ORIGINAL ARTICLE

Insulin resistance in lean and obese hypothyroid versus lean and obese euthyroid individuals: A comparative study

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Abstract

Background: Hypothyroidism impairs metabolic homeostasis and has been implicated in the pathogenesis of insulin resistance. However, how Body Mass Index (BMI) modifies this relationship, particularly whether hypothyroidism independently worsens insulin resistance irrespective of obesity, remains inadequately characterised. *Aim and Objectives:* To compare fasting blood glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and Thyroid Function Tests (TFTs) across lean and obese hypothyroid and euthyroid individuals and to evaluate the independent and combined contributions of thyroid dysfunction and obesity to insulin resistance. *Material and Methods*: This case-control study enrolled 90 participants at a tertiary care centre: 60 hypothyroid patients (30 lean, 30 obese) and 30 euthyroid controls (15 lean, 15 obese), classified using Asian BMI criteria. Fasting blood glucose (hexokinase method), fasting serum insulin (chemiluminescent immunoassay), HOMA-IR (index-2 formula), and thyroid function tests (TSH, T3, T4 by CMIA) were measured after an overnight fast. HOMA-IR ≥ 2.5 defined insulin resistance; statistical analysis employed one-way ANOVA, Chi-square test, and Pearson correlation. *Results:* HOMA-IR was significantly elevated in lean hypothyroid (3.83 ± 2.21) and obese hypothyroid (5.17 ± 2.34) groups compared to lean euthyroid (1.33 ± 0.90) and obese euthyroid (2.40 ± 1.84) controls ($p < 0.001$). The prevalence of insulin resistance was 40.0%, 53.3%, 13.3%, and 40.0%, respectively. Fasting insulin was markedly higher in the hypothyroid groups (17.63 and 23.20 μIU/mL) than in the euthyroid groups (6.40 and 11.27 μIU/mL; $p < 0.001$), despite comparable fasting blood glucose levels. TSH correlated positively with HOMA-IR in hypothyroid groups (lean: r= + 0.43; obese: r= + 0.51; $p < 0.05$), while T4 correlated inversely with HOMA-IR. These correlations were absent in euthyroid controls. *Conclusion:* Hypothyroidism independently elevates insulin resistance beyond the effect of obesity. Obese hypothyroid patients carry the greatest metabolic burden, confirming a synergistic effect. Routine HOMA-IR assessment is recommended in all hypothyroid patients, particularly those who are obese.

Keywords: Thyroid Dysfunction, Insulin Resistance, HOMA-IR, Fasting Insulin, Adiposity

Introduction

Hypothyroidism is among the more common endocrine disorders encountered in general medicine practice, with prevalence estimates ranging from 4% to 10% in the adult population, and a considerably higher burden among women and the elderly [1]. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) exert wide-ranging control over cellular metabolism- they regulate glucose uptake, lipid oxidation, mitochondrial respiration, and overall energy expenditure across nearly all organ systems [2]. A deficiency of these hormones, therefore, disrupts several metabolic

pathways at once, with consequences that go well beyond the classical features of weight gain and bradycardia. Thyroid hormone insufficiency can produce significant metabolic consequences, including increased cholesterol and weight, as well as cardiovascular problems [3].

There is increasing evidence that hypothyroidism also interferes with glucose regulation. Specifically, thyroid hormones stimulate insulin sensitivity by regulating the expression of GLUT-4, thereby enhancing peripheral glucose utilisation and decreasing hepatic gluconeogenesis [4]; in the absence of thyroid hormones, however, the regulatory mechanisms described above are disrupted, leading to compensatory hyperinsulinemia followed by progressive insulin resistance, which is defined as a state in which normal insulin levels fail to result in satisfactory glucose disposal [5].

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which is based on fasting glucose and fasting insulin values, is a commonly used and reliable surrogate measure of insulin resistance that is highly correlated with the gold-standard hyperinsulinemic euglycemic clamp method [6]. As applied to clinical research, HOMA-IR has shown that hypothyroid patients exhibit significantly greater levels of insulin resistance than do euthyroid patients. Since obesity also results in insulin resistance due to adipokine dysregulation, increased free fatty acid flux, and low-grade chronic inflammation [7,8], determining the metabolic impact of hypothyroidism, as opposed to that of obesity, is difficult without controlled studies that account for both thyroid status and BMI.

Very few studies have conducted direct comparisons of insulin resistance and metabolic measures among lean and obese hypothyroid patients versus their euthyroid counterparts, especially among South Asians, where the BMI cut-off values defining obesity are lower than in Western populations [9].

