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ORIGINAL PAPER

Evaluation of the Association between Insulin Resistance and Subclinical Hypothyroidism Using Triglyceride-Glucose Index: a Cross-Sectional Study

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ABSTRACT

Background: *Thyroid disorders and diabetes mellitus are often known to co-exist, implying an interrelationship between thyroid dysfunction and insulin resistance. Triglyceride-glucose (TyG) index is a relatively new surrogate marker of insulin resistance, which is cost-effective and easily calculated with routine lab tests. Data about association of subclinical hypothyroidism (SCH) and insulin resistance, especially with reference to TyG index, is lacking.*

Objectives: *To evaluate the association of SCH and insulin resistance using the TyG index by comparing its value in patients with SCH and age- and gender-matched euthyroid controls. Also, to determine if there is a correlation between TyG index values and thyroid profile parameters (TSH, FT3 and FT4) in both study groups.*

Materials and methods: *Thirty-five patients with SCH and an equal number of age- and gender-matched euthyroid controls were included in the present study. The TyG index was calculated for each group and compared. The correlation between TyG index and thyroid profile parameters (TSH, FT3 and FT4) was also assessed.*

Results: *The TSH values were significantly higher in the SCH group (6.6±1.7 µIU/mL) than the control one (2.5±1.2 µIU/mL; p<0.0001). There was no significant difference in FT3 in the SCH group (2.93±0.49 pg/mL) and the control one (3.05±0.64 pg/mL; p=0.310). The level of FT4 was also not found to be significantly different in SCH subjects (1.23±0.44 ng/dL) and controls (1.4±0.42 ng/dL; p=0.077). The TyG index values were significantly higher in the SCH group (4.8±0.2) as compared to the control one (4.7±0.2; p = 0.015). The TyG index did not show any significant correlation with the thyroid parameters in any of the two groups.*

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Conclusion: *There is a positive association between SCH and insulin resistance in terms of TyG index. This index may thus be helpful in early screening and management of such patients for insulin resistance related conditions like diabetes mellitus, metabolic syndrome and cardiovascular disorders.*

Keywords: subclinical hypothyroidism (SCH), insulin resistance, triglyceride glucose index (TyG index), thyroid profile.

INTRODUCTION

Hypothyroidism and diabetes mellitus (DM) are very common endocrinological conditions encountered in clinical practice. Several studies have shown that the prevalence of hypothyroidism is higher in patients with type 2 DM (T2DM) (1) and *vice versa* (2), suggesting an inter-relationship between thyroid hormone status and insulin sensitivity.

The gold standard test for assessing insulin resistance is the hyperinsulinemic-euglycemic clamp (HEC) technique, which cannot be done routinely because of technical complexities. Hence, various surrogate markers have been used for assessing the same parameter. The homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) have been traditionally used to document insulin resistance. Both these indices have fasting plasma glucose and fasting insulin levels in their formulae; while fasting plasma glucose is routinely tested in clinical practice, fasting insulin levels, unfortunately, are not done routinely and are also not cost-effective. Hence, performing these tests may impose extra financial burden on patients, especially on those who live in a developing country like ours.

Triglyceride-glucose index (TyG index), calculated as Ln(FTG*FBS)/2, where FTG stands for fasting triglyceride and FBS for fasting blood sugar, is a relatively new surrogate marker for assessing insulin resistance (3). A cross-sectional survey concluded that TyG index was a good surrogate marker for evaluating insulin resistance in relation with thyroid function (4). In a large prospective cohort study involving 22 countries across five continents, the TyG index was found to be significantly associated with incident T2DM; also, it requires fasting triglyceride and fasting plasma glucose levels (5), which are routinely done on an out-patient basis making it cost-effective and more feasible when compared to other tests.

