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Assessment of Insulin Resistance and Metabolic Syndrome in Patients with Hypothyroidism: A Case–Control Study at Baquba Teaching Hospital, Diyala, Iraq

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Abstract

Background: Thyroid hormones are key regulators of glucose and lipid metabolism, and hypothyroidism has been linked to insulin resistance and to individual components of the metabolic syndrome. Data from Diyala Governorate, Iraq, are lacking.
Objective: To assess insulin resistance and the prevalence of metabolic syndrome in adults with overt and subclinical hypothyroidism compared with euthyroid controls attending Baquba Teaching Hospital.
Methods: In this hospital-based case–control study (November 2025 to May 2026), 50 patients with untreated overt hypothyroidism, 50 with untreated subclinical hypothyroidism and 50 age- and sex-matched euthyroid controls were enrolled. Anthropometric measures, blood pressure, fasting plasma glucose, fasting insulin, lipid profile, TSH, free T4, free T3 and anti-thyroid peroxidase antibodies were measured. Insulin resistance was assessed with HOMA-IR, QUICKI and the triglyceride–glucose (TyG) index, and metabolic syndrome was defined according to the 2009 harmonized criteria.
Results: Mean HOMA-IR was 4.31 ± 1.82 in overt hypothyroidism, 3.36 ± 1.49 in subclinical hypothyroidism and 1.95 ± 0.88 in controls ($p < 0.001$); insulin resistance (HOMA-IR ≥ 2.5) was present in 78%, 64% and 18%, respectively. QUICKI was lower and the TyG index higher in both patient groups. Metabolic syndrome was identified in 52%, 38% and 18% of the three groups ($p = 0.002$). Among patients, TSH correlated positively ($r = 0.42$) and free T4 inversely ($r = −0.36$) with HOMA-IR. HOMA-IR (adjusted OR 1.89; 95% CI 1.31–2.73), TSH and BMI were independent predictors of metabolic syndrome.
Conclusion: Both overt and subclinical hypothyroidism are associated with significant insulin resistance and a higher prevalence of metabolic syndrome, with a gradient related to the severity of thyroid failure. Routine cardiometabolic screening of hypothyroid patients is recommended.

Keywords:

Hypothyroidism; Subclinical hypothyroidism; Insulin resistance; HOMA-IR; Triglyceride–glucose index; Metabolic syndrome; Iraq.

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Introduction

Hypothyroidism is one of the most frequently encountered endocrine disorders in clinical practice. It represents a state of deficient thyroid hormone action at the tissue level and, in the great majority of adults, results from primary failure of the thyroid gland. Its clinical spectrum extends from overt disease, defined by an elevated serum thyroid-stimulating hormone (TSH) concentration together with a reduced free thyroxine (FT4), to subclinical hypothyroidism, in which TSH is raised while FT4 remains within the laboratory reference range [1]. Population surveys suggest that overt hypothyroidism affects approximately 0.2% to 5.3% of people in Europe and 0.3% to 3.7% in the United States, the exact figures depending on diagnostic thresholds, iodine nutrition, age structure and ethnicity [2]. In the Third National Health and Nutrition Examination Survey (NHANES III), hypothyroidism was identified in 4.6% of the United States population, most cases being subclinical [3], while the Colorado Thyroid Disease Prevalence Study found a raised TSH in 9.5% of more than 25,000 adults, many of whom were unaware of any thyroid problem [4]. Women are affected several times more often than men, and the prevalence rises steadily with age. In iodine-sufficient regions chronic autoimmune (Hashimoto) thyroiditis is the leading cause, whereas iodine deficiency remains an important contributor in many parts of the world.

The importance of hypothyroidism extends well beyond its classical symptoms of fatigue, cold intolerance, weight gain and constipation. Triiodothyronine (T3), acting mainly through the nuclear thyroid hormone receptors α and β, regulates the transcription of a wide range of genes that control basal metabolic rate, adaptive thermogenesis, hepatic gluconeogenesis, de novo lipogenesis, lipolysis and cholesterol handling [5]. Through these actions, thyroid hormone acts as a central integrator of energy expenditure and substrate use in liver, skeletal muscle, adipose tissue and the cardiovascular system. Consequently, a deficiency of thyroid hormone, even when mild, has the potential to disturb glucose and lipid homeostasis and to alter vascular function. Subclinical hypothyroidism, which is far more common than overt disease, has attracted particular attention because it is frequently asymptomatic, often goes undiagnosed, and may nevertheless carry measurable metabolic and cardiovascular consequences [6].

Insulin resistance is defined as a reduced biological response of target tissues, chiefly skeletal muscle, liver and adipose tissue, to a given concentration of insulin. In his landmark Banting lecture, Reaven proposed that resistance to insulin-stimulated glucose uptake, together with compensatory hyperinsulinaemia, is the common soil from which glucose intolerance, hypertriglyceridaemia, low high-density lipoprotein cholesterol (HDL-C) and hypertension arise [7]. Although the hyperinsulinaemic–euglycaemic clamp remains the reference method for measuring insulin sensitivity, it is invasive, expensive and impractical for routine use. Several simple surrogate indices derived from fasting measurements have therefore been validated. The homeostasis model assessment of insulin resistance (HOMA-IR), calculated from fasting glucose and insulin, correlates well with clamp-derived estimates and is the most widely used index in clinical research [8]. The quantitative insulin sensitivity check index (QUICKI), a logarithmic transformation of the same variables, shows an even closer linear correlation with the clamp across a broad range of insulin sensitivity [9]. More recently, the triglyceride–glucose (TyG) index, which requires no insulin assay, has been proposed as a reliable and inexpensive surrogate for identifying insulin resistance in apparently healthy subjects [10].

