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Original Article

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Evaluation of Risk Factors for Malignancy in Patients With Thyroid Nodules

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Abstract

Background: Despite thyroid nodules mostly have benign nature, there are always malignancy risks. Therefore, understanding the mechanisms influencing this potential malignant transformation is highly important in thyroid cancer prevention strategies. We aimed in this case-control study to investigate the relationship of anthropometric parameters, and insulin resistance with thyroid nodules and the malignancy risk in nodular thyroid patients.

Methods: This single-center case-control study included 81 patients with thyroid nodules who were divided into two groups according to post-thyroidectomy pathology: the malignant group included 36 differentiated thyroid carcinoma patients and the benign group included 45 patients. We compared the anthropometric and radiological parameters, homeostasis model assessment of insulin resistance (HOMA-IR), and insulin levels between both groups.

Results: We observed significant differences as regard HOMA-IR, insulin levels and waist circumference between both groups. Benign thyroid nodules volume correlated with weight, waist, body mass index (BMI), fat percentage, age, HOMA-IR, and insulin levels. Malignant thyroid nodules volume did not correlate with any parameters apart from weight. We found that the final significant risk factor was HOMA-IR in stepwise logistic regression analysis.

Conclusions: Malignant thyroid nodules are associated with higher insulin resistance, visceral obesity, and hyperinsulinemia. Furthermore, higher HOMA-IR is a significant risk factor for differentiated thyroid carcinoma.

Keywords: Thyroid nodules; HOMA-IR; Insulin; Waist; Visceral obesity

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Introduction

Thyroid nodules (TNs) are one of the most common thyroid disorders and their prevalence has been rising in the last decades all over the world. This increase could partially attribute to advances in radiology equipment which allows for early diagnosis of TNs. Nevertheless, other factors are also assumed to be involved such as the pandemic of obesity [1]. Even though, benign nature of most of the TNs, there is always risk of malignancy of the nodules. Similarly, there is an increase in the prevalence of thyroid carcinoma which was predicted to become the third most common cancer in women [2]. Therefore, understanding the pathophysiological mechanisms influencing nodular thyroid disease and possible malignant transformation is highly important in thyroid cancer prevention strategies.

On the other hand, obesity constitutes a worldwide epidemic with prevalence rates, which are skyrocketing worldwide. Obesity has been linked to several cancers including breast cancer, endometrial carcinoma, prostate cancer, ovarian cancer, and colorectal cancer [3]. Therefore, investigating the relationship of TNs or malignancy with obesity attracted the attention of researchers over the last few years. Some studies reported increased risk of TNs with obesity [4, 5], metabolic syndrome components [6], and even with child obesity [7]. However, other studies have failed to find a causative link between obesity and either benign nodular thyroid disease or thyroid cancer [8, 9]. Moreover, one study reported that morbid obesity in women according to body mass index (BMI) was associated with a lower prevalence of TNs [10].

In the same vein, adipose tissue is not unique. Adipose tissue can be classified into central and peripheral. Central obesity has already been linked to greater metabolic risks [11]. Metabolic syndrome and central obesity adiposity are strongly

linked to insulin resistance (IR). IR is thought to be a pivotal factor in the development of this syndrome. Furthermore, studies have been reported that hyperinsulinemia can act as a factor in thyroid cell proliferation, which has been demonstrated in cell culture [12]. However, central obesity and IR association with TNs cancer risk are still controversial in observational studies. Few studies linked central obesity to a higher prevalence of TNs [13]. Whereas another study failed to find this association after adjusting for other confounding factors [14]. Hence, the relationship between IR and visceral obesity with the risk of malignancy in TNs merit high clinical importance in an attempt to control possible risk factors for malignant transformation.

Therefore, we aimed in this case-control study to investigate the relationship of anthropometric parameters, and IR with TNs, and the risk of malignancy in patients with nodular thyroid disease.

Patients and Methods

This study proposal was reviewed and approved by the Institutional Research Board at Mansoura Faculty of Medicine. The study was performed according to the Helsinki Declaration 1964.