Subclinical hypothyroidism (SCH) is defined as elevated serum TSH levels (4.5-10.0 mIU/L) (6) with normal FT3 and FT4 levels. Several studies aimed to find an association between SCH and insulin resistance; thus, many of them reported a positive association (7), while few could not show any association (8). Therefore, it is still a matter of debate. Also, there is limited data for TyG index values and its correlation with various thyroid hormone parameters (TSH, T3 and T4) in evaluating insulin resistance in patients with SCH.

Therefore, we aimed to evaluate the association between SCH and insulin resistance using the TyG index by comparing its value in patients with subclinical hypothyroidism and age- and gender-matched euthyroid controls. We also tried to find whether there is any correlation between values of TyG index and thyroid profile (TSH, FT3 and FT4) in such patients. ❑

MATERIALS AND METHODS

Study design

This was a cross-sectional study.

Study setting

Our study was conducted in the Department of Pharmacology and the Department of General Medicine of IGIMS, Patna, India. Participants were selected from the outpatient as well as inpatient Departments of General Medicine.

Study duration

The present study had a six-months duration.

Sample size

With an anticipated mean of 4.8±0.3 for the TyG index value in the SCH group and 4.6 in the control one (C O Kirac *et al*, 2022), with alpha 0.05 and power 80%, the minimum sample size required was calculated to be 70.

Methodology

A total of 35 patients with SCH and an equal number of age- and gender-matched euthyroid controls were included in the present study.

Laboratory measurements

The laboratory test methods used for the estimation of all laboratory parameters, including FT3, FT4, TSH, FBS and FTG, were the same for every participant.

The chemiluminescent immunoassay (CLIA) method was used for estimating FT3, FT4 and TSH values, the hexokinase method for the estimation of FBS values, and glycerol-3-phosphate oxidase-phenol-aminophenazone (GPO-PAP) method for FTG values.

Inclusion criteria

Individuals of either sex aged 18-45 years, patients with SCH (serum TSH 4.5–10.0 mIU/mL and normal FT3 and FT4 levels) (SCH group) and subjects with all three parameters within the normal range (serum TSH 0.27–4.5 mIU/L with normal FT3 and FT4 levels) (control group), and individuals who were willing to participate in the study and provided written informed consent after fully understanding the purpose and nature of the study were included in the present study.

Exclusion criteria

Patients with overt hypothyroidism/ hyperthyroidism, those with previous history of thyroid disorder, treatment with thyroxine or anti-thyroid drugs or radiation, individuals with DM/im-paired glucose tolerance, obese individuals with BMI ≥ 30 kg/m^2, those with chronic infections or systemic illnesses, liver/renal/heart failure patients, alcoholics, females with polycystic ovarian syndrome, pregnancy and menopause, patients on drugs like statins, oral contraceptive pills, anticonvulsants and amiodarone that were likely to affect thyroid function, as well as patients who took drugs like glucocorticoids, that were likely to affect glucose levels, were all excluded.

Ethical approval

The present study was commenced after obtaining the approval of the Ethics Committee of our Institute as well as the written informed consent from all participants.

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements were presented as mean ± SD and those on categorical measurements as percentage. The pattern of data distribution was determined by using the Kolmogorov-Smirnov test. For normally distributed data, the independent t-test was applied for comparing the TyG indices in the two study groups. Mann Whitney U test was used for non-normally distributed data. For assessing the correlation between variables, Pearson correlation coefficient was used for normal distribution and Spearman correlation coefficient for non-normal distribution. A p-value of <0.05 was considered significant. ❑

RESULTS

The current study included 70 patients, of whom 35 in the SCH group and 35 in the control one. Both groups were matched for gender, with 26 female and nine male patients in each group. Also, both groups were matched for age [χ^2 (df = 4, N = 35) = 2.39, p = 0.664] (Table 1).

The mean age of patients in the control and SCH groups was 36.2±7.6 and 35.9±7.4, respectively. The BMI was significantly higher in the SCH group than the control one (p=0.02). The FBS (p=0.042) values were significantly higher in the SCH patients than controls, while the triglyceride values were similar in both groups (p=0.065).