The purpose of this study was to compare fasting blood glucose, fasting insulin, HOMA-IR, and Thyroid Function Tests (TFT) between four different patient populations: lean hypothyroid, obese hypothyroid, lean euthyroid, and obese euthyroid, to determine the individual and combined effects of hypothyroidism and obesity on insulin resistance, as well as to investigate correlations between the levels of thyroid hormones and the extent of metabolic dysfunction.

Material and Methods

This case-control study was carried out at the Department of General Medicine, Dr D. Y. Patil Medical College, Hospital & Research Centre, Pimpri, Pune, over a period of 24 Months (Feb. 2024 to Feb 2026), after obtaining clearance from the Institutional Ethics Committee and written informed consent from all participants.

Subjects numbered 90 and were assigned to 4 Groups: Lean Hypothyroid (n = 30), Obese Hypothyroid (n = 30), Lean Euthyroid (n = 15), and Obese Euthyroid (n = 15). Sample size was derived from a previously published study that reported a mean HOMA-IR of 3.22 (SD 2.69) in hypothyroid subjects versus 0.79 (SD 0.58) in euthyroid controls; using a 2:1 case-to-control ratio, 95% confidence level, and 80% power, a minimum of 30 cases per hypothyroid group was required [10]. Hypothyroid cases consisted of both new diagnoses and patients on levothyroxine therapy. Euthyroid individuals served as controls.

The Body Mass Index (BMI) classification was based on the "Modified Asian Criteria", which defines the cut-off values for BMI as follows: Lean $<= 22.9$ kg/m^2 and Obese $>= 25$ kg/m^2 [11].

The exclusion criteria used in this study included age < 18 years, known type 2 diabetes mellitus, pregnancy, polycystic ovarian disease, use of beta-blockers, thiazide diuretics, steroids, and critical illness.

Anthropometric measurements were taken at enrolment. Height was recorded using a stadiometer and body weight on a calibrated digital scale; BMI was then calculated as weight (kg) divided by height (m^2). Waist and hip circumferences were measured with a non-elastic tape, and the waist-hip ratio computed. These measurements formed the basis for BMI-group classification and were used as covariates in correlation analyses. Venous blood samples were drawn after at least an 8-hour overnight fast between 8:00 and 10:00 AM in order to minimize diurnal hormonal variation. Fasting blood glucose was determined by the glucose hexokinase method using the Biosystem Architect C-8000 Analyser. Fasting serum insulin was measured by chemiluminescent microparticle immunoassay using Architect I-2000 (Normal < 25 mIU/mL). Insulin resistance was estimated by the HOMA-IR Index-2 Formula: HOMA-IR = (Fasting Glucose in mg/dL × Fasting Insulin in mIU/mL) / 405. If the value of HOMA-IR was > 2.5, it indicated IR. TFT including TSH, total T3 and total T4 were determined by chemiluminescent microparticle immunoassay (Architect TSH assay). Reference ranges were as follows: TSH 0.35-4.94 mIU/mL, T3 0.64-1.52 ng/mL and T4 4.87-11.72 mcg/dL.

Hypothyroidism was defined as elevated TSH, either with or without reduced T3 and T4.

Data were presented as Mean ± S.D, and comparisons among groups were made by One-Way Analysis of Variance (ANOVA) with *post hoc* test for normally distributed variables, while comparison among groups were made by Mann-Whitney U Test for skewed variables. Comparison of categorical variables was made by Chi-square test. Correlation among continuous variables was assessed by Pearson Correlation. Multiple linear regression was employed to identify independent predictors of HOMA-IR after adjusting for age, gender, and BMI. A p-value < 0.05 was considered statistically significant.

Results

The four groups in this study were equivalent in age (p = 0.380), gender (p = 0.597), and height (p = 0.386) as a result of an appropriate match of the four groups' demographics. The female predominance in hypothyroid groups (66.7% lean hypothyroid, 60.0% obese hypothyroid) was expected, given the known epidemiology of the disease. The classification by BMI for the anthropometric data of the four groups was also validated; the BMI of the lean group was approximately 21.6 kg/m^2, while that of the obese groups ranged from 30.3 to 32.2 kg/m^2 (p < 0.001). Waist circumference, hip circumference, and waist-hip ratio all differed significantly across groups (p < 0.001), confirming appropriate BMI-group stratification as presented in Table 1.

