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Surrogate Insulin Resistance Indices in Turkish Adults with Hypothyroidism

Hipotrioidizmli Türk Erişkinlerde Aday İnsülin Direnci Endeksleri

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ABSTRACT

Objectives: Despite various studies on the effect of thyroid status on insulin sensitivity in recent years, there are conflicting data. Thyroid dysfunction leads to changes in glucose and lipid metabolism, which is an important risk factor for cardiovascular diseases. For this reason, the patient must be carefully monitored and treated to prevent future diseases. Here we investigated the association between hypothyroidism and insulin resistance (IR) indices

Materials and Methods: 41 hypothyroidism patients and 249 healthy age and sex matched controls in the age group of 18 to 65 years were taken for the study. Care was taken to ensure that all participants were non-diabetic. Glucose (Glu), Trigliserid (TG), insulin (I), Total cholesterol (CHOL), HDL Cholesterol (HDL), as well as Thyroid Stimulating Hormone (TSH), free thyroxin (fT4) and free triiodotronin (fT3) values were examined in the patient and control groups. Afterwards, IR parameters like HOMA-IR, TyG index, TG/HDL, ISI, QUICKI were calculated and investigated whether there was a significant difference between the groups.

Results: The groups were statistically equal in terms of age and gender. (P=0,29, P= 0,32). When we examined the insulin resistance indexes, we observed that there were significant differences in the TyG index and TG/HDL ratio (P=0.03, P=0.04). Apart from this, we did not find any significant difference in HOMA-IR, QUICKI and ISI parameters and their p values were 0.27, 0.27 and 0.1 respectively. The AUC values after the receiver operating characteristic (ROC) analysis for TyG index and TG/HDL were 0.602 and 0.598, respectively, and p values were 0.045 and 0.04, respectively.

Conclusion: This study highlights the effectiveness of the TyG index and TG/HDL ratio as a diagnostic tool for IR in patients with hypothyroidism and establishes it as an effective alternative to HOMA-IR, ISI and QUICKI.

Keywords: Hypothyroidism, Insulin resistance, TyG index, TG/HDL ratio.

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ÖZET

Amaçlar: Son yıllarda tiroid durumunun insülin duyarlılığı üzerindeki etkisine dair çeşitli çalışmalar yapılmış olmasına rağmen, çelişkili veriler bulunmaktadır. Tiroid disfonksiyonu, kardiyovasküler hastalıklar için önemli bir risk faktörü olan glikoz ve lipid metabolizmasında değişikliklere yol açar. Bu nedenle, gelecekteki hastalıkları önlemek için hasta dikkatlice izlenmeli ve tedavi edilmelidir. Burada hipotiroidizm ve insülin direnci (IR) endeksleri arasındaki ilişkiyi araştırdık

Materyaller ve Yöntemler: Çalışmaya 18 ila 65 yaş aralığında 41 hipotiroidizm hastası ve 249 sağlıklı, yaş ve cinsiyet eşleştirilmiş kontrol alındı. Tüm katılımcıların diyabetsiz olduğundan emin olunmasına dikkat edildi. Hasta ve kontrol gruplarında Glikoz (Glu), Trigliserid (TG), İnsülin (I), Total Kolesterol (CHOL), HDL Kolesterol (HDL) ve Tiroid Uyarıcı Hormon (TSH), Serbest Tiroksin (fT4) ve Serbest Triiyodotronin (fT3) değerleri incelendi. Daha sonra HOMA-IR, TyG indeksi, TG/HDL, ISI, QUICKI gibi IR parametreleri hesaplandı ve gruplar arasında anlamlı bir fark olup olmadığı araştırıldı.

Sonuçlar: Gruplar yaş ve cinsiyet açısından istatistiksel olarak eşitti. (P=0,29, P=0,32). İnsülin direnci indekslerini incelediğimizde TyG indeksi ve TG/HDL oranında anlamlı farklılıklar olduğunu gözlemledik (P=0,03, P=0,04). Bunun dışında HOMA-IR, QUICKI ve ISI parametrelerinde anlamlı bir fark bulamadık ve bunların p değerleri sırasıyla 0,27, 0,27 ve 0,1 idi. TyG indeksi ve TG/HDL için ROC analizinden sonra AUC değerleri sırasıyla 0,602 ve 0,598 ve p değerleri sırasıyla 0,045 ve 0,04 idi.