The TSH values were significantly higher in the SCH group as compared to the control one (p<0.0001). However, there was no significant difference in FT3 (p=0.310) and FT4 (p=0.077) values between the two groups.

The TyG index values were significantly higher in the SCH group than the control one (Table 2).

The TyG index did not show any significant correlation with thyroid parameters in any of the two groups (Table 3).

The BMI had a significant correlation with the TyG index in the SCH group [Pearson's r (68) = .556, p= .0005, CI 0.274 to 0.750], while no significant correlation between the two variables was

TABLE 1. Age group distribution in the control and subclinical hypothyroidism (SCH) groups

Group	Age group (years)					Count
	18-25	26-30	31-35	36-40	41-45	N=70
Control	4	3	8	8	12	35 (9 males, 26 females)
SCH	4	6	4	9	12	35 (9 males, 26 females)

TABLE 2. Characteristics of the control and subclinical hypothyroidism groups

	Control group	SCH group	p-value
Age (years)	36.2±7.6	35.9±7.4	0.768
BMI (kg/m²)	24.67±2.14	25.78±2.21	0.037
FBS (mg/dL)	91.3±10.9	96.6±10.2	0.042
Tg (mg/dL)	144.1±46.1	176.0±77.4	0.065
TSH (µIU/mL)	2.5±1.2	6.6±1.7	<0.0001
FT3 (pg/mL)	3.05±0.64	2.93±0.49	0.310
FT4 (ng/dL)	1.4±0.42	1.23±0.44	0.077
TyG index	4.7±0.2	4.8±0.2	0.015

BMI: body mass index; FBS: fasting blood sugar; Tg: triglyceride; SCH: subclinical hypothyroidism

TABLE 3. Correlation of TyG index with thyroid profile parameters

	Control			SCH		
	FT3	FT4	TSH	FT3	FT4	TSH
TyG index	r = 0.115	r = -0.041	r = 0.031	r = -0.135	r = -0.252	r = -0.033
	p = 0.512	p = 0.817	p = 0.859	p = 0.440	p = 0.144	p = 0.853

r: correlation coefficient (Pearson's/Spearman's based on distribution characteristic); p: p-value (significance level < 0.05); SCH: subclinical hypothyroidism

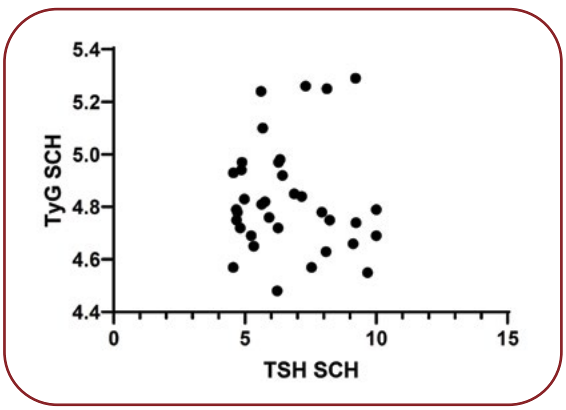

FIGURE 1. Correlation graph of TyG index with TSH in the SCH group (TSH: thyroid stimulating hormone; TyG: triglyceride-glucose index; SCH: subclinical hypothyroidism)

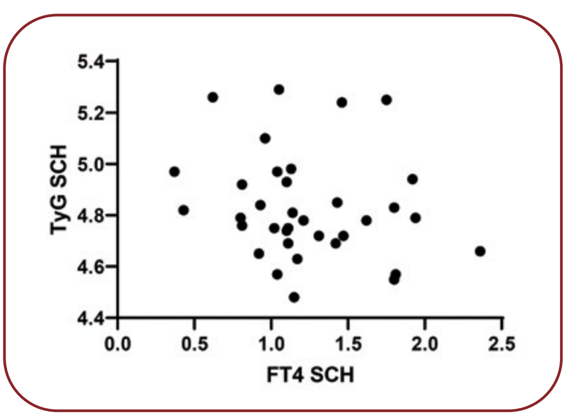

FIGURE 2. Correlation graph of TyG index with FT4 in the SCH group (TyG: triglyceride-glucose index; SCH: subclinical hypothyroidism; FT4: free thyroxine)

found in the control group [Pearson's r (68) = 0.032, p= .854, CI -0.304 to 0.362]. ❑