Study population

We conducted a single-center case-control study that included patients with euthyroid TNs who underwent thyroid surgery in the Surgical Oncology Unit at Mansoura University Oncology Center (OCMU) between July 2020 and July 2021. Inclusion criteria were patients with TNs, normal thyroid function; single or multiple; both sex; and ages above 18 years old. Exclusion criteria were: patients with undifferentiated thyroid carcinoma; patients with known thyroid autoimmunity, neck irradiation history; neck surgery history, previous thyroid replacement or suppression therapy at any time; exposure to iodinated contrast materials in the last 6 months; pregnancy and lactation; diabetic patients; and patients on medication affecting IR. Normal thyroid function was defined as having normal levels of thyroid-stimulating hormone (TSH), free thyroxine (free T4), and free triiodothyronine (free T3). All patients who participated in the study provided informed consent, stating unequivocally what would be done and guaranteeing complete confidentiality.

There have been no recent studies that have looked at the iodine status in our area. However, the World Health Organization (WHO) classified Egypt as a country with adequate iodine intake and optimal iodine nutrition. Furthermore, a recent study in the coastal governorate reported urinary iodine median value to be 150 µg/L [15].

Clinical assessment and anthropometric measurement

All patients were subjected to a thorough medical examination, that included: a medical history with a focus on the duration of thyroid disease, any family history of TNs, smoking history, diabetes mellitus and hypertension history; a thorough physical examination of the thyroid gland and draining lymph nodes was performed; and anthropometric parameter measurements. Height (cm) and body weight (kg) were measured in a standing position and minimally clothed without shoes. BMI was determined by dividing weight in kilograms by height in meters squared (kg/m^2). The body fat percentage (BFP) was calculated based on BMI according to the formula:BFP = (1.20 × BMI) + (0.23 × age) - (10.8 × sex) - 5.4, where age is in years and sex is set to 0 for women and 1 for men [16].

Biochemical, radiological, and pathological evaluations

All blood samples were taken between 8:00 and 9:00 in the morning and after 8 h of fasting. Samples were stored at -70 °C until the day of the test. Patients were tested for: fasting blood glucose (FBG); insulin level; thyroid profile including TSH, free T3, and free T4; preoperative laboratory test including complete blood count, liver function test, and creatinine. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by dividing the product of glucose (mg/dL) and insulin (mU/L) by 405. IR was defined by a HOMA index of 2.5 [17].

Thyroid ultrasonic examination was performed by a collaborative radiologist with 7.5 - 10 MHz linear array transducer. Thyroid gland was scanned while patient was in a supine position, with his neck being slightly overextended by pillow under the shoulders. The volume of the TNs was calculated by using the following formula: length × width × depth × $\pi/6$ [18].

Most of the patients were investigated by preoperative fine needle aspiration cytology. However, the permanent postoperative pathological examination was done for all patients.

Statistical analysis

The Statistical Package for the Social Sciences Version 22.0 (SPSS22.0, IBM Corp, Armonk, NY, USA) was used to analyze the statistical data. All data were checked for normality of distribution. All continuous variables were expressed as the mean ± standard deviation (SD) or median and interquartile range according to the normality of distribution. Categorical variables were expressed as a percentage. The Mann-Whitney U test was used to compare the non-normally distributed variables. An independent *t*-test was used to compare the variables with normal distribution. Patients with malignant TNs were compared to those with benign nodules using independent *t*-tests, Mann-Whitney U test, and Chi-square test. Pearson correlation was used to determine parameters significantly correlated with TN volume in each group. The risk factors associated with malignant TNs were assessed by stepwise logistic regression analysis. The odds ratio (OR) and 95% confidence interval (CI) were calculated. $P \leq 0.05$ was considered statistically significant.