Sonuç: Bu çalışma, TyG indeksi ve TG/HDL oranının hipotiroidili hastalarda IR için bir tanı aracı olarak etkinliğini vurgulamakta ve bunu HOMA-IR, ISI ve QUICKI'ye etkili bir alternatif olarak ortaya koymaktadır.

Anahtar kelimeler: Hipotiroidizm, İnsülin direnci, TyG indeksi, TG/HDL oranı.

INTRODUCTION

Thyroid hormones regulate basal energy expenditure via protein, carbohydrate, and lipid metabolism pathways, either by direct action or by modification of regulatory hormones like insulin and catecholamines. [1] Hypothyroidism has been associated with disorders of glucose-insulin metabolism, such as inadequate insulin response to glucose, hyperinsulinemia, altered peripheral glucose disposal, and insulin resistance. [2] IR is a condition that occurs when tissues such as muscle, fat and liver fail to respond properly to insulin. Researchers have determined indexes for IR such as homeostatic model assessment (HOMA-IR) [3], metabolic IR score (METS-IR) [4], quantitative insulin sensitivity control index (QUICKI) [5] and Matsuda index [6]. In recent studies, the triglyceride-glucose (TyG) index calculated from fasting blood glucose (FPG) and triglycerides (TG) has been suggested as a useful and reliable method to assess peripheral IR [7] and can also be used as a potential risk factor. Previous studies have shown that there is a close relationship between hypothyroidism and metabolic disorders, and even small changes in TSH levels have been shown to be associated with IR. [8,9] The effect of thyroid hormone deficiency on glucose and insulin metabolism is controversial. While one study showed that hypothyroidism had no effect on IR measured by HOMA-IR [10], other studies have demonstrated that not only overt hypothyroidism but also subclinical hypothyroidism produces impaired and resistant glucose metabolism, and fasting insulin levels are significantly different between euthyroid and subclinical hypothyroid subjects. [11, 12]

In this study, we aimed to compare the insulin resistance indices of non-diabetic patients with hypothyroidism with the healthy control group and to determine the cutoff values of those with significant differences from these indices.

MATERIALS and METHODS

This retrospective study was conducted with 41 hypothyroid patients who referred to İstanbul Training and Research Hospital outpatient clinics and whose ages ranged

from 18 to 65, with high TSH levels and decreased free T3, free T4 or normal fT3, fT4, and a control group consisting of 249 healthy people matched with the patient group in terms of age and gender. The study was approved by the ethic committee of Istanbul Training and Research Hospital. We collected data by examining patient files and computer records. Taking into account the ADA criteria, those with FPG values over 126 mg/dl, those with Hba1c values over 5.7 (in order to exclude prediabetes), those with postprandial blood sugar levels over 200 mg/dl, and those with diagnosed diabetes in the previous period were excluded from the study. Subjects with triglyceride levels ≥ 400 mg/dl and pregnant women were not included in the study. In this way, it was thought that the relationship between insulin resistance indices and thyroid hormones could be determined more clearly.

All samples were taken in the morning after at least 10 hours of fasting. Serum TSH, fT4, Ft3, insulin levels were analysed by electrochemiluminescence immunoassays (ECLIA), other biochemical assays (FPG, TG, HDL cholesterol (HDL), total cholesterol (CHOL), LDL cholesterol (LDL)) were measured by using C8000 modular analyser (Roche Diagnostics, Mannheim, Germany).

The Insulin resistance (IR) surrogate indicators were calculated using the following formulas:

HOMA-IR = (FPG (mmol/l)X fasting insulin (mIU/L)) / 22.5

TyG index = log (fasting TG × FPG/2)

ISI = exp[2.63 - 0.28*ln(I0) - 0.31*ln(TG)] [13]

QUICKI= 1/[log(I0) + log(G0)] [24]

TG_HDL = TG/ HDL

Statistical Analysis

All analyses were conducted using SPSS version 26 (SPSS Inc., Chicago, IL). Kolmogrov Smirnov test was used to evaluate the distribution of data. Student t-test and Mann-Whitney U tests were used to determine the difference of variables between two groups according to the distribution of data. Descriptive statistics were shown as weighted means with 95% confidence intervals (95%CI) for numerical data. Linear regression analyses were performed to evaluate associations between thyroid hormone level and IR parameters and the results were expressed as beta coefficients and 95% CIs. The rate comparisons were found by Chi-square and Fisher exact tests, according to the research groups of gender which are categorical variables. The receiver Operating Characteristic (ROC) Curves were implemented to discern decision levels (cut-offs) of IR indices in early diagnosis of metabolic syndrome. The results were regarded as significant with p value less than 0.05.

