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The relationship between papillary thyroid cancer and triglyceride/glucose index, which is an indicator of insulin resistance

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Abstract. – OBJECTIVE: The incidence of thyroid cancer and metabolic syndrome has been increasing at the same rate over the past few decades. We hypothesized that there would be a direct relationship between thyroid papillary cancer and triglyceride/glucose index (TyG).

PATIENTS AND METHODS: A total of 382 operated patients were divided into two groups: patients operated on for papillary thyroid cancer and for non-malignant reasons. Each patient's age, gender, operation times, presence of neck dissection, serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4), fasting blood glucose and triglyceride levels were scanned retrospectively from the archive system.

RESULTS: TyG index was statistically higher in the malignant group. Receiver operating characteristic (ROC) curves obtained for TyG levels at the time of diagnosis of thyroid papillary cancer were AUC: 0.608. The threshold value for TyG was 6,252. The sensitivity of this value was 62.8% and the specificity was 49.2%.

CONCLUSIONS: In this study, we investigated the predictive effect of the TyG index in differentiating thyroid papillary carcinoma from non-malignant thyroid lesions. We concluded that the TgY index can be used to identify people at high risk of thyroid papillary cancer and to plan treatment.

Key Words:
Thyroid cancer, Benign thyroid lesions, Triglyceride glucose index.

Introduction

Solitary and multiple thyroid nodules (TN) are frequently seen in admissions to the General Surgery outpatient clinic. Approximately 5% of nodules with biocide indication are reported as malignant[1]. Thyroid cancer has become more common all over the world in recent years. The most common subtypes of thyroid cancer are follicular carcinoma and papillary thyroid cancer (PTC)[2]. Raising the diagnostic ratio has the critical goal of detecting suspected thyroid cancers as soon as possible and avoiding needless thyroid surgery. The advancement of ultrasonography (particularly the use of high-resolution ultrasound) has boosted the diagnosis of thyroid nodules and thyroid malignancies[3].

Many common metabolic problems, such as excessive weight, dysglycemia, hypertension, and dyslipidemia, are included in the Metabolic Syndrome (MS)[4]. Although metabolic syndrome is not a disease in and of itself, it increases the chance of developing diseases including type 2 diabetes, heart disease, and stroke[5]. Insulin resistance (IR) is increasingly acknowledged as a crucial component in carcinogenesis, since it is crucial in the development of the metabolic syndrome. Endometrium, lung, pancreatic, hepatocellular, prostate, colorectal, and breast cancer incidence have all been linked to insulin resistance and metabolic syndrome[6-12].

The triglyceride glucose index (TyG) is a novel metabolic syndrome biomarker with high sensitivity and specificity. Also, TyG is a novel and accurate biomarker of insulin resistance[13,14]. Metabolic syndrome and insulin resistance are reported to be significant variables linked to an increased risk of thyroid cancer[15]. However, the findings of this research have not been verified and should be confirmed by further research. In this study, we aim at evaluating the role of triglyceride glucose index in PTC risk, which is an indication of insulin resistance.

Patients and Methods

Study Population

Our research was conducted in a retrospective and cross-sectional method after it was approved

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by the Hitit University Clinical Research Ethics Committee with the decision No.: 2022-42. We collected data by examining patient files and computer records. The patients who applied to the Department of General Surgery who underwent bilateral total thyroidectomy between 2013 and 2021 were scanned and a total of 1,517 patients were identified. The patients with papillary thyroid carcinoma and the patients operated on for colloidal hyperplasia were divided into two groups and 852 patients were identified. Random cluster sampling was used to select the study population. We planned the study within the scope of the Helsinki Declaration. This study included patients who had ultrasonography results and full clinical data. Of these, 470 patients under age 18, with unsatisfactory results, were removed from the study, including patients with a history of radiotherapy or surgery in the head and neck, a history of serious neurological or psychiatric disease, pregnant women, breastfeeding women and participants with other disorders such as liver, heart and kidney disorders. Then, 382 patients were included in the study.