Results

A total of 81 patients with nodular thyroid disease were included into this study, including 12 males and 69 females with the

Table 1. Demographic, Clinical, and Laboratory Characteristics Comparison Between Study Groups

	Malignant nodules (n = 36)	Benign nodules (n = 45)	P value
Age[a] (years)	36.5 (24.5)	35 (13.5)	0.152
Sex[b]			0.758
Male	6 (13.3%)	6 (16.7%)	
Female	30 (86.7%)	39 (83.3%)	
Hypertension[b]	7 (19.4 %)	4 (9.1%)	0.208
Body weight[c] (kg)	82.5 ± 18.2	76.33 ± 16.43	0.122
Height[a] (m)	1.6 (0.12)	1.6 (0.06)	0.913
BMI[c] (kg/m^2)	31.59 ± 7.09	29.22 ± 5.6	0.107
WC[c] (cm)	110.71 ± 16.21	102.74 ± 13.25	0.021
BFP[c]	39.96 ± 8.95	36.69 ± 11.62	0.168
Thyroid volume[a] (mL)	6.38 (27.41)	9.03 (14.65)	0.459
Largest dimension[a] (cm)	2.8 (1.48)	2.54 (1.48)	0.251
FBG[a] (mg/dL)	99 (25)	96.72(45)	0.704
Insulin[a] (µIU/mL)	13.39 (10.29)	9.94 (9.05)	0.032
Insulin[c] (log)	1.14 ± 0.23	1.001 ± 0.25	0.020
HOMA-IR[c]	4.01 ± 1.93	2.97 ± 1.57	0.014

[a]Data were expressed as mean (interquartile range) according to normality of distribution. [b]Data were expressed in parentheses are percentages. [c]Data were expressed as mean ± standard deviation. BMI: body mass index; WC: waist circumference; BFP: body fat percentage; FBG: fasting blood glucose; HOMA-IR: homeostasis model assessment of insulin resistance.

age range of 18 - 77 years old. According to post-thyroidectomy pathology, these patients were divided into two groups: 45 patients were in the benign TNs group, and 36 patients were in the malignant TNs group.

In the comparison of clinical, radiological, and laboratory parameters between benign and malignant TNs group, the means of HOMA-IR (P = 0.014) and waist circumference (WC) (P = 0.021) were significantly different between the two groups. Both medians of insulin levels (P = 0.020) and the insulin levels logarithm 10 (log) (P = 0.032) were significantly different between the two groups. There were no significant differences between the two groups as regards to these variables: anthropometric parameters including BMI, weight, height, and BFP; clinical parameters such as age, sex, and hypertensive patients' percentage; radiological parameters such as TN volume and largest nodular dimension; and FBG. More details were presented in Table 1.

In the benign TNs group, our results showed that TN volume significantly correlated with anthropometric parameters including WC, BMI, weight, and BFP; age; laboratory parameters such as HOMA-IR and insulin levels (log). In the malignant group, we did not find any significant correlation between the TN volume and other parameters except weight (r = 0.338). Other details were shown in Table 2.

Table 2. Pearson Correlation Between Nodule Size and Other Parameters

	All patients (n = 81)		Malignant nodules (n = 36)		Benign nodules (n = 45)	
	r	P value	r	P value	r	P value
Age (log)	0.29[a]	0.01	0.18	0.290	0.43[b]	0.003
Height (log)	0.22	0.06	0.25	0.137	0.17	0.283
Weight	0.41[b]	0.001	0.34[a]	0.044	0.54[b]	0.001
BMI	0.34[b]	0.002	0.23	0.176	0.54[b]	0.001
WC	0.26[a]	0.026	0.191	0.280	0.37[a]	0.015
BFP	0.3[a]	0.009	0.2	0.241	0.47[b]	0.002
HOMA-IR	0.25[a]	0.038	0.21	0.266	0.37[a]	0.015
Insulin (log)	0.23	0.059	0.05	0.812	0.45[b]	0.003
FBG (log)	0.05	0.661	0.05	0.814	0.07	0.676

[a]Correlation is significant at the 0.05 level (two-tailed). [b]Correlation is significant at the 0.01 level (two-tailed); BMI: body mass index; WC: waist circumference; BFP: body fat percentage; HOMA-IR: homeostasis model assessment of insulin resistance; FBG: fasting blood glucose.