RESULTS

Baseline characteristics of subjects according to thyroid dysfunction are presented in Table 1. The mean age of the subjects was 47±12 years and 69% of subjects were female. The groups were similar in terms of age and gender dispersion (P=0,29, P=0,32). When TSH averages were reviewed, the mean hypothroid was determined as 5,2(4,7-6,8), and control group was 1,69 (1,5-1,8) mIU/L. The mean of hypothyroid group was significantly higher (P<0,001). The mean fT3 of hypothyroid patients was determined to be 3,38(3,19-3,61). This average was not significantly different than the average of the control group, which was 3,51(3,47-3,58) (P=0.08). When fT4 averages were evaluated, the average of hypothyroid was found to be 0,77(0,67-0,85) and the average of control group was found to be 0,82(0,81-0,84) (P=0.001). No significant difference was observed between the two groups in terms of glucose, HDL, TG, CHOL, Hba1c, Insulin values (P=0,06, P=0,16, P=0,07, P=0,5, P=0,99, P=0,43).

The mean HOMA index of hypothyroid patients (n=41) was 2,08 and the control group was 1,8. The difference between the

mean HOMA-IR index of metabolic syndrome in the control and hypothyroid groups was not statistically significant (P=0.27). When we examined the insulin resistance indexes, the ones with significant differences between the hypothyroid and control groups were the TyG index and TG/HDL ratio. (P=0,03 and P=0,04)

When ROC analyses were performed for TyG index and TG/HDL, the AUC values of each parameters were 0.602 and 0.598, respectively, and both were significant. (P=0,043, P=0,048) In the ROC analysis while the cutoff value for the TyG index was >4.74, the sensitivity of the test was 58,5 and the specificity was 67,5. For the TG/HDL ratio, the cutoff value was >2,43 and the sensitivity of the test was 59 and specificity was 65,9. When we evaluated all insulin resistance indices with ROC analysis, from the largest AUC value to the smallest, they were TyG index, TG/HDL ratio, ISI value and HOMA-IR, QUICKI, respectively. (0,602, 0,598, 0,579, 0,554, 0,554)

When we examined the associations between IR indices and TSH and fT4 using linear regression test, we found that there was a significant positive association between TyG index and TSH. (β=0,118, P=0.045) We concluded that there was no trend between other indices and thyroid hormones. (Table 2, Table 3)

Table 1. Basic characteristics and biochemical values of hypothyroid and control groups
Tablo 1. Hipotiroidi ve kontrol gruplarının temel özellikleri ve biyokimyasal değerleri

TEST	Hypothyroid	Control	p value
n	41	249	
Age	46(38-52)	49(46-52)	0,29
Glucose(mg/dl)	96 (91-100)	91(90-93)	0,06
Hba1c	5,6(5,5-5,7)	5,6(5,5 -5,6)	0,99
HDL	48 (43-53)	52(49-53)	0,16
HOMA-IR	2,08(1,56-2,49)	1,8(1,63-1,93)	0,27
Insulin	8,78(6,35-11,5)	7,94(7,3-8,6)	0,43
ISI	6,6(5,73-7,43)	7,1(6,9-7,5)	0,1
CHOL	210(190-228)	214(209-222)	0,5
QUICKI	0,342(0,333-0,357)	0,349(0,345-0,354)	0,27
fT3	3,38(3,19-3,61)	3,51(3,47-3,58)	0,08
fT4	0,77(0,67-0,85)	0,82(0,81-0,84)	0,001
TyG index	4,76 (3,81-5,69)	4,62(4,57-4,67)	0,03
TSH	5,2(4,7-6,8)	1,69(1,5-1,8)	<0,001
TG	133(114-160)	113(101-121)	0,07
TG/HDL	2,9(2,4-3,5)	2,2(1,97-2,35)	0,04
Gender(F/M)	31 / 17	170 / 79	0,32

