-containing lipoproteins are complexed with one reagent, followed by solubilizing HDL particles by another reagent. LDL-C was calculated using the Friedewald-formula and was used to determine serum Apo B and Apo A-I. The Apo B had been standardized against the reference standard, and Apo A-I was standardized against the IFCC SP1-01 standard.

Statistical analysis
Multiple linear regression models were performed for associations of thyroid function with serum lipid concentrations and with the various metabolic syndrome traits, with and without adjustment for age, sex, and HOMA-IR. TG, TSH, glucose, and insulin concentrations and HOMA-IR values were logs transformed to improve the fit of the linear regression models. $P < 0.05$ was considered statistically significant.
Results

Even in the euthyroid range, TSH was positively associated with HDL-C, TG, and Apo A-I. FT4 was negatively associated with total cholesterol, LDL-C, and TG. FT3 was negatively associated with total cholesterol, LDL-C, TG, and Apo B. There were significant positive correlations between age and serum total cholesterol \((r = 0.344; P < 0.001)\), LDL-C \((r = 0.339; P < 0.001)\), TG \((r = 0.237; P < 0.001)\), and Apo B \((r = 0.269; P < 0.001)\), and a significant negative correlation between age and HDL-C \((r = -0.100; P < 0.001)\). Total cholesterol, LDL-C, TG, and Apo B were significantly higher in men than women \((P < 0.01)\), and HDL-C and Apo A-I were significantly lower in men than women \((P < 0.01)\). After adjustment for age and sex, the relationships of TSH with TG and Apo A-I of FT4 with total cholesterol, LDL-C, and TG, and of FT3 With total cholesterol, LDL-C, and TG remained significant. The relationship of FT4 with both HDL-C and Apo B also became significant, whereas the relationship of TSH with HDL was no longer significant. Finally, further adjustment for obesity (adjustment for both BMI as a continuous variable and BMI > 30 kg/m²) did not significantly change any of the associations (Table – 1).

| Table – 1: Association of thyroid function with serum lipid concentrations and the components of the metabolic syndrome. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | HOMA-IR (tertile) |                  |                  |
|                                | Lowest (range 0.15–1.20) | Middle (range 1.21–2.05) | Highest (range 2.05–30.67) |
| Total cholesterol (mmol/L)     | 5.4 ± 1.1         | 5.6 ± 1.1         | 5.9 ± 1.2         | <0.001          |
| LDL-C (mmol/L)                 | 3.4 ± 1.0         | 3.7 ± 1.1         | 3.8 ± 1.1         | <0.001          |
| HDL-C (mmol/L)                 | 1.5 ± 0.4         | 1.4 ± 0.4         | 1.2 ± 0.3         | <0.001          |
| TG (median, mmol/L)            | 0.9 (0.7–1.2)     | 1.1 (0.8–1.5)     | 1.5 (1.1–2.2)     | <0.001          |
| Apo A-I (g/L)                  | 1.5 ± 0.3         | 1.4 ± 0.3         | 1.3 ± 0.3         | <0.001          |
| Apo B (g/L)                    | 0.9 ± 0.3         | 1.0 ± 0.3         | 1.1 ± 0.3         | <0.001          |
| Fasting glucose (median, mmol/L)| 4.0 (3.7–4.3)     | 4.4 (4.1–4.7)     | 4.9 (4.4–5.4)     | <0.001          |
| Fasting insulin (median, mU/L) | 4.8 (3.8–5.6)     | 8.0 (7.1–9.0)     | 14.1 (11.6–19.2)  | <0.001          |
| TSH (median, mIU/L)            | 1.34 (1.00–1.88)  | 1.35 (0.98–1.88)  | 1.44 (1.03–2.01)  | NS               |
| FT4 (pmol/L)                   | 13.0 ± 1.8        | 12.8 ± 1.7        | 12.6 ± 1.7        | <0.001          |
| FT3 (nmol/L)                   | 3.7 ± 0.7         | 3.7 ± 0.9         | 3.7 ± 0.7         | NS               |