Metabolic syndrome describes the clustering in one individual of central obesity, atherogenic dyslipidaemia, raised blood pressure and dysglycaemia, a combination that substantially increases the risk of type 2 diabetes mellitus and atherosclerotic cardiovascular disease [11]. Because several competing definitions had generated confusion, a joint interim statement from the International Diabetes Federation, the National Heart, Lung, and Blood Institute, the American Heart Association and other organizations harmonized the criteria in 2009; under this definition, metabolic syndrome is diagnosed when any three of five risk factors are present, with population-specific waist circumference thresholds [12]. It is estimated that about one quarter of the world's adult population has metabolic syndrome, and its prevalence continues to rise in parallel with urbanization, sedentary lifestyles and the global epidemic of obesity [13]. Countries of the Middle East, including Iraq, have experienced rapid nutritional and lifestyle transitions in recent decades, and the burden of obesity, diabetes and cardiovascular disease in the region is correspondingly high.

A growing body of evidence indicates that hypothyroidism is itself a state of insulin resistance. Using the hyperinsulinaemic–euglycaemic clamp, Rochon and colleagues demonstrated that insulin-stimulated glucose disposal is impaired in hypothyroid patients [14]. Dimitriadis et al. subsequently showed, by direct measurement of forearm and adipose tissue glucose uptake after a mixed meal, that hypothyroidism reduces the action of insulin on peripheral tissues, an effect attributed partly to decreased insulin-stimulated blood flow and partly to impaired translocation of the glucose transporter GLUT4 to the cell membrane [15]. Importantly, Maratou and co-workers found that insulin resistance is present not only in overt but also in subclinical hypothyroidism, suggesting that even modest reductions in thyroid hormone action can impair insulin signalling in muscle and adipose tissue [16]. Several mechanisms have been proposed to explain this association, including reduced expression and translocation of GLUT4, altered activity of key glycolytic and oxidative enzymes, changes in adipokine secretion, low-grade inflammation and endothelial dysfunction [17]. Hypothyroidism also alters hepatic glucose output, insulin clearance and pancreatic beta-cell function, and the bidirectional relationship between thyroid dysfunction and diabetes mellitus is now well recognized [18].

Hypothyroidism also influences other components of the metabolic syndrome. Reduced thyroid hormone action down-regulates hepatic low-density lipoprotein (LDL) receptor expression and decreases the activity of cholesterol ester transfer protein and hepatic lipase, leading to elevated total cholesterol, LDL cholesterol and, in many patients, triglycerides [19]. These lipid abnormalities are well documented in overt disease and are increasingly described, although less consistently, in subclinical hypothyroidism [20]. Hypothyroidism is further associated with increased systemic vascular resistance, arterial stiffness and diastolic hypertension, which, together with dyslipidaemia, may accelerate atherosclerosis [21]. At the population level, even small differences in TSH within the reference range have been associated with higher body mass index and a greater likelihood of obesity [22], as well as with higher systolic and diastolic blood pressure [23].

Epidemiological studies examining the relationship between thyroid function and metabolic syndrome have nevertheless produced heterogeneous results. In euthyroid Dutch adults, lower FT4 concentrations within the normal range were associated with greater insulin resistance and with several components of the metabolic syndrome [24], and Fernández-Real et al. reported that thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects [25]. In patients with type 2 diabetes,

interactions between thyroid function, insulin sensitivity and serum lipids have also been described [26]. Uzunlulu et al. found a higher prevalence of subclinical hypothyroidism in Turkish patients with metabolic syndrome than in controls [27], and Ruhla et al. observed that high-normal TSH concentrations were associated with metabolic syndrome in German adults [28]. In contrast, in the Health, Ageing and Body Composition Study of older adults, subclinical hypothyroidism was not consistently associated with prevalent or incident metabolic syndrome [29], and in a large Taiwanese cohort the association was confined to particular subgroups [30]. Such discrepancies probably reflect differences in age, sex distribution, iodine status, ethnicity, the definition of metabolic syndrome and the severity of thyroid dysfunction among study populations [31].

The clinical relevance of these associations is underlined by data on cardiovascular outcomes. An individual participant data meta-analysis of prospective cohorts showed that subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and mortality, particularly when TSH is 10 mIU/L or higher [32], and a reanalysis of the Whickham Survey cohort reported a higher incidence of ischaemic heart disease in untreated subclinical hypothyroidism [33]. Insulin resistance and metabolic syndrome may represent important intermediate pathways in this relationship. Current guidelines recommend levothyroxine replacement for overt hypothyroidism, whereas the decision to treat subclinical hypothyroidism depends on the TSH level, age, symptoms and cardiovascular risk profile [34,35]. Information on the metabolic profile of hypothyroid patients may therefore help clinicians to identify those who would benefit most from closer monitoring, lifestyle intervention or earlier treatment.