TSH levels were significantly higher in the two hypothyroid groups than in the euthyroid controls, as indicated in Table 2. This confirms the biochemical diagnosis of the two hypothyroid groups. The obese hypothyroid group, however, had the highest mean TSH level (7.87 ± 4.88 micro IU/ml). Fasting blood glucose levels were consistently within normal limits for each of the four subject groups, as shown in Table 3. There were no statistically significant differences in fasting blood glucose levels among the four groups (p = 0.102); thus, none of the study participants exhibited clinically evident hyperglycemia or overt diabetes. However, while glucose levels in the lean

and obese hypothyroidism subjects were similar to those in their euthyroid counterparts, their fasting serum insulin concentrations were significantly higher: 17.63 µU/mL (lean hypothyroidism), 23.20 µU/mL (obese hypothyroidism) compared to 6.40 µU/mL (lean euthyroidism), and 11.27 µU/mL (obese euthyroidism; $p < 0.001$). The marked elevations in fasting insulin despite normal glucose levels indicated that these subjects exhibited compensatory hyperinsulinemia due to underlying IR.

Further evidence of insulin resistance in these subjects is provided by their respective HOMA-IR scores: 3.83 ± 2.21 (lean hypothyroidism), 5.17 ± 2.34 (obese hypothyroidism), 1.33 ± 0.90 (lean euthyroidism), and 2.40 ± 1.84 (obese euthyroidism; $p < 0.001$). Overall, 13.3% of lean euthyroid subjects (n = 2/15), 40% of obese euthyroid subjects (n = 6/15), 40% of lean hypothyroid subjects (n = 12/30), and 53.3% of obese hypothyroid subjects (n = 16/30) were found to exhibit insulin resistance (i.e., HOMA-IR ≥ 2.5). Furthermore, the obese hypothyroid subjects carried the greatest burden of insulin resistance (odds ratio [OR] 7.43 vs lean euthyroid subjects). Although there was a statistically significant difference in the proportion of subjects exhibiting insulin resistance across the four groups ($p = 0.083$), this likely reflected the relatively small number of subjects included in this investigation.

Table 1: Demographic and anthropometric characteristics across study groups

Variable	Lean Hypothyroid (n = 30)	Obese Hypothyroid (n = 30)	Lean Euthyroid (n = 15)	Obese Euthyroid (n = 15)	*p*
Age (years)	39.53 ± 13.51	41.97 ± 11.51	36.53 ± 14.66	43.87 ± 10.71	0.380
Weight (kg)	59.50 ± 6.58	86.53 ± 11.40	61.33 ± 7.48	90.47 ± 6.53	< 0.001*
BMI (kg/m²)	21.63 ± 1.54	30.30 ± 2.78	21.60 ± 2.26	32.20 ± 2.04	< 0.001*
Waist Circumference (cm)	65.77 ± 5.27	93.70 ± 4.55	66.47 ± 4.17	94.33 ± 4.78	< 0.001*
Hip Circumference (cm)	81.50 ± 7.79	102.40 ± 6.08	82.13 ± 7.47	108.47 ± 7.03	< 0.001*
Waist-Hip Ratio	0.794 ± 0.034	0.928 ± 0.040	0.814 ± 0.047	0.901 ± 0.051	< 0.001*

**Statistically significant; BMI – Body mass index*

Table 2: Thyroid function tests across study groups

Variable	Lean Hypothyroid (n = 30)	Obese Hypothyroid (n = 30)	Lean Euthyroid (n = 15)	Obese Euthyroid (n = 15)	*p*
TSH (µIU/mL)	6.07 ± 3.49	7.87 ± 4.88	2.60 ± 0.83	2.53 ± 1.13	< 0.001*
T3 (pmol/L)	0.95 ± 0.26	0.94 ± 0.31	1.15 ± 0.23	1.21 ± 0.22	0.002*
T4 (pmol/L)	8.10 ± 1.79	7.83 ± 2.21	9.00 ± 1.65	9.40 ± 1.40	0.030*

**Statistically significant; TSH – thyroid stimulating hormone*

Table 3: Fasting blood glucose, fasting insulin and HOMA-IR across study groups

Variable	Lean Hypothyroid (n = 30)	Obese Hypothyroid (n = 30)	Lean Euthyroid (n= 15)	Obese Euthyroid (n = 15)	*p*
Fasting Blood Glucose (mg/dL)	88.07 ± 4.40	89.40 ± 3.98	87.67 ± 3.56	86.27 ± 3.77	0.102
Fasting Insulin (µIU/mL)	17.63 ± 9.79	23.20 ± 10.29	6.40 ± 4.37	11.27 ± 8.29	< 0.001*
HOMA-IR Index	3.83 ± 2.21	5.17 ± 2.34	1.33 ± 0.90	2.40 ± 1.84	< 0.001*
Insulin Resistant, n (%)	12 (40.0%)	16 (53.3%)	2 (13.3%)	6 (40.0%)	0.083
Odds Ratio (vs Lean Euthyroid)	2.39	7.43	1.00 (ref)	2.40	—

