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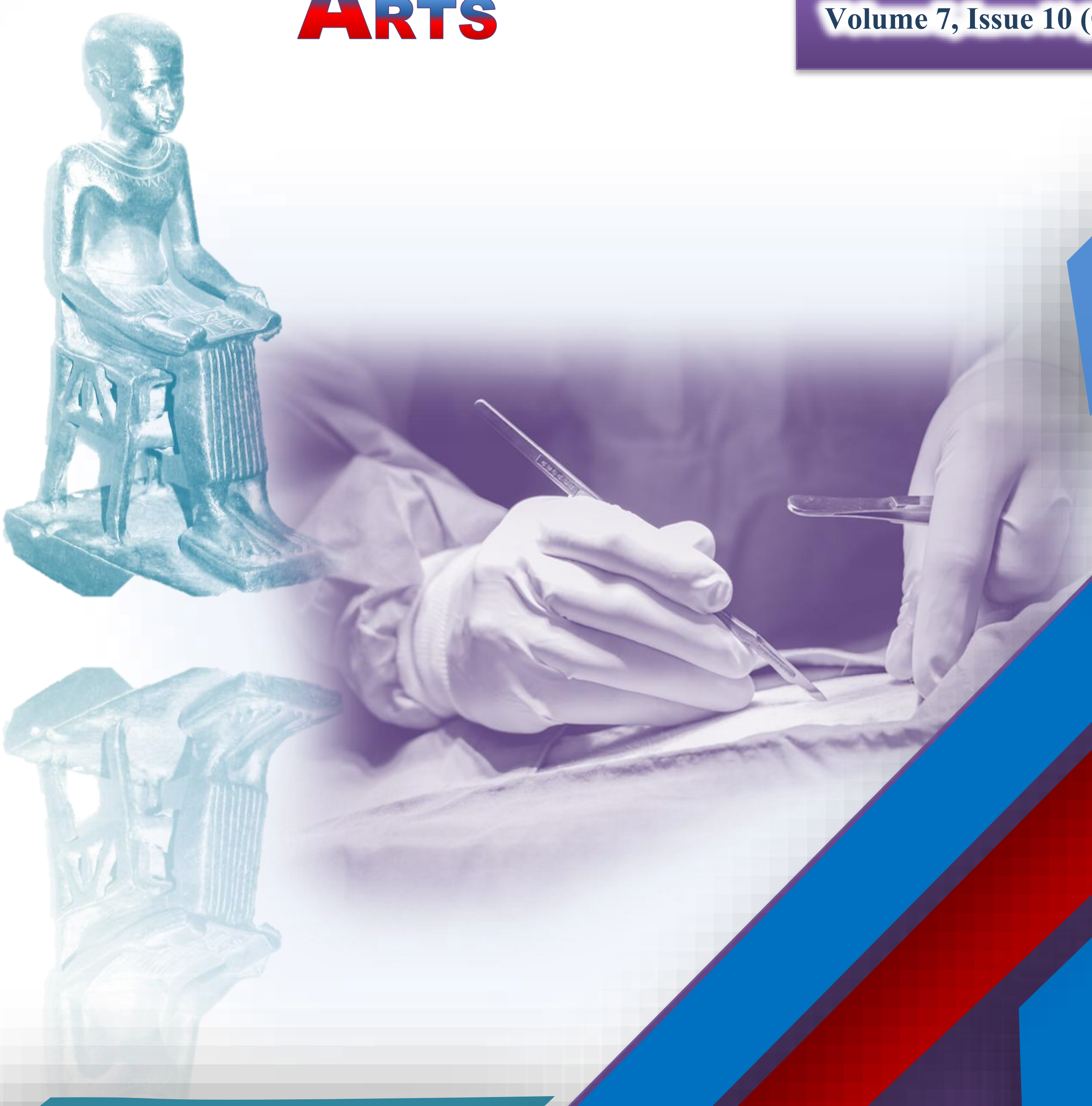

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Original Article

Correlation Between Thyroid Nodules and Insulin Resistance in Egyptian Patients Without Diabetes Mellitus

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Abstract

Background: Thyroid nodules [TNs] exhibit a higher prevalence in individuals with type 2 diabetes mellitus compared to those without diabetes. The underlying mechanisms encompass insulin resistance, enhanced oxidative stress, and elevated thyroid stimulating hormone levels.

The aim of the work: This study aimed to study the association between clinically relevant thyroid nodules and insulin resistance in euthyroid individuals without diabetes mellitus.