Laboratory Analysis

Samples were taken from the cubital vein of each patient for fasting blood glucose after at least 12 hours of fasting. The triglyceride/glucose index (TyG) was added to the study with the formula of "Fasting TG [mg/dl] x fasting glucose [mg/dl] /2" on the basis of the values obtained during admission of the patients to the hospital.

Statistical Analysis

The IBM SPSS Statistics for Windows program was used for all statistical analyses (version 26; IBM Corp., Armonk, NY, USA). For categorical variables, descriptive statistics were provided using numbers and percentages numeric variables were reported with mean, standard deviation, and median in parenthesis. Data normal distribution was evaluated with a Shapiro-Wilks' test. The relations between the variables were investigated through Pearson or Spearman correlation coefficient in accordance with the data distribution. The comparison of numerical measurements by research groups for two independent groups was evaluated with two-sample *t*-tests for age alone in accordance with the data distribution.

The surgery durations, TSH, fT3, fT4, glucose, triglyceride, and triglyceride glucose rates were evaluated with the Mann-Whitney U test. The rate comparisons were found by Chi-square and Fisher exact tests, according to the research groups of gender and neck dissection, which are categorical variables. The ROC curve was used so as to indicate the distinctiveness of the variables that were statistically significant and the cut-off values for markers were found by using the field below it and the Youden index. The sensitivity, specificity, PPV, NPV, and accuracy values were calculated for these cut-off values. The odds ratio values were calculated according to the cut-offs. In terms of statistical significance level, $p<0.05$ was considered significant.

Results

A total of 382 patients were included in the study. Of the 382 patients, 128 patients were operated on for non-malignant reasons, and 254 patients had papillary thyroid carcinoma. In the non-malignant group (Group I), while the female patient ratio was 69.5%, in the PTC group (Group II) this ratio was 77.2%. Statistically, no significant difference was observed (p=0.106, Table I).

The average age of the two groups was 51.55±11.94 (53) years for Group I and 50.19±13.24 (50) years for Group 2. No significant difference was observed in this respect (p=0.325). No significant difference was observed between the surgery periods of both groups. The mean duration of all the operations was determined to be 115.77±32.61 (112) minutes (p=0.736). Neck dissection was required in 11% (28) of PTCs and bilateral neck dissection was performed in 25%[7] of them (Table I).

When TSH averages were reviewed, the mean of Group I was determined as 3.53±15.86 (0.99), and Group II was 10.71±29.56 (1.18). The mean of Group II was significantly higher (p=0.05). The mean fT3 of non-malignant patients was determined to be 3.29±2.2 (3.18). This average was significantly higher than the average of the other group, which was 2.86±1.65 (3, p=0.004). When fT4 averages were evaluated, the average of Group I was found to be 1.27±0.47 (1.21) and the average of Group II was found to be 1.39±0.58 (1.35) ($p<0.001$).

In non-malign patients, the glucose average was determined to be 112.98±48.26 (97), and in patients with PTC, it was observed higher with an average of 143.05±45.59 (127.50, $p<0.001$). The mean triglyceride averages of the patients were

Table I. Comparison between groups.

Variables	Non-Malign	Papillary	*p*-value
Gender			0.106
Male, n (%)	39 (30.5)	58 (22,8)	
Female, n (%)	89 (69.5)	196 (77.2)	
Age, year, mean ± SD (median)	51.55 ± 11.94 (53)	50.19 ± 13.24 (50)	0.325
Operation Duration minute ± SD (median)	115.19 ±29.8 (116.5)	116.07 ± 33.99 (110.5)	0.736
TSH, uU/ml, mean ± SD (median)	3.53 ± 15.86 (0.99)	10.71 ± 29.56 (1.18)	0.05
fT3, pg/mL, mean ± SD (median)	3.29 ± 2.2 (3.18)	2.86 ± 1.65 (3)	0.004
fT4, ng/dL, mean ± SD (median)	1.27 ± 0.47 (1.21)	1.39 ± 0.58 (1.35)	< 0.001
Glucose, mg/dL, mean ± SD (median)	112.98 ±4 8.26 (97)	143.05 ± 45.59 (127.50)	< 0.001
Triglyceride, mg/dL, mean ± SD (median)	144.21 ± 76.63 (126.5)	152.24 ± 163.53 (122.5)	0.691
TyG	8,303.46 ± 5,896.20 (6,446)	10,603.06 ± 9,795.03 (8,506.5)	0.001
Neck Dissection			
No Dissection	128 (100%)	226 (89%)	
Dissection	0 (0)	28 (11%)	
Dissection Side			
Unilateral		21 (75%)	
Bilateral		7 (25%)	