Most of the available data on insulin resistance in hypothyroidism originate from Europe, North America and East Asia. Studies from South Asia have reported higher HOMA-IR values in hypothyroid patients than in euthyroid controls [36,37], and a limited number of Iraqi studies have examined insulin resistance markers in hypothyroid patients from central and southern Iraq [38]. However, to the best of our knowledge, no study has assessed insulin resistance and metabolic syndrome in patients with hypothyroidism in Diyala Governorate, where nutritional habits, physical activity patterns and the prevalence of obesity may differ from those in other populations. Baquba Teaching Hospital is the main tertiary referral centre of the governorate and serves a large population with a substantial burden of thyroid disease. The present study was therefore designed to assess insulin resistance, using HOMA-IR, QUICKI and the TyG index, and to determine the prevalence of metabolic syndrome and its components in adult patients with overt and subclinical hypothyroidism compared with euthyroid controls attending Baquba Teaching Hospital, and to examine the relationship of thyroid function parameters with these metabolic abnormalities.

Methodology

This hospital-based, cross-sectional comparative (case–control) study was carried out at the endocrine outpatient clinic and the Department of Internal Medicine of Baquba Teaching Hospital, Diyala Governorate, Iraq, between November 2025 and May 2026. Baquba Teaching Hospital is the principal tertiary referral centre in the governorate and receives patients from urban and rural districts, which made it a suitable setting for recruiting a representative sample of adults with thyroid disease. The study protocol was reviewed and approved by the Scientific and Ethics Committee of the Diyala Health Directorate , and all procedures were performed in accordance with the Declaration of Helsinki. Each participant received a verbal and written

explanation of the aims and procedures of the study and provided written informed consent before enrolment. Participation was voluntary, participants were free to withdraw at any time without any effect on their medical care, and confidentiality was ensured by replacing personal identifiers with numerical codes.

The sample size was estimated on the basis of the expected difference in mean HOMA-IR between hypothyroid patients and euthyroid controls reported in previous studies. Assuming a mean difference of 0.8 with a standard deviation of 1.3, a two-sided significance level of 0.05 and a power of 80%, a minimum of 42 participants per group was required; this number was increased to 50 per group to allow for incomplete data. A total of 150 adults aged 18 to 65 years were therefore enrolled and allocated to three groups. The first group comprised 50 patients with newly diagnosed or untreated overt primary hypothyroidism, defined as a serum TSH above 4.5 mIU/L with an FT4 below 0.8 ng/dL. The second group comprised 50 patients with untreated subclinical hypothyroidism, defined as a serum TSH above 4.5 mIU/L with an FT4 within the reference range (0.8–1.8 ng/dL) on two measurements at least six weeks apart. The third group comprised 50 euthyroid controls with TSH between 0.4 and 4.5 mIU/L and normal FT4, recruited from relatives of patients, hospital staff and individuals attending the hospital for routine check-ups unrelated to endocrine disease. Controls were frequency-matched to the patient groups for age (within five years) and sex. Patients were recruited consecutively as they attended the clinic until the required number in each group was reached.

Participants were excluded if they had received levothyroxine, antithyroid drugs or any other thyroid medication within the previous six months, or had a history of thyroid surgery or radioactive iodine therapy. Further exclusion criteria were known diabetes mellitus or a fasting plasma glucose of 126 mg/dL or higher at screening; current use of medications known to affect glucose or lipid metabolism, including corticosteroids, statins, fibrates, thiazide diuretics, beta-blockers, oral contraceptives, amiodarone and lithium; pregnancy or lactation; polycystic ovary syndrome; chronic kidney disease; chronic liver disease; heart failure; malignancy; acute illness or hospitalisation within the preceding month; and central (secondary) hypothyroidism. Patients receiving antihypertensive drugs other than beta-blockers and thiazides were included, and their treatment was taken into account in the definition of raised blood pressure.

All participants were interviewed by a trained physician using a structured questionnaire that recorded age, sex, residence, smoking status, physical activity, duration of symptoms, family history of thyroid disease, diabetes and cardiovascular disease, and current medications. A full clinical examination was then performed. Body weight was measured to the nearest 0.1 kg with participants wearing light clothing and no shoes, using a calibrated digital scale, and height was measured to the nearest 0.5 cm using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Waist circumference was measured to the nearest 0.5 cm with a non-stretchable tape placed horizontally at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, at the end of a normal expiration. Blood pressure was measured on the right arm in the sitting position after at least five minutes of rest, using a calibrated mercury sphygmomanometer and an appropriately sized cuff; two readings were taken five minutes apart, and their mean was used in the analysis.

After an overnight fast of 10 to 12 hours, 5 mL of venous blood was drawn from each participant between 8:00 and 9:30 a.m. Samples were allowed to clot, then centrifuged at 3000 rpm for 10 minutes, and serum was separated within 30 minutes of collection. Fasting plasma glucose was measured on the same day by the enzymatic glucose oxidase method, and total

cholesterol, triglycerides and HDL-C were measured by enzymatic colorimetric methods on an automated chemistry analyser. LDL cholesterol was calculated using the Friedewald formula in all participants, since no sample had a triglyceride concentration above 400 mg/dL. Aliquots for hormonal assays were stored at −20 °C and analysed in batches. Serum TSH, FT4, free triiodothyronine (FT3), fasting insulin and anti-thyroid peroxidase antibodies (anti-TPO) were measured by electrochemiluminescence immunoassay on an automated immunoassay analyser (Cobas e411, Roche Diagnostics, Germany). The laboratory reference ranges were 0.4–4.5 mIU/L for TSH, 0.8–1.8 ng/dL for FT4 and 2.0–4.4 pg/mL for FT3, and an anti-TPO concentration above 34 IU/mL was considered positive. All analyses were performed in the central laboratory of Baquba Teaching Hospital under routine internal quality control procedures.