Patients and Methods: This case-control study was conducted on sixty-two patients presenting concerns regarding thyroid nodules at the Endocrinology Outpatient Clinic at Al-Azhar University Hospital in Damietta. Further, fifty-three healthy volunteers, matched for age, sex, and body mass index, were selected as a control group without clinical, laboratory, or radiological evidence of thyroid dysfunction. The thyroid profile and the Homeostatic Model Assessment for Insulin Resistance [HOMA-IR] were determined for all participants. In addition to clinical assessment, the thyroid was evaluated using ultrasonographic imaging.

Results: HOMA-IR was significantly higher in subjects with thyroid nodules compared to controls [P<0.001] and elevated HOMA-IR was an independent predictor of thyroid nodule occurrence. The cutoff point of HOMA-IR above which thyroid nodularity risk increased was 1.59 with 85.48% sensitivity and 86.79% specificity [AUC=0.874, P<0.001]. Nevertheless, HOMA-IR didn't differ among individuals with either solitary or multiple nodules and it shows no significant variations concerning the Thyroid Imaging Reporting and Data System [TIRAD] scoring [P<0.57].

Conclusion: Our findings suggest that HOMA-IR serves as a reliable marker for distinguishing patients with substantial thyroid nodules. However, no correlation between this marker and the TIRAD score was observed.

Keywords: Insulin Resistance; Diabetes Mellitus; Thyroid Nodules; Thyroid Imaging Reporting and Data System [TIRAD] score.

INTRODUCTION

Thyroid nodules represent one of the most prevalent thyroid disorders, with the majority of these nodules being asymptomatic. Only nodules measuring 1 cm or more in size can be detected through careful thyroid palpation, with an estimated prevalence of 4–7% [1, 2].

Many risk factors are associated with thyroid nodules, including genetics, female gender, iodine deficiency/excess, aging, goitrogens, radiation exposure, and smoking [3-6].

Over the past two decades, there has been increased interest regarding the role of insulin resistance in inducing thyroid disorders. Several studies have also suggested an association between insulin resistance and thyroid nodules [7- 9].

In general, thyroid disorder is recognized to be more prevalent in patients with type 2 diabetes mellitus compared to those free of diabetes [10], with an approximately two-fold increased likelihood of developing thyroid nodules [11]. Insulin resistance is considered the primary pathophysiological mechanism for thyroid cell proliferation [8]. Other potential mechanisms include hyperglycemia-induced enhancement of thyroid oxidative stress enzymes, and elevated thyroid stimulating hormone [TSH] [12,13].

With the increased resolution of imaging techniques, thyroid ultrasound can detect nodules as small as 1–2 mm. Consequently, the prevalence of thyroid nodules has significantly increased among healthy adults, ranging from 20% to 70% in current literature [1, 2, 5, 14- 16].

Nevertheless, most of the insulin resistance research defined nodules based on ultrasound screening, including participants with nodules measuring only a few millimeters. Additionally, in this field, some investigations were conducted in regions with iodine deficiency[9] where a relationship between thyroid nodules and insulin resistance cannot be established [17]. Therefore, the present study was designed to investigate the association between clinically relevant thyroid nodules and insulin resistance in euthyroid individuals residing in Damietta, a coastal region in northern Egypt.

PATIENTS AND METHODS

This case control study was conducted at the Endocrinology Clinic, Al-Azhar University Hospital in Damietta from October 2023 to March 2024. The study included 115 participants divided into two groups. Patients aged 18 to 60 years who presented with thyroid swellings, normal thyroid function, and radiologically confirmed thyroid nodules were included and assigned to group 1. Additionally, fifty-three healthy volunteers matched for age, sex, and BMI without clinical, laboratory, or radiological evidence of thyroid illness were assigned to the control group [group 2].

Diabetes mellitus, a history of exposure to neck radiotherapy or surgery, chronic diseases, and pregnancy were all exclusion criteria. Patients taking drugs affecting the thyroid axis or insulin sensitivity [e.g., amiodarone, metformin, corticosteroids] were also excluded.

All cases were evaluated by the same physician for historical information, clinical examinations, and body mass index [BMI] measurements.

Laboratory examinations: Blood samples [~ 10 mL] were collected from each patient after an overnight fast for fasting insulin and glucose levels, and thyroid profile [TSH, free thyroxine, and free triiodothyronine]. Additionally, blood samples were taken 2-hour postprandial for prandial glucose assessment.

Serum insulin was estimated by the ELISA technique using a kit supplied by DRG International, Inc., USA.

The Homeostatic Model Assessment for Insulin Resistance [HOMA-IR] equation was utilized to evaluate the insulin resistance index. HOMA-IR = Fasting Insulin [μU/ml] x fasting glucose [mg/dl] /405 [18].