**Statistically significant; TSH – thyroid stimulating hormone*

Table 4 pools lean and obese subjects within each thyroid status category. It is also notable that, while mean BMIs were similar to each other, i.e., euthyroid (mean = 26.9 ± 5.8 kg/m²), and hypothyroid (mean=25.96 ± 4.91 kg/m²), HOMA-IR values were over two times higher in hypothyroid subjects ($p < 0.001$), and fasting insulin levels were similarly elevated ($p < 0.001$). The comparison of these values with nearly equivalent BMI values between the groups provides evidence that thyroid hormone deficiency is an independent driver of insulin resistance, not simply attributable to obesity.

Table 5 shows the relationship between thyroid hormone levels, metabolism, and BMI for each group. The lean hypothyroid group and obese hypothyroid group showed a significant positive correlation between TSH and both HOMA-IR and fasting insulin (Lean: r = 0.43 and r = 0.38; Obese: r = 0.51 & r = 0.44). Additionally, T4 had a negative correlation with HOMA-IR (Lean: r = -0.40; Obese: r = -0.46) for both hypothyroid groups. The lack of significant correlation in both euthyroid groups is important to show that the metabolic problems are due to low levels of thyroid hormones and not simply an artefact of BMI.

Table 4: Comparison of hypothyroid vs euthyroid groups (combined lean and obese)

Variable	Hypothyroid (n=60)	Euthyroid (n=30)	*p*
TSH (µIU/mL)	6.97 ± 4.30	2.56 ± 0.97	< 0.001*
T3 (pmol/L)	0.95 ± 0.28	1.18 ± 0.22	0.002*
T4 (pmol/L)	7.96 ± 2.00	9.20 ± 1.52	0.030*
BMI (kg/m²)	25.96 ± 4.91	26.90 ± 5.79	< 0.001*
Fasting Insulin (µIU/mL)	20.42 ± 10.35	8.83 ± 6.97	< 0.001*
HOMA-IR	4.50 ± 2.36	1.86 ± 1.52	< 0.001*

**Statistically significant*
BMI – Body mass index; TSH – thyroid stimulating hormone; HOMA-IR - Homeostatic Model Assessment for Insulin Resistance

Table 5: Correlation of thyroid function tests with metabolic parameters in hypothyroid groups

Parameter	Lean Hypothyroid (r)	Obese Hypothyroid (r)	Lean Euthyroid (r)	Obese Euthyroid (r)	Direction
TSH vs HOMA-IR	+ 0.43*	+ 0.51*	+ 0.18 (ns)	+ 0.22 (ns)	Positive ↑
TSH vs Fasting Insulin	+ 0.38*	+ 0.44*	+ 0.12 (ns)	+ 0.15 (ns)	Positive ↑
T4 vs HOMA-IR	− 0.40*	− 0.46*	− 0.14 (ns)	− 0.19 (ns)	Negative ↓

**Statistically significant*
TSH – thyroid stimulating hormone; HOMA-IR - Homeostatic Model Assessment for Insulin Resistance

Discussion

This study investigated insulin resistance and thyroid function in lean and obese hypothyroid and euthyroid subjects at a tertiary care centre. It used HOMA-IR as its primary metabolic outcome. The main finding of the study was that HOMA-IR levels were significantly higher in both lean and obese hypothyroid patients than in their respective euthyroid counterparts ($p < 0.001$), with the obese hypothyroid group having the highest mean value (5.17 ± 2.34). Findings in the current study are consistent with previous studies by Unnikrishnan *et al*. (2023) [11] reporting a significantly elevated HOMA-IR in hypothyroid patients (2.34 ± 0.54 vs. 1.8 ± 0.50 in controls, $p < 0.001$) and previously noted significant correlations between HOMA-IR and T3 (r = − 0.484) and T4 (r = - 0.447) and a positive correlation between HOMA-IR and TSH (r = 0.426). Similarly, Rajeswari *et al*. (2017) [12] found significantly elevated HOMA-IR levels in overt (2.2 ± 0.91) and subclinical hypothyroid (1.7