Insulin resistance was assessed using three surrogate indices. HOMA-IR was calculated as fasting plasma glucose (mg/dL) multiplied by fasting insulin (μIU/mL) and divided by 405, and a HOMA-IR value of 2.5 or higher was taken to indicate insulin resistance. QUICKI was calculated as 1 / [log fasting insulin (μIU/mL) + log fasting glucose (mg/dL)], lower values indicating lower insulin sensitivity. The TyG index was calculated as the natural logarithm of [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2].

Metabolic syndrome was defined according to the 2009 harmonized criteria as the presence of at least three of the following five components: waist circumference of 94 cm or more in men or 80 cm or more in women, the thresholds recommended for Middle Eastern populations; serum triglycerides of 150 mg/dL or more; HDL-C below 40 mg/dL in men or below 50 mg/dL in women; systolic blood pressure of 130 mmHg or more, diastolic blood pressure of 85 mmHg or more, or current antihypertensive treatment; and fasting plasma glucose of 100 mg/dL or more.

Data were entered and analysed using the Statistical Package for the Social Sciences (SPSS), version 26 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was examined with the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation and were compared among the three groups using one-way analysis of variance followed by Tukey's post hoc test. Skewed variables, namely TSH, fasting insulin and HOMA-IR, were log-transformed before parametric testing or compared with the Kruskal–Wallis test followed by Mann–Whitney U tests with Bonferroni correction, as appropriate. Categorical variables are expressed as numbers and percentages and were compared using the chi-square test, or Fisher's exact test when expected cell counts were below five. Within the combined hypothyroid group, the relationship of TSH, FT4 and FT3 with metabolic variables was examined using Spearman's rank correlation coefficient. Multivariable binary logistic regression was used to identify independent predictors of metabolic syndrome among hypothyroid patients, entering age, sex, BMI, TSH, HOMA-IR and anti-TPO status as covariates; results are reported as adjusted odds ratios with 95% confidence intervals. Model fit was assessed with the Hosmer–Lemeshow test, and multicollinearity was excluded by examining variance inflation factors. A two-tailed p value below 0.05 was considered statistically significant.

Results

A total of 150 participants were analysed: 50 with overt hypothyroidism, 50 with subclinical hypothyroidism and 50 euthyroid controls. Women constituted 80% of the whole

sample. As shown in Table 1, the three groups did not differ significantly in age or sex distribution, confirming the adequacy of matching. However, BMI, waist circumference, and systolic and diastolic blood pressure were significantly higher in both hypothyroid groups than in controls, with the highest values observed in overt hypothyroidism. Post hoc comparisons showed that the differences in BMI and waist circumference between the two hypothyroid groups did not reach statistical significance, whereas systolic and diastolic blood pressure were significantly higher than in controls only in the overt group. The proportion of current smokers and the reported level of physical activity were comparable across the three groups (data not shown).

Table 1. Demographic, anthropometric and clinical characteristics of the study groups

Variable	Overt HT (n = 50)	Subclinical HT (n = 50)	Controls (n = 50)	p value
Age (years)	41.6 ± 10.8	39.8 ± 11.2	40.2 ± 10.5	0.68
Female sex, n (%)	40 (80.0)	41 (82.0)	39 (78.0)	0.88
BMI (kg/m²)	30.4 ± 4.9 a	28.7 ± 4.6 a	26.1 ± 3.8	<0.001
Waist circumference (cm)	99.8 ± 11.2 a	95.6 ± 10.4 a	88.3 ± 9.1	<0.001
Systolic BP (mmHg)	132.4 ± 14.6 a	127.8 ± 13.9	121.5 ± 11.7	<0.001
Diastolic BP (mmHg)	84.6 ± 9.2 a	81.9 ± 8.7	78.1 ± 7.6	0.001

Values are mean ± SD or n (%). HT, hypothyroidism; BMI, body mass index; BP, blood pressure. p values from one-way ANOVA or chi-square test. a p < 0.05 versus controls (Tukey post hoc test).

Thyroid function parameters differed markedly among the groups, as expected from the inclusion criteria (Table 2). Mean TSH was 28.6 mIU/L in overt and 7.4 mIU/L in subclinical hypothyroidism. FT3 was significantly lower in both patient groups than in controls. Anti-TPO positivity was found in 76% of patients with overt and 62% of those with subclinical hypothyroidism, compared with 8% of controls, indicating that autoimmune thyroiditis was the predominant aetiology. FT4 did not differ significantly between patients with subclinical hypothyroidism and controls, whereas it was markedly reduced in the overt group.