Radiological analysis

Using a 7.5–10 MHz linear array transducer [Toshiba Xario and LOGIQ P7 and P9 systems], the thyroid gland was examined while the subject was in a supine position, with a pillow placed under the shoulders to slightly extend the neck. The scanning protocol involved both transverse and longitudinal real-time imaging of the thyroid gland. Thyroid nodules were characterized according to composition, echogenicity, margins, shape, and the presence of different types of echogenic foci. Points were assigned according to the American College of Radiology Thyroid Imaging Reporting and Data System [ACR-TIRADs] [19]. The [dominant] nodule was categorized into a TIRADS category from 1 to 5, and its largest diameter was measured as an indicator of nodule size.

Statistical analysis: The collected data was coded, processed, and analyzed using the Statistical Package for Social Sciences [SPSS] version 23 for Windows® [IBM SPSS Inc, Chicago, IL, USA]. Statistical significance was considered at $P \leq 0.05$ considering 2-tailed significance. Continuous data are presented as mean [± standard deviation], assessed for normality using Shapiro-Wilk and Kolmogorov Smirnov tests, and compared using an independent samples *t*-test. Categorical variables are reported as frequency and within groups percentage, and comparisons were performed using the chi-square [χ^2] or Fisher's tests as appropriate. ***A one-way ANOVA test*** was performed to analyze continuous variables between 3 or more groups, followed by a ***post-HOC* test** in case of significant results. ***Pearson correlation*** was calculated to indicate the strength and direction of association between two numerical variables. ***Regression analysis*** studied the effect of clinically relevant independent variables on dependent variables [thyroid nodules]. Multivariate analysis [Enter method] for significant variables in univariate regression was conducted. Further**, *Receiver operator characteristic [ROC] curve analysis*** was employed for determining sensitivity, specificity, and area under the curve [AUC] of HOMA-IR levels to distinguish cases of thyroid nodularity. The optimal cutoff value was determined using ***Youden index J***.

Ethical consideration: The study protocol was approved by The Faculty Ethics Committee [DFM-IRB00012367-23-04-006]. Confidentiality and personal privacy were respected at all levels of the study.

RESULTS

Group 1 comprised 51 female and 11 male participants with thyroid nodularity, with ages ranging from 20 to 60 [mean 42.19 years]. The control group [group 2] consisted of 53 healthy subjects without thyroid dysfunction, with ages ranging from 20 to 53 [mean 40.21 years]. The control group was matched with the patient group in terms of age, gender, BMI, and frequency of prediabetes ***[Table 1]***.

In the male cohort, 5 and 3 individuals were smokers in group 1 and group 2 respectively, while no female participants smoked. All subjects reported no alcohol consumption or radiation exposure. Diabetes mellitus [64.50% - P<0.001], hypertension [58.10% - P=0.02], and thyroid diseases [51.60% - P<0.001] were the most prevalent positive findings in the family history of patients with thyroid nodules ***[Table 1].***

As an indicator of insulin resistance, HOMA-IR was significantly higher in subjects with thyroid nodules compared to controls [P<0.001]. ***[Table 2].*** Furthermore, univariate regression analysis indicates that elevated HOMA-IR independently predicted thyroid nodule occurrence ***[Table 3].*** However, HOMA-IR showed no association with nodule size [r= -0.058, P<0.665] **[*Fig. 1a, b].*** The HOMA-IR threshold above which thyroid nodularity risk increased was 1.59 ***[Fig. 2].*** The sensitivity and specificity were 85.48% and 86.79% respectively [AUC=0.874, P<0.001]. ***Fig. 3*** demonstrates an inverse relationship between fasting insulin and prandial glucose levels [r=-0.34, P<0.001], yet no significant correlation with fasting glucose was observed**.**

In terms of HOMA-IR, our findings indicate no significant difference between cases with solitary nodules or multinodular goiters [***Fig. 4a].*** Further, there were no variations in HOMA-IR values with different TIRAD scoring [P<0.57] ***[Fig. 4b]***.

Table [1]: Demographic and clinical data in the study population.