lower than the average in Group I, 144.21±76.63 (126.5), and in Group II, 152.24±163.53 (122.5); however, no statistical significance was observed (p=0.691).

When the triglyceride glucose value was calculated and analyzed, it was determined that non-malignant patients had a statistically significantly lower value with a mean of 8,303.46±5,896.20 (6,446) compared to the patients with papillary thyroid carcinoma whose mean was 10,603.06±9,795.03 (8,506.5, p<0.001).

The triglyceride glucose value, which is significantly different for the separation of both groups, was evaluated with the area below the ROC curve and the Youden index. Triglyceride glucose value was determined as 6,252 with 62.8% sensitivity, 49.2% specificity, 72.9% positive predictive value, 44.4% negative predictive value and 62.3% precision (OR 2.147, CI 95% 1.387-3.323, p<0.001) (Figure 1). It was determined that a patient with a triglyceride glucose value of 6,252 and above was 114% more likely to be within the PTC group than a patient with a triglyceride glucose value of 6,252 and below (Table II).

Discussion

We investigated the effect of TyG on thyroid papillary cancer incidence and we demonstrated for the first time that triglyceride glucose index may predict thyroid papillary cancer incidence. The triglyceride glucose index was first reported as an indicator of insulin resistance. The triglyceride glucose index is calculated using fasting triglycerides and plasma glucose[16]. Therefore, some studies[17-20] that have used this index have also specified the predictability of type 2 diabetes, colorectal cancer, and bladder cancer. We also concluded that the triglyceride glucose index value of 6,252 is a cut-off value for thyroid papillary cancer.

A number of human studies[21-25] have looked into the link between insulin resistance and thyroid function in the past. Choi et al[21] found that

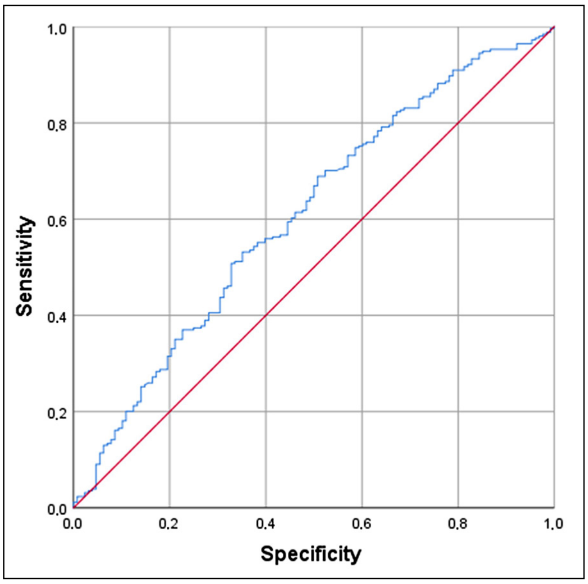

Figure 1. Receiver operating characteristic (ROC) curves obtained for TyG, glucose and triglyceride levels.

Table II. Cut-off points and diagnostic values of variables for distinction between papillary thyroid carcinoma and non-malignant lesions.