Table 3. Logistic Regression Analysis for Determination of Risk Factors of Malignancy in Thyroid Nodules

	B	SE	Wald	P value	Odds ratio	95% CI for odds ratio	
						Lower	Upper
HOMA-IR	0.328	0.148	4.921	0.027	1.389	1.039	1.856
Constant	-1.468	0.580	6.398	0.011	0.230		

HOMA-IR: homeostasis model assessment of insulin resistance; B: estimated coefficient; SE: standard error; CI: confidence interval. Variable(s) entered on step 1 backward Stepwise (Conditional) logistic regression analysis: insulin (Log), waist circumference, homeostasis model assessment of insulin resistance, age (log), body mass index, sex, body fat percentage.

Backward stepwise logistic regression analysis was used to determine the risk factors for malignancy in the nodular thyroid disease. The variables included in step 1 were: insulin (log), WC, HOMA-IR, age (log), BMI, sex, and BFP. Our result showed that the final significant risk factor was HOMA-IR (P = 0.027, 95% CI: 1.039 - 1.856) and the odd ratio was 1.389 (Table 3).

Discussion

Obesity prevalence has skyrocketed worldwide, and the incidence of thyroid cancer has risen in lockstep in recent decades. Growing evidence suggests that the rise in obesity prevalence is linked to an increase in thyroid cancer rates [19].

The main result in this case-control study was that differentiated malignant thyroid disorders were associated with higher IR estimated by HOMA-IR and hyperinsulinemia. In this study, we found that malignant TNs patients had higher IR, insulin levels, and WC. Furthermore, HOMA-IR was a significant risk factor for malignancy of TNs in regression analysis.

The association of IR with TNs, goiter, and thyroid cancer risks has recently become a controversial topic in the field of thyroid disorders. The results in the current study were consistent with the scarce studies results that evaluated IR in cancer thyroid patients in Asian, European, and Caucasian races [20-23]. These studies observed that TNs were more common in people with IR and concluded that IR could be a significant risk factor for TNs malignancy. Furthermore, IR is linked with malignant TN size [20, 22]. On the other hand, our results were in contrast with the other two studies in Asian and Caucasian ethnicity [14, 24].

In the same vein, in this study we found HOMA-IR and insulin levels correlated with benign TNs volume. Similarly, IR was linked to thyroid disorders and thyroid volume in observational studies [20, 25], high prevalence of benign TNs [26], and thyroid ultrasound feature [27]. However, we did not observe this correlation in malignant TNs, which were in contrast with the other two studies [20, 22] that observed this correlation. The previous two studies had different study designs from our study, which could lead to this controversy in results. Our results could suggest that IR and hyperinsulinemia could promote the growth of benign TNs. However, a larger study is still needed to confirm these results.

In this study, we found malignant TNs were correlated with higher WC. The association between obesity parameters and thyroid cancer risks has been reported in meta-analysis [28], population-based [29], and observational studies [30]. Nevertheless, the magnitudes of this association were different across studies according to the parameters that were used to assess obesity, patient selection, ethnicity, and comorbidity. No wonder, the visceral adiposity is strongly linked to IR. IR is a pathognomonic feature among patients who have metabolic syndrome, obesity, type 2 diabetes, polycystic ovarian disease, or pre-diabetes [31]. Furthermore, WC and BMI were correlated with the volume of benign TNs but not with malignant nodules. The association between TNs volume and IR has been observed by many studies [14, 25, 32]. Our result suggested that visceral obesity is more correlated to risk of thyroid malignancy than general obesity expressed in BMI, even though many studies reported an association between thyroid cancer and BMI [28].

The specific pathophysiological mechanisms by which adiposity enhances the risks of thyroid cancer are still unclear. Therefore, several potential mechanisms have been postulated. IR and subsequent hyperinsulinemia are well-known risk factors for tumorigenesis [33]. Insulin has structural homology with insulin-like growth factor-1 (IGF-1), which attaches to the IGF-1 receptors and functions as a potent growth factor in various types of cells, playing key roles in malignant transformation of the cell, tumor cell proliferation, and metastasis [34]. TSH is a significant hormone that controls the growth, proliferation, and differentiation of thyroid cells. It was reported that TSH levels are associated with IR and metabolic syndrome. Furthermore, one study concluded that increased thyroid volume in metabolic syndrome and IR patients is related to TSH [14]. One cell culture study proved that supraphysiological concentrations of insulin can promote thyroid cell proliferation and tumor cell migration [35].