		Group *1* N⁰ 62 [Mean ±SD]	Group *2* N⁰ 53[Mean ±SD]	*t [X²]*	*P*	95% Confidence Interval	
						Lower	Upper
Age [year]		42.19±10	40.21±8.60	1.13	0.26	-1.50	5.47
Gender	**Female [N⁰, %]**	51 [82.30%]	43 [81.10%]				
	Male [N⁰, %]	11 [17.70%]	10 [18.90%]	0.02	0.98		
Height [cm]		166.37±5.23	162.13±6.98	3.64	<0.001*	1.92	6.55
Weight [kg]		82.79±12.02	82.45±15.75	0.13	0.90	-4.92	5.59
BMI [kg/m²]		29.88±3.94	31.38±5.76	-1.60	0.11	3.36	0.36
SBP [mmHg]		118.87±8.51	123.08±11.62	-2.18	0.03*	-8.03	-0.38
DBP [mmHg]		78.23±6.41	76.70±9.59	0.99	0.33	-1.55	4.61
Heart rate [beat/min]		79.16±4.13	79.92±8.55	-0.59	0.56	-3.33	1.80
IGT/IFG		10 [16.10%]	7 [13.20%]	0.19	0.79		
HTN		12 [19.40%]	7 [23.30%]	0.2	0.78		
FH of T2DM		40 [64.50%]	18 [34.00%]	10.67	<0.001*		
FH of HTN		36 [58.10%]	19 [35.80%]	5.65	0.02*		
FH of thyroid disease		32 [51.60%]	12 [22.60%]	10.15	<0.001*		

Data are presented as mean [±SD] or N⁰ [% within groups], BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure, IGT: impaired glucose tolerance, IFG: impaired fasting glucose, FH: family history, T2DM: type 2 diabetes mellitus, HTN: hypertension.

Table [2]: Comparison of laboratory investigations and insulin resistance markers between individuals with thyroid nodules and control.

	Group 1 N⁰ 62 [Mean ±SD]	Group 2 N⁰ 53[Mean ±SD]	*t*	*P*	95% Confidence Interval	
					Lower	Upper
TSH [IU/L]	2.06±0.70	2.08±1.11	-0.12	0.90	-0.37	0.33
Free T3 [pg/dl]	3.23±0.60	2.59±0.78	4.67	<0.001*	0.36	0.90
Free T4 [ng/dl]	1.27±0.20	1.15±0.31	2.36	0.02*	0.02	0.22
Fasting glucose [mg/dl]	86.65±11.97	82.08±8.40	2.39	0.02*	0.79	8.35
2-h PP plasma glucose [mg/dl]	111.74±20.98	131.81±10.25	-6.66	<0.001*	-26.05	-14.09
HOMA-IR	2.67±1.03	1.31±0.59	8.79	<0.001*	1.05	1.66

Data are presented as mean [±SD], HOMA-IR: homeostasis model assessment-estimated insulin resistance, TSH: thyroid stimulating hormone [0.27–4.2 IU/L], FT3: free triiodothyronine [1.5- 4.5 pg/dl], FT4: free thyroxine [0.93–1.7 ng/dl], PP postprandial plasma [up to 140 mg/dl].

Table [3]: Univariate and multivariate regression analysis for predictors of thyroid nodules.

Variable	Univariate analysis: Standardized Coefficients Beta	t	P	Multivariate analysis: OR	P	95% Confidence Interval for Exp[B]: Lower Bound	Upper Bound
[Constant]		-0.83	0.41				
Age	-0.08	-0.69	0.49				
IGT/IFG	-0.15	-1.15	0.25				
HTN	-0.11	-1.003	0.32				
FH of T2DM	0.04	0.40	0.68				
FH of HTN	-0.09	-0.99	0.32				
FH of thyroid diseases	0.15	1.52	0.13				
BMI	-0.21	-1.93	0.06				
TSH	-0.07	-0.81	0.41				
HOMA-IR	0.60	2.11	0.03	8.261	<0.001*	3.212	21.835

OR: odds ratio: IGT: impaired glucose tolerance, IFG: impaired fasting glucose, FH: family history, T2DM: type 2 diabetes mellitus, HTN: hypertension, HOMA-IR: homeostasis model assessment-estimated insulin resistance, BMI: body mass index, TSH: thyroid stimulating hormone [0.27–4.2 IU/L].