Table 2. Associations between TSH and IR indices
Tablo2. TSH ve IR indeksleri arasındaki ilişkiler

Index	Beta	P value
TG/HDL	0,066	0,294
HOMA-IR	0,023	0,39
TyG	0,118	0,045
QUICKI	-0,037	0,531
ISI	-0,073	0,213

Table 3. Associations between Ft4 and IR indices
Tablo 3. Ft4 ve IR endeksleri arasındaki ilişkiler

Index	Beta	P value
TG/HDL	-0,067	0,255
HOMA-IR	-0,087	0,137
TyG	-0,064	0,279
QUICKI	0,084	0,151
ISI	0,066	0,265

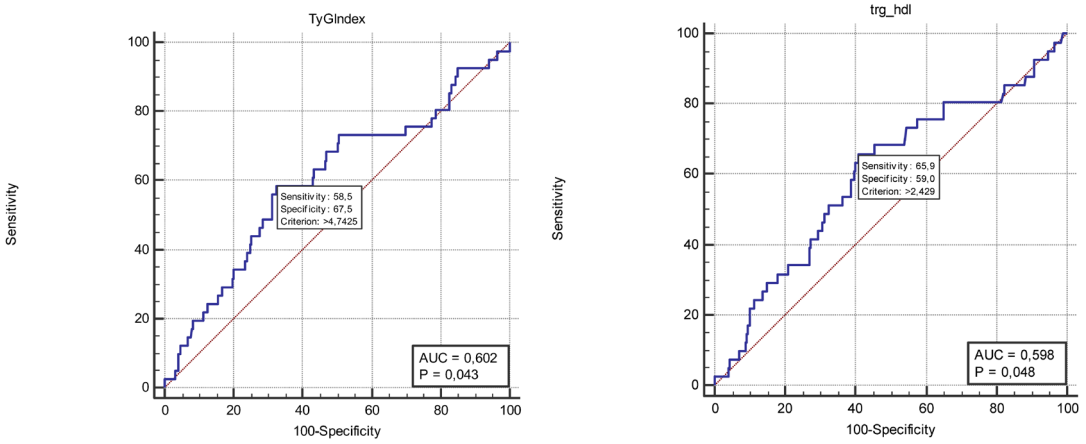
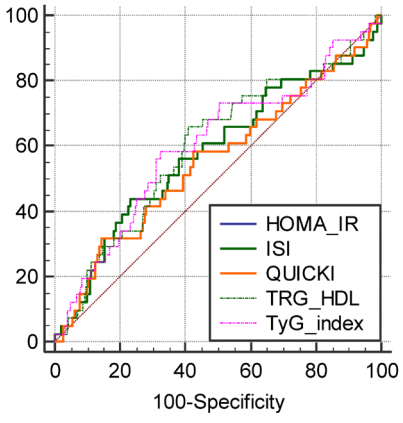


Figure 1. ROC Curves Analyses, area under curve (AUC), sensitivity, specificity, cutoff levels for TyG index and TG/HDL



Variable	AUC	SE [a]	95% CI [b]
HOMA_IR	0,554	0,0525	0,494 to 0,612
ISI	0,579	0,0524	0,520 to 0,637
QUICKI	0,554	0,0525	0,494 to 0,612
TG_HDL	0,598	0,0501	0,539 to 0,655
TyG_index	0,602	0,0511	0,543 to 0,659

Figure 2. ROC Curves for HOMA-IR, ISI, QUICKI, TG/HDL, indeces

DISCUSSION

Tissue insülin resistance (IR) is an important factor related to cardiovascular disease, metabolic syndrome and diabetes. Therefore, it is important to notice IR in order to perform therapeutic intervention at the pre-disease stage. In our study, we evaluated the surrogate parameters listed in the literature as indicators of IR in patients with hypothyroidism. Multiple studies have been conducted in the past to evaluate the diagnostic effectiveness of HOMA-IR, TyG index, TG/HDL, ISI, QUICKI index and an optimal cut-off point has been designed for these indexes. [14-17] However, studies on how effective these parameters are in patients with hypothyroidism and what their cutoff values are limited. Thyroid hormones have important effects on many metabolic events and developmental processes. Thyroid hormones affect carbohydrate metabolism through positive transcriptional

regulation of muscle and adipose tissue-specific GLUT4 receptors and stimulate lipolysis in skeletal muscle and adipose tissue. All these steps occur under the influence of insulin. [18] Thyroid hormones can further alter carbohydrate metabolism by interacting with leptin, adiponectin, and ghrelin.