Another hypothesized mechanism is the role of inflammation. Obesity is considered a chronic inflammatory status. Adipose tissue secretes inflammatory cytokines that could be involved in carcinogenesis, such as tissue necrosis factor-alpha (TNFα) and interleukin 6, which are linked to oncogene activation [36]. Consequently, this inflammatory microenvironment could be involved in the carcinogenesis and progression of thyroid cancer [37].

Another mechanism involves the impact of leptin on the hypothalamic-pituitary-thyroid axis. Leptin is an adipokine that could disturb negative feedback regulation of thyroid hormones at the pituitary and hypothalamic levels; and several reports linked IR to high leptin levels [38]. Therefore, IR contribution to the increase of serum TSH levels could be mediated through its effects on serum leptin concentrations [39]. In

the same vein, adiponectin is another adipokine whose levels are inversely proportional to adipose tissue mass. Adiponectin could suppress tumor cell proliferation via many pathways such as the AMP-activated protein kinase (AMPK) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) pathways [40]. An inverse association between serum adiponectin levels and the incidence of malignant thyroid disorders has been reported [41].

Another mechanism involves the pleotropic effect of vitamin D. Vitamin D deficiency could link TNs with IR and obesity. Low vitamin D levels were reported in TNs [15], obesity [42], and IR [43]. Vitamin D had a pleiotropic effect and was reported to have an anti-neoplastic and anti-inflammatory effect which could be involved in thyroid cancer tumorigenesis [44]. Vitamin D could inhibit tumor cells growth [44], induce apoptosis of tumor cell through activating pro-apoptotic proteins and suppression of anti-apoptosis proteins, promote differentiation, decrease invasiveness, and arrest cell cycles [45].

Finally, thyroid autoimmunity may link obesity with thyroid cancer. Obesity is significantly associated with thyroid autoimmunity [45]. Thyroid autoantibodies were reported to be a risk factor for papillary thyroid carcinoma [46].

Study strengths and limitations

Our study has some points of strength. First, on-site height and weight measurements allowed us to identify significant associations between anthropometric measurements and TNs. Second, our pathology and imaging results were interpreted by experienced pathologists and radiologists in Mansoura Oncology Center. Finally, all patients' diagnosis were based on permanent post-thyroidectomy pathology.

This study also has some potential limitations. First, this was a single-center study in a tertiary hospital. Therefore, patient selection bias might exist. Second, we did not assess other potential confounders such as lifestyle, diet, smoking, and physical exercises in our study. Third limitation was the relatively small number of participants. Finally, we did not assay anti-thyroid antibodies. However, most of our study patients had negative results done before study time with variable time; and we excluded patients with a positive test for thyroid autoimmunity and with proven thyroiditis in post-thyroidectomy pathology examination.

Conclusions

The differentiated thyroid cancer was associated with increased IR, visceral obesity, and hyperinsulinemia. Furthermore, increased IR evaluated by HOMA-IR was a significant risk factor for differentiated thyroid cancer in nodular thyroid patients. We highlighted the role of visceral obesity and IR in TNs malignancy risks and the high clinical value of controlling IR and visceral obesity in patients with TNs. However, more longitudinal and observational studies are still required for better estimation of the effects of IR and hyperinsulinemia on thyroid cancer cell tumorigenesis and proliferation.

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Financial Disclosure

This research did not receive any fund.

Conflict of Interest

Authors have declared that no competing interest.

Informed Consent

All patients who participated in the study provided informed consent, stating unequivocally what would be done and guaranteeing complete confidentiality.

Author Contributions

AZ, MS and IE performed the thyroidectomy. RA performed the pathological examination. DK performed the radiological examination. AE performed the laboratory tests. AZ, MS, IE, EE, SG and MA contributed to patients' selection, clinical examination, and follow-up. MH, EE, SG and MA contributed to the conception, interpretation of the data, and statistical analysis. All the authors were involved in writing, reviewing, editing and have approved the final manuscript and authors list.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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