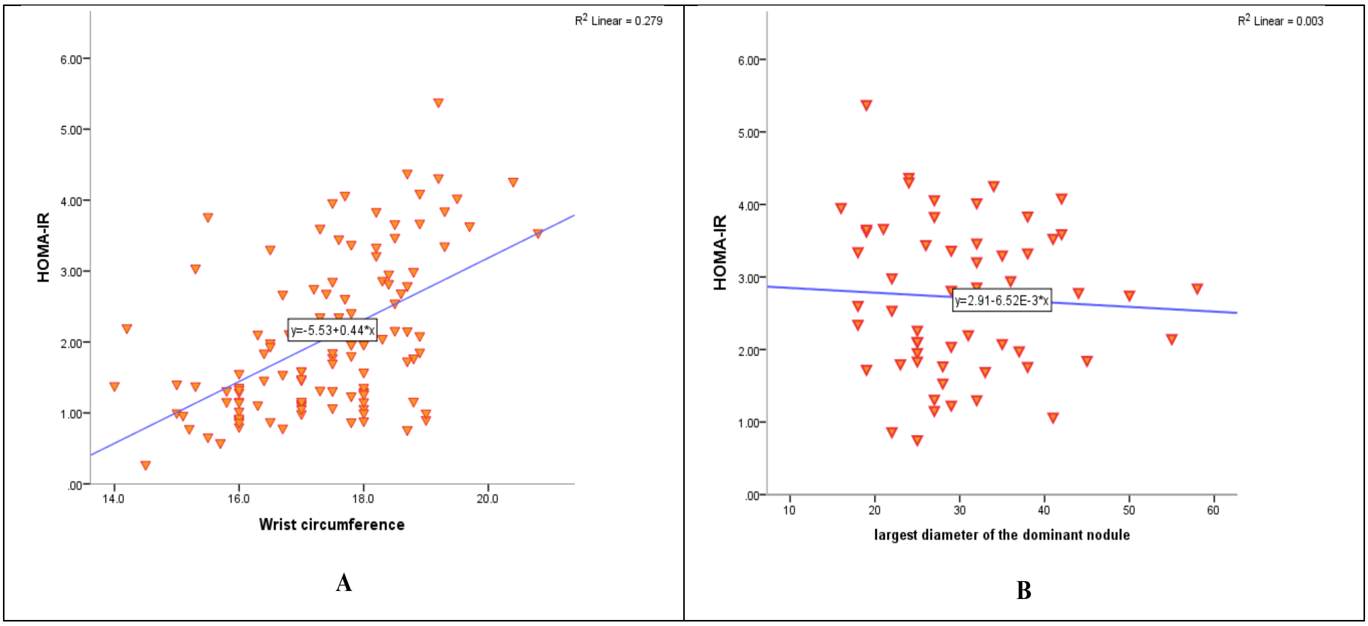

Figure [1]: a: correlation between HOMA-IR and wrist circumference in the study populations [r = 0.53, P <0.001]. b. HOMA-IR correlation with the largest diameter of the dominant nodule in patients with thyroid nodules [*r*= -0.058, *P*<0.665].

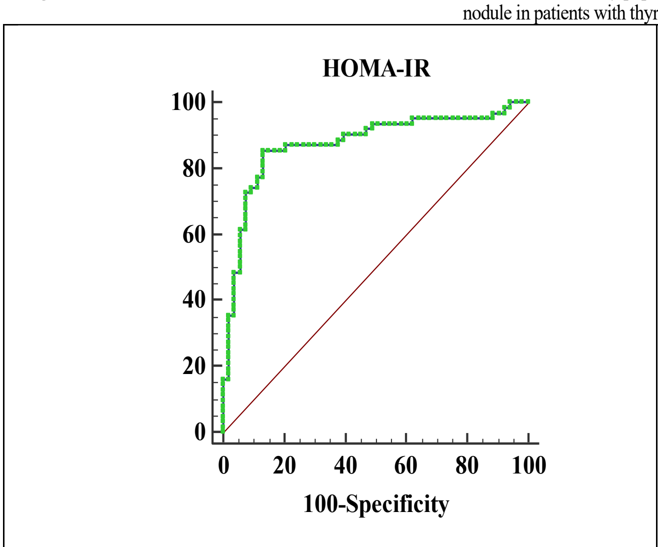

Figure [2]: ROC curve analysis of HOMA-IR for discrimination cases with thyroid nodules; cutoff point 1.59, sensitivity 85.48%, specificity 86.79%, AUC 0.874, P<0.001]