Table 2. Thyroid function parameters and thyroid autoimmunity in the study groups

Variable	Overt HT (n = 50)	Subclinical HT (n = 50)	Controls (n = 50)	p value
TSH (mIU/L)	28.6 ± 14.2 a,b	7.4 ± 1.9 a	2.1 ± 0.9	<0.001
Free T4 (ng/dL)	0.62 ± 0.14 a,b	1.08 ± 0.17	1.21 ± 0.18	<0.001
Free T3 (pg/mL)	2.11 ± 0.42 a,b	2.86 ± 0.39 a	3.12 ± 0.36	<0.001
Anti-TPO positive, n (%)	38 (76.0)	31 (62.0)	4 (8.0)	<0.001

Values are mean ± SD or n (%). TSH, thyroid-stimulating hormone; anti-TPO, anti-thyroid peroxidase antibodies. TSH compared after log transformation. a p < 0.05 versus controls; b p < 0.05 versus subclinical HT.

Glycaemic indices and lipid parameters are presented in Table 3. Fasting plasma glucose and fasting insulin were significantly higher in both hypothyroid groups than in controls. Mean HOMA-IR increased progressively from controls (1.95 ± 0.88) to subclinical (3.36 ± 1.49) and overt hypothyroidism (4.31 ± 1.82; $p < 0.001$), and post hoc testing showed significant differences between each pair of groups. Insulin resistance, defined as HOMA-IR ≥ 2.5, was present in 78% of patients with overt hypothyroidism, 64% of those with subclinical hypothyroidism and 18% of controls. QUICKI was significantly lower and the TyG index significantly higher in both patient groups. Total cholesterol, LDL-C and triglycerides were elevated and HDL-C reduced in hypothyroid patients compared with controls. Total cholesterol and fasting insulin were also significantly higher in overt than in subclinical hypothyroidism, while differences in triglycerides, HDL-C and the TyG index between the two patient groups were not significant. Thus, insulin resistance indices and atherogenic lipid changes followed a stepwise pattern across the three groups.

Table 3. Glycaemic indices, insulin resistance indices and lipid profile in the study groups

Variable	Overt HT (n = 50)	Subclinical HT (n = 50)	Controls (n = 50)	p value
Fasting plasma glucose (mg/dL)	101.8 ± 12.6 a	97.2 ± 11.4 a	89.6 ± 8.9	<0.001
Fasting insulin (µIU/mL)	16.9 ± 6.1 a,b	13.8 ± 5.2 a	8.7 ± 3.4	<0.001
HOMA-IR	4.31 ± 1.82 a,b	3.36 ± 1.49 a	1.95 ± 0.88	<0.001
HOMA-IR ≥ 2.5, n (%)	39 (78.0)	32 (64.0)	9 (18.0)	<0.001
QUICKI	0.309 ± 0.018 a,b	0.320 ± 0.020 a	0.346 ± 0.024	<0.001
TyG index	9.14 ± 0.48 a	8.99 ± 0.45 a	8.66 ± 0.41	<0.001
Total cholesterol (mg/dL)	226.5 ± 38.2 a,b	209.8 ± 35.6 a	182.3 ± 30.4	<0.001
Triglycerides (mg/dL)	182.4 ± 58.6 a	164.7 ± 52.3 a	128.3 ± 41.5	<0.001
HDL-C (mg/dL)	41.3 ± 8.6 a	43.1 ± 8.9 a	47.6 ± 9.4	0.002
LDL-C (mg/dL)	146.2 ± 32.8 a	132.6 ± 30.1 a	108.9 ± 26.7	<0.001

Values are mean ± SD or n (%). HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; TyG, triglyceride–glucose index. Insulin and HOMA-IR compared after log transformation. a $p < 0.05$ versus controls; b $p < 0.05$ versus subclinical HT.

Metabolic syndrome was diagnosed in 52% of patients with overt hypothyroidism, 38% of those with subclinical hypothyroidism and 18% of controls ($p = 0.002$), as shown in Table 4. All five individual components were more frequent in the hypothyroid groups, the largest differences being observed for raised fasting glucose, elevated triglycerides and central obesity. Among the 45 hypothyroid patients with metabolic syndrome, 29 (64.4%) met three criteria and 16 (35.6%) met four or five criteria, compared with 7 of 9 controls (77.8%) who met only three criteria.

Table 4. Prevalence of metabolic syndrome and its components (2009 harmonized criteria)

Variable	Overt HT (n = 50)	Subclinical HT (n = 50)	Controls (n = 50)	p value
Metabolic syndrome	26 (52.0)	19 (38.0)	9 (18.0)	0.002
Elevated waist circumference	37 (74.0)	33 (66.0)	22 (44.0)	0.006
Triglycerides ≥ 150 mg/dL	31 (62.0)	26 (52.0)	15 (30.0)	0.005
Reduced HDL-C	30 (60.0)	27 (54.0)	18 (36.0)	0.044
Elevated blood pressure	23 (46.0)	18 (36.0)	10 (20.0)	0.022
Fasting glucose ≥ 100 mg/dL	24 (48.0)	18 (36.0)	7 (14.0)	0.001

Values are n (%). p values from the chi-square test. Elevated waist circumference: ≥ 94 cm (men), ≥ 80 cm (women); reduced HDL-C: < 40 mg/dL (men), < 50 mg/dL (women); elevated blood pressure: ≥ 130/85 mmHg or antihypertensive treatment.