		Diagnostic values					ROC curve			Odds ratio		
Variables	Cut-Off	Sensitivity	Specifity	PPV	NPV	Accuracy	Area (SE)	% 95 CI	*p*-value	Odds ratio	% 95 CI	*p*-value
TyG	6252	62.8%	49.2%	72.9%	44.4%	62.3%	0.608 (0.031)	0.548-0.668	0.001	2.147	1.387-3.323	0.001

among euthyroid Korean individuals, low-normal thyroid function is related to a higher triglyceride glucose index. Furthermore, it was shown in the same study that insulin resistance is an effective surrogate metric for assessing the link between triglyceride glucose index and thyroid function. Furthermore, Choi et al[22] found that insulin resistance and thyroid hormones had a substantial association. While most cancers associated with obesity, gastric cancers, colorectal cancer, and small-cell lung cancer have been investigated for triglyceride glucose index in the carcinogenesis of many cancers. This study is of clinical importance as it represents the first study to conclude that insulin resistance can be used as a predictable marker for thyroid papillary cancer[23-25].

Insulin resistance activates the PI3K/Akt/mTOR/S6K signal pathway for cancers, increasing the amount of insulin to supply glucose to the tumor cell[26]. In addition, serum TG increases and induces Akt signaling pathway with the activation of G protein wound receptor[27]. Through these pathways, the hyperinsulinemia caused by insulin resistance contributes to the progression of thyroid papillary cancer and the increase of the tumor cells.

Insulin-like growth factor-1 (IGF-1), as it is well known, sustains the survival of the cell and activates angiogenesis and cell proliferation[28]. Additionally, IGF-1 increases the production of vascular endothelial growth factors, which increases insulin resistance and supports tumor growth[29]. A human study[30] has shown that an increase in IGF-1 and its receptors increases with an increase in the size of the tumor in thyroid papillary cancer.

Hyperglycemia causes a rise in intracellular glucose, according to studies[31] like NF- κB. However, it has been shown that NF- κB plays an important role in thyroid cancer due to its ability to control proliferative and anti-apoptotic signaling pathways in thyroid neoplastic cells[32]. Park et al[33] showed that peroxisome proliferator-activated receptor gamma (PPARγ) may be involved in thyroid carcinogenesis. In addition, many studies have shown that the drugs developed against the PPARγ receptor will cause antiproliferation and apoptosis in the tumor cell[34,35]. The link between PPARy and insulin resistance in adipocytes was depicted by Kubota et al[36]. Furthermore, in human individuals, both blood plasma glucose and triglyceride levels are linked to an increased risk of thyroid cancer[37-39]. Thus, the triglyceride glucose index is comprised of triglyceride and glucose levels, and the triglyceride glucose index is expected to be a more beneficial risk indicator for thyroid cancer.

Limitations and Strengths

There are certain limitations to our research. Our research was a retrospective one with a small number of participants. In addition, TG values of some thyroid patients were not examined. Therefore, there were patients that we could not include in the study. We did not put together the patients who were obese and already had insulin resistance in a separate group. Finally, in this study, the Triglyceride glucose index was only included in the analysis during the first visit, and we did not take into account the factors of healing and deterioration during the follow-up.

Although triglyceride glucose index was used in many cancers, our study is the first to investigate it in thyroid cancers. Furthermore, the triglyceride glucose index is cheap, easy to access, and easy to calculate the index, which is valuable in terms of its predictive value.

Conclusions

The triglyceride glucose index is a useful and accessible tool for predicting thyroid cancer in patients with nodules in the thyroid. For the early detection of thyroid cancer, we should encourage those with a high triglyceride glucose index to be scanned for thyroid cancer, which is 6,252 as a result of our study.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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None.

Ethical Approval

Hitit University Clinical Research Ethics Committee with the approval number: 2022-42.

Informed Consent

Because the study was retrospectively designed, informed consent was not required from participants.

Availability of Data and Material

The data supporting the conclusions of this article will be made available by the authors without undue reservation.

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Authors' Contribution

EGA: Idea/Concept, design, analysis, literature review, references, writing the article; VBT: Control/supervision, analysis, literature review, critical review; MBT: Data collection, statical analysis, writing the article, FŞ: Data collection, writing the article, KC: Data collection, writing the article.

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