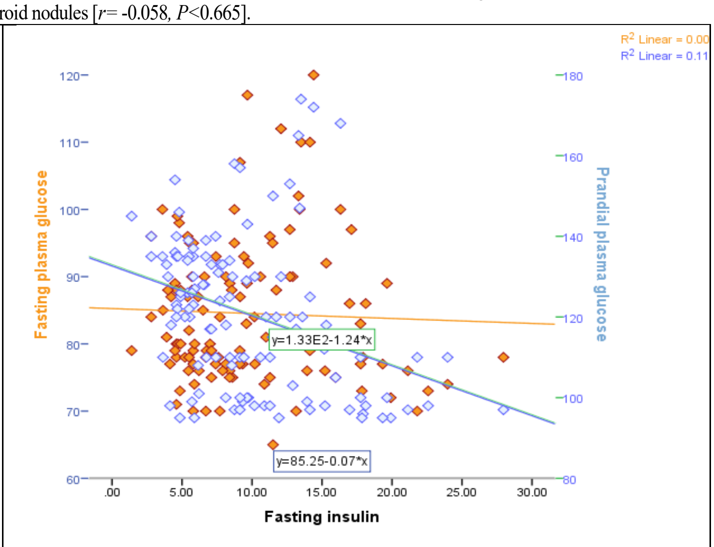

Figure [3]: Correlation between fasting insulin and both fasting and prandial glucose levels among all participants of the study {r=-0.04 [P=0.70], r=-0.34 [P<0.001] respectively}

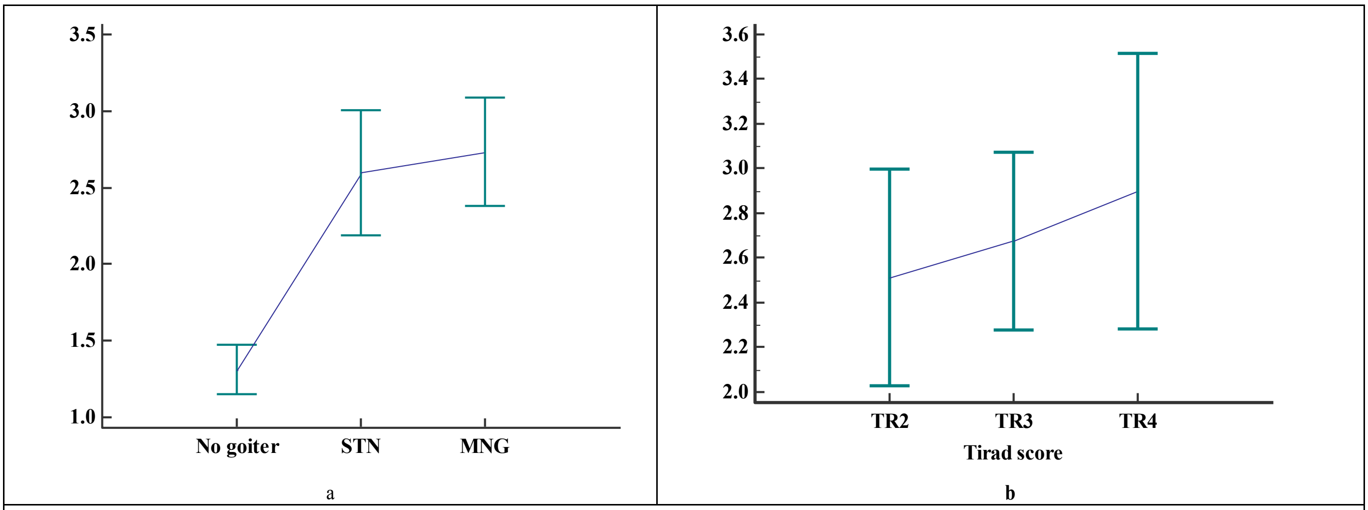

Figure [4]: HOMA-IR levels; *a:* in relation to clinical types of goiters in all participants [$P<0.001$] with a significant difference by Post HOC test between both solitary thyroid nodule [STN] and multinodular goiter [MNG] versus absence of goiter]; *b:* in relation to TIRAD score among the cohort of cases with thyroid nodularity [$P=0.57$].

DISCUSSION

The results of the current work demonstrated a notable link between the presence of thyroid nodules and elevated HOMA-IR. Patients with thyroid nodules exhibited significantly higher HOMA-IR values than the control group. Moreover, regression analysis revealed HOMA-IR as an independent risk factor for nodule development.

In addition, the study group with thyroid nodularity exhibited a higher frequency of diabetes and hypertension running in their family compared to controls. These findings collectively clarify how insulin resistance played a pivotal role in the formation of nodules among the study participants.

The role of insulin resistance in thyroid nodule development manifests through two primary mechanisms; First, the insulin/IGF-1 signaling pathway has a stimulatory action on thyroid cell growth and development [20, 21]. Second, the insulin resistance state with associated visceral fat proliferation enhances TSH production [22].

The combined action of TSH and IGF-1 stimulates the proliferation of thyrocytes [23].

Indeed, the close association between insulin resistance and thyroid nodules has previously been demonstrated in clinical studies. According to Moradi et al. [2023], thyroid nodule patients had a considerably higher mean HOMA-IR score than controls [24].