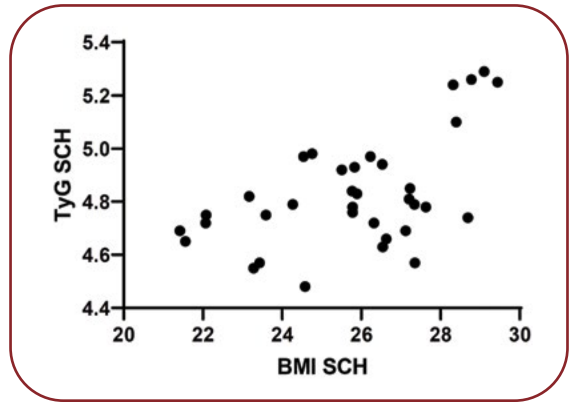

FIGURE 3. Correlation graph of TyG index with BMI in the SCH group (TyG: triglyceride-glucose index; SCH: subclinical hypothyroidism; BMI: body mass index)

DISCUSSION

In the present study, we investigated the association of insulin resistance with SCH using the TyG index values. Age- and gender-matched controls (euthyroid individuals) were compared with the SCH patients. The majority of study participants were females (74.3% in each group), with most of them in the age group of 41-45 years (34% in each group), suggesting female preponderance of the disease, which is also in accordance with many previous studies.

The BMI values were found to be significantly higher in the SCH group than the control one, which is in agreement with a study by Singh *et al* (11). Also, we found that BMI was significantly correlated with the TyG index in the SCH group, while no significant correlation was found between the two variables in the control group. Increased BMI, as found in various previous studies (12, 13), is in itself a risk factor for insulin resistance, which is also supported by our study results.

The FBS was found to be significantly higher in the SCH group when compared to the control one, while there was no significant difference between the Tg values in the two groups. Both FBS and Tg values are used in the calculation of TyG index.

The TyG index values were found to be significantly higher in the SCH group as compared to the control one. In fact, this is the most important finding of our study, because it supports the idea that insulin resistance is associated with SCH and the latter could be an important risk factor for insulin resistance associated disorders. Many studies have evaluated this association, but their results have been conflicting, with few demonstrating it (10, 14, 16), while others showing insignificant results (15). Also, in the studies conducted by Choi *et al* and Kirac *et al*, TyG served to be a better indicator for insulin resistance than HOMA-IR, which has been conventionally used for assessing insulin resistance, and this could be a possible reason for insignificant result in the few studies assessing the association between SCH and insulin resistance (15).

Our study did not show any significant correlation between TyG index and thyroid profile parameters (FT3, FT4, TSH), but Kirac *et al* found a significant positive correlation between TyG index and TSH. This difference could be due to the fact that only obese females were included in the above-mentioned study.

Study limitations

Like any cross-sectional study, ours had inherent limitations. Study subjects could not be followed up to assess the incidence of insulin resistance-related disorders in study participants with high TyG index values, which would give the actual picture of this association. Long-term prospective studies assessing this association are thus warranted in future. ❑

CONCLUSION

Our study findings reveal a positive association of insulin resistance with subclinical hypothyroidism using the TyG index, a relatively new surrogate marker for evaluating insulin resistance which can be easily calculated with routine tests; no exclusive test like fasting insulin is required – hence, no extra cost. Thus, our study highlights the fact that TyG index can be routinely used in patients with SCH to allow timely screening and management of insulin resistance-associated disorders like diabetes mellitus, metabolic syndrome and cardiovascular disorders in such patients. ❑

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Patient informed consent obtained.

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