Insulin resistance: Median HOMA index was 1.55 (interquartile range 1.03–2.42). We found a clear, negative relationship of HOMA index with FT4 \((β = -0.120; P < 0.001)\), independent of waist circumference. After adjustment for age and sex, this relationship remained significant \((β = -0.133; P < 0.001)\), whereas the relationship of HOMA index with TSH also became significant \((β = 0.055; P = 0.024)\). These associations did not significantly change after further adjustment for obesity. FT4 was significantly related to four of five of the metabolic syndrome traits (all but hypertension) when adjusted for age and sex. FT3 was significantly related to two and TSH only to one metabolic syndrome trait. When further adjusted for insulin resistance, associations of FT4 with waist, TG and HDL-C became slightly weaker but remained significant. In contrast, the relation of FT4 with systolic and diastolic BP became significant now. The relation of FT4 with fasting glucose was no longer significant after adjustment for insulin resistance. Finally, further adjustment for obesity with BMI as a continuous variable and separately...
with BMI as a dichotomized variable (BMI >30 kg/m²) did not materially change any of the associations presented except the association between FT4 and waist circumference, which lost significance.

Discussion
In this population-based study, we found a significant negative correlation between thyroid hormone levels (FT4 and FT3) and both total cholesterol, as well as the atherogenic LDL-C and it is Apo B within euthyroid subjects. The finding is consistent with the well-known association of (subclinical) hypothyroidism with elevated levels of total cholesterol and LDL-C [4]. Moreover, low normal FT4 levels were significantly associated with higher insulin resistance [5]. Finally, FT4 was significantly related to four of five metabolic syndrome traits. These findings might implicate that subjects with low normal thyroid function are already at increased cardiovascular risk [6]. To the best of our knowledge, this is the first community-based study that has investigated this association in subjects with normal thyroid function. It shows that the influence of thyroid function on lipid metabolism extends into the euthyroid range [7]. The pathophysiological process behind the influence of thyroid function on lipid metabolism is known from subjects with overt thyroid dysfunction. Hypercholesterolemia in hypothyroidism, characterized by elevated levels of LDL-C and Apo B, is caused by a decreased catabolism of LDL due to a reduction in the number of LDL receptors on liver cell surfaces [8]. It is the process is under the control of T3. Moreover, changes in plasma LDL-C in the transition from hypothyroidism or hyperthyroidism to euthyroidism were found to correlate with changes [9]. Our data showed that these pathophysiological mechanisms are already operative in the euthyroid state. Adjustment for age and sex changed several associations of thyroid function with lipids. We think that sex is a confounder in the association of TSH with HDL-C. The association of FT4 with HDL-C appeared to be significant after adjustment for age and sex, whereas its association with Apo A-I was not. Further adjustment for TG did not change the significant association of FT4 with HDL-C. Seemingly, the known effect of thyroid hormone on cholesteryl ester transfer protein mass and activity underlies the association, rather than an effect of TG [10]. The stronger association of FT4 with LDL-C after adjustment for age and sex is consistent with the finding that FT4 and Apo B were significantly associated after adjustment for age and sex. After further adjustment for insulin resistance, the association with Apo B was no longer significant [11]. It is generally hypothesized that the major underlying pathophysiological process is insulin resistance. In our study, we found an association of low normal FT4 with insulin resistance. This is consistent with our finding that low normal FT4 was associated with higher TG, lower HDL-C, and abdominal obesity [12]. However, these associations were independent of insulin resistance, indicating that other mechanisms than those associated with insulin resistance underlie the relation of FT4 with these components of the metabolic syndrome [13]. Our results indicate that, in the euthyroid range, FT4 and FT3 rather than TSH are related to cardiovascular risk factors [14]. Seemingly there is, at least in the euthyroid range, a discrepancy between effects that thyroid hormone has on peripheral tissues and the effect that the hormone has on central feedback inhibition of TSH release [15]. Polymorphisms in the TSH receptor have influenced ratios of plasma TSH and thyroid hormones, and can, therefore, also play a role in inducing a discrepancy between central and peripheral tissues. A limitation of this study is that it has a cross-sectional design, implicating that cause and effect relationships cannot be discerned [16].

Conclusion
In conclusion, we demonstrated that thyroid function and lipid levels are associated even in subjects classified as being euthyroid, thereby extending the established relation between (sub) clinical hypothyroidism and hyperlipidemia in
the normal range. Moreover, low normal FT4 levels were significantly associated with increased insulin resistance and with four of five metabolic syndrome traits. These findings are consistent with an increased cardiovascular risk in subjects with low normal thyroid function.

References