In addition, **Guo *et al.*** explored an independent correlation between insulin resistance and the development of thyroid nodules [25]. Similarly, research by **Rezzonico *et al.*** revealed a higher prevalence of thyroid nodules among people with insulin resistance [8].

Additionally, a study conducted by **Yasar *et al.*** showed that insulin resistance was identified as a contributing factor to thyroid nodule development in patients recently diagnosed with T2DM [26].

Diabetes is also recognized as a risk factor for thyroid nodule formation. Studies showed that individuals with T2DM have increased thyroid volume and a higher prevalence of nodules. Additionally, thyroid volume is positively associated with hyperglycemia [9, 11, 27].

Therefore, excluding individuals with diabetes in our study minimizes the impact of hyperglycemia on the findings and provides insulin resistance per se the opportunity to be the main player. Consequently, our data denotes comparable frequency of IGT/IFG in the two main groups of the study. This attenuates the risk of prediabetes for the occurrence of thyroid nodules and represents one of the strength points in the present study. In accordance with our findings, a Turkish study documented a significant relationship between nodule formation and insulin resistance in patients without diabetes [28].

On the other hand, the link between obesity and insulin resistance is not so clear. Some authors suggested that thyroid nodules are positively correlated with obesity, even apart from insulin resistance. Higher TSH concentrations associated with obesity may be a contributing factor in the development of thyroid nodules [29].

Conversely, Cappelli et al. hypothesized that thyroid nodules could be less common in women who are morbidly obese [30].

Sousa *et al.*, however, explored no significant difference between the normal BMI subjects and severely obese people regarding the prevalence of thyroid nodules [31].

For this reason, the present study counteracts the impact of obesity in the results by the selection of a BMI-matched control group with the thyroid nodularity group.

The current study's findings indicate that subjects with thyroid nodules have more diabetes, hypertension, and thyroid disorders running in their families. These findings suggest common genetic and lifestyle factors including increasing insulin resistance.

Although not reaching diabetic thresholds, patients with nodules demonstrated elevated fasting plasma glucose levels than the control. This finding is consistent with the study of **Xu *et al.*'s** which showed significantly higher fasting plasma glucose levels in individuals with Thyroid nodules compared to those without [32]. Additionally, the community-based research by Guo et al. indicated that fasting plasma glucose was independently associated with the formation of thyroid nodules [25].

Furthermore, our findings exhibited a negative correlation between prandial glucose and fasting insulin levels suggesting a metabolic impact of hyperinsulinemia.

Taking into consideration the physiological states of insulin resistance in pregnancy, puberty, and in the elderly populations [33], the present study was designed to alleviate these effects. Thus, we excluded pregnant women and limited participation to individuals aged 18 to 60. Additionally, the control group was age-matched with the nodular thyroid group. The study also excluded patients using medications that could impair insulin sensitivity, such as corticosteroids.

Iodine deficiency is another considerable risk factor in implementing thyroid nodularity [3, 34]. This condition, however, may interfere with a proper correlation between thyroid nodules and insulin resistance [17].

In that context, the present study was performed in Damietta, a coastal area in the north of Egypt known to be an area of iodine sufficiency. People in this region regularly eat seafood and consume the nationally available iodine-supplemented salts.

It is well established that thyroid disorders, including thyroid nodules, are more common in women than in men [4, 35]. **Knudsen *et al.*** explored that women have a 2—to 10-fold higher chance of developing goiter than men [35]. In our study, the number of women included was nearly five times higher than that of their male counterparts; however, to counteract the gender factor on TN occurrence, we selected gender-matched control subjects.

To the best of our knowledge, no prior studies have examined the relationship between HOMA-IR values and TIRAD scores. Our current findings, based on a sample of patients with substantial nodules, revealed no significant link in this regard. Moreover, HOMA-IR values did not differ among our participants with either solitary or multiple nodules.

The current data may suggest that insulin resistance while contributing to nodule formation does not influence the progression of the neoplastic processes.

In order to investigate the impact of insulin resistance on thyroid nodularity while controlling other potential risk factors, our study focused on a homogeneous cohort of euthyroid individuals residing in the coastal region of Damietta, where iodine deficiency was not anticipated. Elderly individuals [>60 y] and those with diabetes were primarily excluded. Additionally, control subjects were carefully selected to match the thyroid nodule group in terms of age, sex, and BMI. Notably, comparative analysis between the two primary study groups revealed no significant disparities in female-to-male ratio, prediabetes prevalence, or smoking habits Moreover, all study participants reported neither alcohol consumption nor radiation exposure history. These methodological considerations strengthen the validity of our findings, which highlight the crucial role of insulin resistance in thyroid nodule development.