Among the 100 hypothyroid patients, TSH correlated positively, and FT4 and FT3 inversely, with HOMA-IR, the TyG index, triglycerides and waist circumference, while HDL-C correlated negatively with TSH (Table 5). The strongest correlation was between TSH and HOMA-IR ($r = 0.42$, $p < 0.001$).

Table 5. Spearman correlation of thyroid parameters with metabolic variables in hypothyroid patients (n = 100)

Variable	TSH r	TSH p	FT4 r	FT4 p	FT3 r	FT3 p
HOMA-IR	0.42	<0.001	−0.36	<0.001	−0.29	0.003
QUICKI	−0.39	<0.001	0.33	0.001	0.26	0.009
TyG index	0.34	0.001	−0.30	0.002	−0.23	0.021
Triglycerides	0.31	0.002	−0.27	0.007	−0.22	0.028
HDL-C	−0.25	0.012	0.20	0.046	0.15	0.137
Waist circumference	0.24	0.016	−0.21	0.036	−0.18	0.073
Systolic BP	0.22	0.028	−0.19	0.058	−0.12	0.234

r, Spearman's rank correlation coefficient; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine.

In multivariable logistic regression among hypothyroid patients (Table 6), HOMA-IR (adjusted OR 1.89, 95% CI 1.31–2.73), TSH (adjusted OR 1.04 per 1 mIU/L, 95% CI 1.01–1.08) and BMI (adjusted OR 1.14, 95% CI 1.02–1.27) were independent predictors of metabolic

syndrome, whereas age, sex and anti-TPO positivity were not. The Hosmer–Lemeshow test indicated adequate model fit (p = 0.61).

Table 6. Multivariable logistic regression of predictors of metabolic syndrome among hypothyroid patients (n = 100)

Predictor	Adjusted OR	95% CI	p value
Age (per year)	1.03	0.99–1.07	0.142
Female sex	1.21	0.42–3.48	0.724
BMI (per kg/m²)	1.14	1.02–1.27	0.021
TSH (per 1 mIU/L)	1.04	1.01–1.08	0.012
HOMA-IR (per unit)	1.89	1.31–2.73	0.001
Anti-TPO positivity	1.48	0.55–3.98	0.437

OR, odds ratio; CI, confidence interval. Dependent variable: metabolic syndrome (yes = 45, no = 55). Hosmer–Lemeshow test p = 0.61; Nagelkerke R² = 0.38.

Discussion

The present study assessed insulin resistance and metabolic syndrome in adults with overt and subclinical hypothyroidism attending Baquba Teaching Hospital and compared them with age- and sex-matched euthyroid controls. The principal findings were that both forms of hypothyroidism were associated with significantly greater insulin resistance, as demonstrated consistently by three different surrogate indices, and with a higher prevalence of metabolic syndrome. These abnormalities showed a clear gradient, being most pronounced in overt hypothyroidism, intermediate in subclinical hypothyroidism and least frequent in controls. Within the hypothyroid population, TSH correlated positively and thyroid hormone levels inversely with insulin resistance and with several metabolic risk factors, and HOMA-IR, TSH and BMI emerged as independent predictors of metabolic syndrome. Taken together, these results support the view that thyroid hormone deficiency, even when mild, is accompanied by a clinically relevant deterioration in cardiometabolic health.

Our finding of increased HOMA-IR in hypothyroid patients agrees with the clamp studies that first established hypothyroidism as an insulin-resistant state. Rochon et al. showed that insulin-stimulated glucose disposal is reduced in hypothyroidism [14], and Dimitriadis et al. demonstrated impaired insulin action on glucose uptake in both muscle and adipose tissue [15]. Maratou et al. extended these observations to subclinical hypothyroidism, finding that insulin resistance in muscle and adipose tissue was of similar magnitude in subclinical and overt disease [16]. In our study, insulin resistance was also clearly present in subclinical hypothyroidism, although it was less marked than in overt disease, a difference that may reflect the higher BMI and waist circumference of our patients with overt hypothyroidism or methodological differences between surrogate indices and direct tissue measurements. Comparable increases in HOMA-IR have been reported in hypothyroid patients from India by Singh et al., who studied women attending a tertiary care hospital [37], and by Kapadia et al.,

who found insulin resistance across both hypothyroid and hyperthyroid states [36]. In Iraq, Jafar et al. likewise reported higher insulin resistance markers in hypothyroid patients from Najaf than in healthy controls [38]. The consistency of our findings with those of studies conducted in different ethnic groups and settings suggests that the association is robust and not explained by local factors alone.

Several mechanisms may explain why thyroid hormone deficiency impairs insulin sensitivity. Thyroid hormone stimulates the expression of GLUT4 and promotes its translocation to the plasma membrane of skeletal muscle and adipocytes; in hypothyroidism, reduced GLUT4 availability limits insulin-stimulated glucose uptake [17]. Hypothyroidism also reduces insulin-stimulated tissue blood flow, which restricts the delivery of glucose and insulin to muscle [15]. In addition, thyroid hormone regulates key enzymes of glycolysis, glycogen synthesis and mitochondrial oxidation, and its deficiency is accompanied by reduced oxidative capacity and lower energy expenditure [5]. Alterations in adipokines such as leptin and adiponectin, increased low-grade inflammation and endothelial dysfunction may further aggravate insulin resistance [17,18]. Interestingly, hypothyroidism is associated with reduced hepatic glucose output, which may partly offset peripheral insulin resistance in the fasting state; this might explain why fasting glucose, although higher in our patients, remained mostly within the non-diabetic range. The relationship between thyroid hormones and insulin sensitivity is, however, not entirely linear. Lambadiari et al. found that thyroid hormone levels were positively associated with insulin resistance early in the development of type 2 diabetes [39], indicating that the metabolic effects of thyroid hormones may vary with the underlying glycaemic state and that both deficiency and relative excess can disturb glucose homeostasis.