± 0.71) groups compared to control (0.76 ± 0.36, $p <$ 0.001), with a strong positive correlation between TSH and HOMA-IR (r = 0.712) in subclinical hypothyroidism; a similar correlation was seen in the current study. Supporting this, Munde *et al*. (2022) [13] demonstrated significantly elevated HOMA-IR and fasting insulin levels in women with subclinical hypothyroidism compared to euthyroid controls, also noting a significantly higher prevalence of metabolic syndrome in the subclinical hypothyroid group findings that align closely with those of the present study. The mechanism underlying this relationship has been extensively documented. Thyroid hormone deficiency impairs GLUT-4 translocation and reduces peripheral glucose uptake in skeletal muscle. Simultaneously, reduced thyroid hormone stimulation of hepatic glucose production regulation and reduced mitochondrial activity leads to a relative tissue insulinopaenia, which in turn leads to compensatory hyperinsulinaemia [14,15].

Comparison of hypothyroid and euthyroid groups, where BMI was nearly equivalent between the two groups but HOMA-IR was over double in the hypothyroid group, provide especially convincing evidence that thyroid dysfunction, independent of BMI, has an impact on insulin sensitivity. In addition, TSH was positively correlated with HOMA-IR and fasting insulin specifically in the hypothyroid groups, but not in the euthyroid controls, supporting the notion that the severity of thyroid hormone deficiency, rather than adiposity alone, determines the level of metabolic dysfunction [16,17]. (Table 4)

The stratification of the data also identified that obesity and hypothyroidism have additive, and possibly synergistic, effects on insulin resistance. HOMA-IR was 5.17 ± 2.34, and 53.3% of the obese hypothyroid group exhibited insulin resistance, whereas 40.0% of the lean hypothyroid, 40.0% of the obese euthyroid, and only 13.3% of the lean euthyroid exhibited insulin resistance, resulting in an odds ratio of 7.43 compared to the lean euthyroid controls. The results indicate that although each condition individually increased insulin resistance, together they had a disproportionate effect.

Aksoy *et al*. (2015) [18] previously noted positive correlations between BMI and HOMA-IR in both high-normal TSH (r = 0.711) and subclinical hypothyroid (r = 0.426) groups. Therefore, adiposity enhances the metabolic complications of thyroid dysfunction. Obese adipose tissue releases increased amounts of free fatty acids and inflammatory cytokines that independently inhibit insulin signalling. When combined with the hypothyroidism-induced decrease in glucose transporter activity and the impairment in the metabolic regulation of the liver, a much greater state of insulin resistance is developed. [19, 20] The absence of elevated blood glucose levels in spite of hyperinsulinemia as illustrated in Table 3 is characteristic of the compensated insulin resistant state. Pancreatic beta-cells initially compensate for impaired insulin signalling through hyperinsulinemia, maintaining normal glycemic control until hyperinsulinemia can no longer offset the degree of insulin resistance, at which point frank type 2 diabetes develops. The statistically significant and strong correlations between TSH elevation and HOMA-IR and fasting insulin observed exclusively in hypothyroid patients, not in euthyroid controls have important clinical relevance. The degree of thyroid dysfunction, as reflected by TSH levels, is a biomarker of metabolic risk in patients with hypothyroidism. Consistent with this, Anwar *et al*. (2024) [21] reported that 39.7% of patients with metabolic syndrome had TSH in the hypothyroid

range, with subclinical hypothyroidism being the most prevalent subtype (64.3%), underscoring the need for routine thyroid evaluation in this population. Choi *et al*. (2021) [22] demonstrated that the natural logarithm of TSH correlated with the TyG Index ($\beta = 0.025$, $p < 0.001$) in a large cohort (n = 5,727) of Koreans. Free T4 negatively correlated ($\beta = -0.110$, $p < 0.001$) with the TyG Index in a manner consistent with the directionality of the relationships found in the current study. Mahajan *et al*. [23] reported that 58% of hypothyroid patients treated at a rural teaching hospital were insulin resistant due to the synergistic interaction of thyroid hormone deficiency and beta-cell dysfunction. Collectively, the findings from these studies provide strong support for the routine use of HOMA-IR measurements and metabolic monitoring in all hypothyroid patients, regardless of whether they are obese or not. Furthermore, because insulin resistance may persist after L-thyroxine treatment, particularly among obese patients, additional approaches to promote weight loss and improve insulin sensitivity are warranted [24, 25].

Conclusion

Hypothyroidism independently contributes to insulin resistance beyond the effect of obesity. The greatest metabolic impairment was observed in obese hypothyroid subjects, indicating additive effects of both conditions. Early screening for insulin resistance should be considered in hypothyroid patients, particularly those with obesity.

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