Limitations of the present study come from the small sample size. The data were extracted from patients with sizable nodules, and it is not known whether they can be generalized to patients with small nodules [e.g. few millimeters].

Conclusion:

The present investigation revealed a notable link between insulin resistance and thyroid nodules in euthyroid Egyptian individuals without diabetes mellitus, after controlling for age, body mass index, diabetes mellitus, and other common risk factors. HOMA-IR proved to be an effective indicator for identifying patients with thyroid nodules. Nevertheless, no connection was observed between HOMA-IR and the TIRAD score. This suggests that insulin resistance is related to the formation of thyroid nodules rather than how the neoplastic process is advanced.

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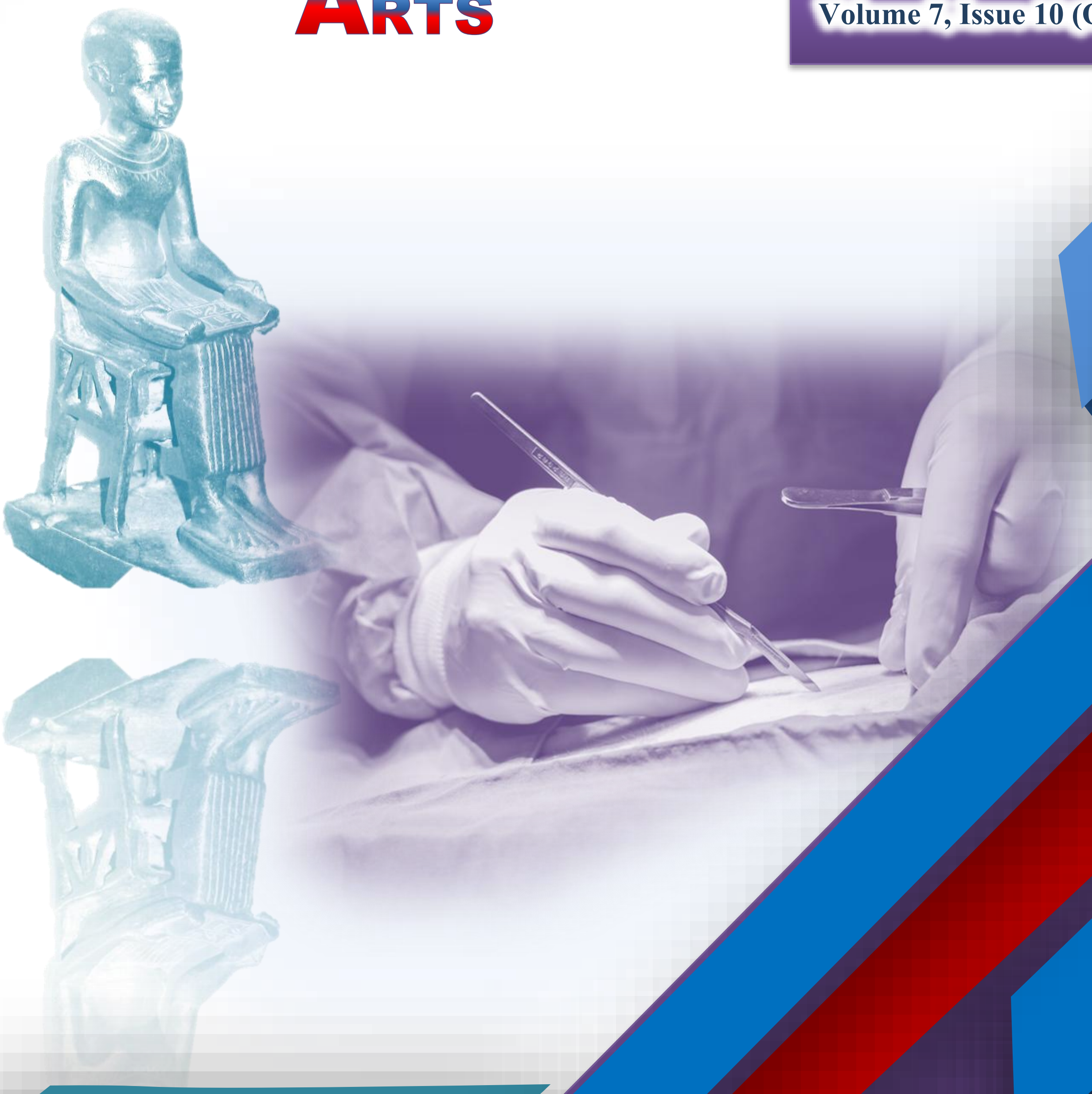

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