An additional strength of the present analysis is the use of three complementary surrogate indices. HOMA-IR reflects mainly hepatic insulin resistance in the fasting state [8], QUICKI correlates closely with clamp-derived insulin sensitivity [9], and the TyG index captures the combined effect of glucose and triglycerides without the need for an insulin assay [10]. The concordant results obtained with all three indices strengthen confidence that the observed differences reflect a genuine reduction in insulin sensitivity rather than an artefact of a single method. The TyG index may be particularly useful in hospitals such as ours, where insulin assays are not always available, because it can be calculated from routine biochemical measurements.

The prevalence of metabolic syndrome in our hypothyroid patients was considerably higher than in controls, and the difference persisted for subclinical hypothyroidism. These findings are consistent with those of Uzunlulu et al., who reported a significantly higher prevalence of subclinical hypothyroidism among Turkish patients with metabolic syndrome [27], and with the observations of Ruhla et al., who showed that even high-normal TSH concentrations were associated with metabolic syndrome [28]. Roos et al. similarly found that lower FT4 levels, within the euthyroid range, were associated with insulin resistance, higher triglycerides and lower HDL-C [24], and Fernández-Real et al. described a close link between thyroid function and insulin sensitivity in healthy subjects [25]. On the other hand, Waring et al. did not find a consistent association between subclinical hypothyroidism and metabolic syndrome in older adults [29], and Wang et al. reported that the relationship in Taiwanese adults depended on sex and age [30]. The relatively young age of our participants, the predominance of women, the high frequency of autoimmune thyroiditis and the inclusion of untreated patients only may explain why the association was more evident in our study than in older community-based cohorts [31].

Analysis of the individual components showed that all five criteria were more frequent in hypothyroid patients. The higher triglycerides, total cholesterol and LDL-C, and the lower HDL-C, are consistent with the known effects of thyroid hormone deficiency on hepatic LDL receptor expression and on the enzymes of lipoprotein metabolism [19]. Lipid abnormalities in subclinical hypothyroidism have been less consistent in previous studies [20], but in our patients they were clearly present and were accompanied by insulin resistance, which itself promotes hypertriglyceridaemia and low HDL-C through increased hepatic production of very-low-density lipoprotein. The higher blood pressure in our patients agrees with reports of increased peripheral vascular resistance and diastolic hypertension in hypothyroidism [21] and with population data linking higher TSH to higher blood pressure [23]. The greater BMI and waist circumference of hypothyroid patients are in line with the observation that small differences in thyroid function are associated with differences in body weight [22]. Interactions between thyroid function, insulin sensitivity and serum lipids, similar to those described in the Fremantle Diabetes Study [26], were also apparent in the correlation analysis of our patients.

The logistic regression analysis provides further insight into these relationships. HOMA-IR remained independently associated with metabolic syndrome after adjustment for age, sex, BMI and TSH, suggesting that insulin resistance is an important intermediate pathway linking thyroid hormone deficiency with metabolic syndrome, in keeping with Reaven's concept of insulin resistance as the core abnormality of the syndrome [7]. TSH was also an independent predictor, which implies that the severity of thyroid failure contributes to metabolic risk beyond its effect on insulin sensitivity. Anti-TPO positivity was not independently associated with metabolic syndrome, indicating that the metabolic abnormalities are related to the degree of thyroid hormone deficiency rather than to thyroid autoimmunity itself, although a contribution of autoimmune-related inflammation cannot be excluded.

These findings have practical implications. Metabolic syndrome and insulin resistance are established precursors of type 2 diabetes and cardiovascular disease [11,12], and subclinical hypothyroidism has been linked with an increased risk of coronary heart disease and mortality, particularly at higher TSH levels [32,33]. Insulin resistance may therefore represent one of the mechanisms through which hypothyroidism increases cardiovascular risk. In a region where the burden of metabolic syndrome is rising rapidly [13], routine assessment of waist circumference, blood pressure, fasting glucose and lipids in patients with hypothyroidism is a simple and inexpensive way to identify those at high cardiometabolic risk. Current guidelines recommend levothyroxine for overt hypothyroidism and individualized decisions for subclinical disease [34,35], and the presence of metabolic abnormalities may be one factor favouring treatment in patients with subclinical hypothyroidism [6]. Whether levothyroxine replacement improves insulin sensitivity and reduces the prevalence of metabolic syndrome remains uncertain, and this question deserves evaluation in prospective interventional studies.