The effect of hypothyroidism on insulin resistance and glucose metabolism is controversial. In Oweckietal's study, it was shown that thyroid functions had no effect on insulin sensitivity measured by HOMA-IR. [10] Another study, also using KNHANES VI data from children and adolescents, could not demonstrate any correlation between thyroid hormone level and IR.[19] In the study by Real et al., in addition to the idea that hypothyroidism directly causes insulin resistance, it is suggested that serum TSH increase and insulin resistance occur simultaneously with the underlying factors, and the resulting dyslipidemia causes changes in endothelial functions even at normal TSH levels. [20] Ambrosi et al demonstrated higher TSH levels in obese patients with IR and found that TSH was positively associated with the HOMA-IR and negatively associated with the QUICKI, respectively.[21] In our study, when we evaluated insulin resistance by taking HOMA-IR values into account, it was found that although the mean value (2.08) was higher in hypothyroid patients than in the control group (1.8), there was no significant difference between the groups when evaluated statistically (p=0.27). Some studies have indicated that constituents of metabolic syndrome are associated with increased TSH levels. [22,23] In our study, we found a positive association between TSH and TyG index. (β=0,118, P=0.045)

When we compare ROC curves; TyG index (0,602) had the highest area under curve followed by TG/HDL (0,598) and ISI (0,579), while QUICKI (0,554) and HOMA-IR (0,554) had the lowest area under curve. (fig.2) When we consider the statistically significant parameters for hypothyroid patients, TyG index and TG/HDL ratio are included. The cutoff value for TyG index was >4.74, while the cutoff value for TG/HDL was >2.43. (fig1)

The ISI index was shown to have better reproducibility compared to other indices in the study by Hancox et al. The mean ISI (McAuley) index in this population was 6.72 and was highest in obese and lowest in normal weight adolescents. [24] Although the ISI value was found to be <6.02 for hypothyroid patients in our study, the p value was not significant (P=0,127) In other studies the most sensitive and specific indirect method was McAuley's score (ISI).[17, 25]

Although QUICKI and HOMA are similar, QUICKI transforms the data by taking both the logarithm and the inverse of the glucose and insulin values. These mathematical calculations allow us to take into account factors such as the non-Gaussian distribution of the results in the general population in the final calculation. The purpose of calculation changes according to such distribution is to increase the correlation of the obtained results with the gold standard (metabolic clamp). As expected in the study by Katz et al.,given the similarities between QUICKI and HOMA, the two methods correlate well. Nevertheless, the correlation between QUICKI and the metabolic clamp is significantly better than the correlation between HOMA and the metabolic clamp. [26] In our study, we could not detect any significant difference between hypothyroid and euthyroid normal populations for HOMA-IR and QUICKI indices. (p=0,27) The reason for this can be explained by the low number of participants in the hypothyroid group.

This study has some limitations. First, since some of the metabolic syndrome diagnostic criteria (basal metabolic index, waist circumference, whether the patients have hypertension, etc.) were missing in the study, it was not possible to separate patients with metabolic syndrome. In our study, the failure to adjust for lean mass may have biased the

cutoff point because insulin resistance was significantly overestimated in overweight individuals. However, this should be considered in future studies. In addition, the data should be confirmed with studies with a higher number of hypothyroid patients.

In conclusion: Our study is one of the rare studies investigating insulin resistance indices in hypothyroidism. In addition, the significant parameters; TyG index and TG/HDL ratio analyses are cost effective, easy to access and calculate, which is valuable in terms of predictive value. As a result, it was determined that the most significant insulin resistance indices in hypothyroid patients were TyG and TG/HDL means low thyroid function was associated with a higher TyG index and TG/HDL. The TyG index cut-off value for hypothyroid patients was >4.74, while the cut-off value for TG/HDL was >2.43.

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