This study has several limitations. Its cross-sectional design does not allow causal inferences, and the direction of the association between hypothyroidism and insulin resistance cannot be determined with certainty. The sample size was moderate and the study was carried out in a single centre, which may limit the generalizability of the results to the wider Iraqi population. Insulin resistance was estimated with surrogate indices rather than with the hyperinsulinaemic–euglycaemic clamp, and an oral glucose tolerance test and glycated haemoglobin were not performed. Iodine status, dietary intake, physical activity and adipokine levels were not measured, and residual confounding by these factors is possible. The predominance of women reflects the epidemiology of hypothyroidism but limits conclusions

regarding men. Despite these limitations, the strengths of the study include the careful exclusion of patients taking medications that influence glucose and lipid metabolism, the inclusion of both overt and subclinical disease with an age- and sex-matched control group, and the use of three complementary indices of insulin resistance. Future multicentre prospective studies in Iraq should evaluate the effect of levothyroxine therapy on insulin resistance and metabolic syndrome and should examine whether metabolic screening improves long-term cardiovascular outcomes in hypothyroid patients.

Conclusion

Patients with overt and subclinical hypothyroidism attending Baquba Teaching Hospital showed significantly greater insulin resistance, as assessed by HOMA-IR, QUICKI and the TyG index, and a higher prevalence of metabolic syndrome than euthyroid controls, with a gradient that paralleled the severity of thyroid failure. TSH correlated positively and thyroid hormones inversely with insulin resistance and with several metabolic risk factors, and insulin resistance, TSH and BMI independently predicted metabolic syndrome. These results indicate that hypothyroidism, including its subclinical form, should be regarded as a cardiometabolic risk state. Routine screening for insulin resistance and the components of metabolic syndrome is recommended in hypothyroid patients, and prospective studies are needed to determine whether timely thyroid hormone replacement improves these metabolic abnormalities.

References

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;390(10101):1550-62.
2. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14(5):301-16.
3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489-99.
4. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526-34.
5. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014;94(2):355-82.
6. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76-131.
7. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
9. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 2000;85(7):2402-10.

10. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008;6(4):299-304.
11. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
12. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
13. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):12.
14. Rochon C, Tauveron I, Dejax C, Benoit P, Capitan P, Fabricio A, et al. Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. Clin Sci (Lond). 2003;104(1):7-15.
15. Dimitriadis G, Mitrou P, Lambadiari V, Boutati E, Maratou E, Panagiotakos DB, et al. Insulin action in adipose tissue and muscle in hypothyroidism. J Clin Endocrinol Metab. 2006;91(12):4930-7.
16. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol. 2009;160(5):785-90.
17. Brenta G. Why can insulin resistance be a natural consequence of thyroid dysfunction? J Thyroid Res. 2011;2011:152850.
18. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. Endocr Rev. 2019;40(3):789-824.
19. Duntas LH. Thyroid disease and lipids. Thyroid. 2002;12(4):287-93.
20. Pearce EN. Update in lipid alterations in subclinical hypothyroidism. J Clin Endocrinol Metab. 2012;97(2):326-33.
21. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab. 2003;88(6):2438-44.
22. Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab. 2005;90(7):4019-24.
23. Asvold BO, Bjøro T, Nilsen TI, Vatten LJ. Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. J Clin Endocrinol Metab. 2007;92(3):841-5.
24. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007;92(2):491-6.
25. Fernández-Real JM, López-Bermejo A, Castro A, Casamitjana R, Ricart W. Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. J Clin Endocrinol Metab. 2006;91(9):3337-43.

26. Chubb SA, Davis WA, Davis TM. Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations: the Fremantle diabetes study. J Clin Endocrinol Metab. 2005;90(9):5317-20.
27. Uzunlulu M, Yorulmaz E, Oguz A. Prevalence of subclinical hypothyroidism in patients with metabolic syndrome. Endocr J. 2007;54(1):71-6.
28. Ruhla S, Weickert MO, Arafat AM, Osterhoff M, Isken F, Spranger J, et al. A high normal TSH is associated with the metabolic syndrome. Clin Endocrinol (Oxf). 2010;72(5):696-701.
29. Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonsick EM, Miljkovic I, et al. Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing and Body Composition Study. Clin Endocrinol (Oxf). 2012;76(6):911-8.
30. Wang CY, Chang TC, Chen MF. Associations between subclinical thyroid disease and metabolic syndrome. Endocr J. 2012;59(10):911-7.
31. Iwen KA, Schröder E, Brabant G. Thyroid hormones and the metabolic syndrome. Eur Thyroid J. 2013;2(2):83-92.
32. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010;304(12):1365-74.
33. Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab. 2010;95(4):1734-40.
34. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012;22(12):1200-35.
35. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670-751.
36. Kapadia KB, Bhatt PA, Shah JS. Association between altered thyroid state and insulin resistance. J Pharmacol Pharmacother. 2012;3(2):156-60.
37. Singh BM, Goswami B, Mallika V. Association between insulin resistance and hypothyroidism in females attending a tertiary care hospital. Indian J Clin Biochem. 2010;25(2):141-5.
38. Jafar I, Ali HA, Ali RA, Al-rufaie MM. Assessing the role of serum pentraxin-3 (PTX3) levels in hypothyroidism patients as risk marker of insulin resistance. Curr Issues Pharm Med Sci. 2023. doi:10.2478/cipms-2023-0030.
39. Lambadiari V, Mitrou P, Maratou E, Raptis AE, Tountas N, Raptis SA, et al. Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. Endocrine. 2011;39(1):28-32.