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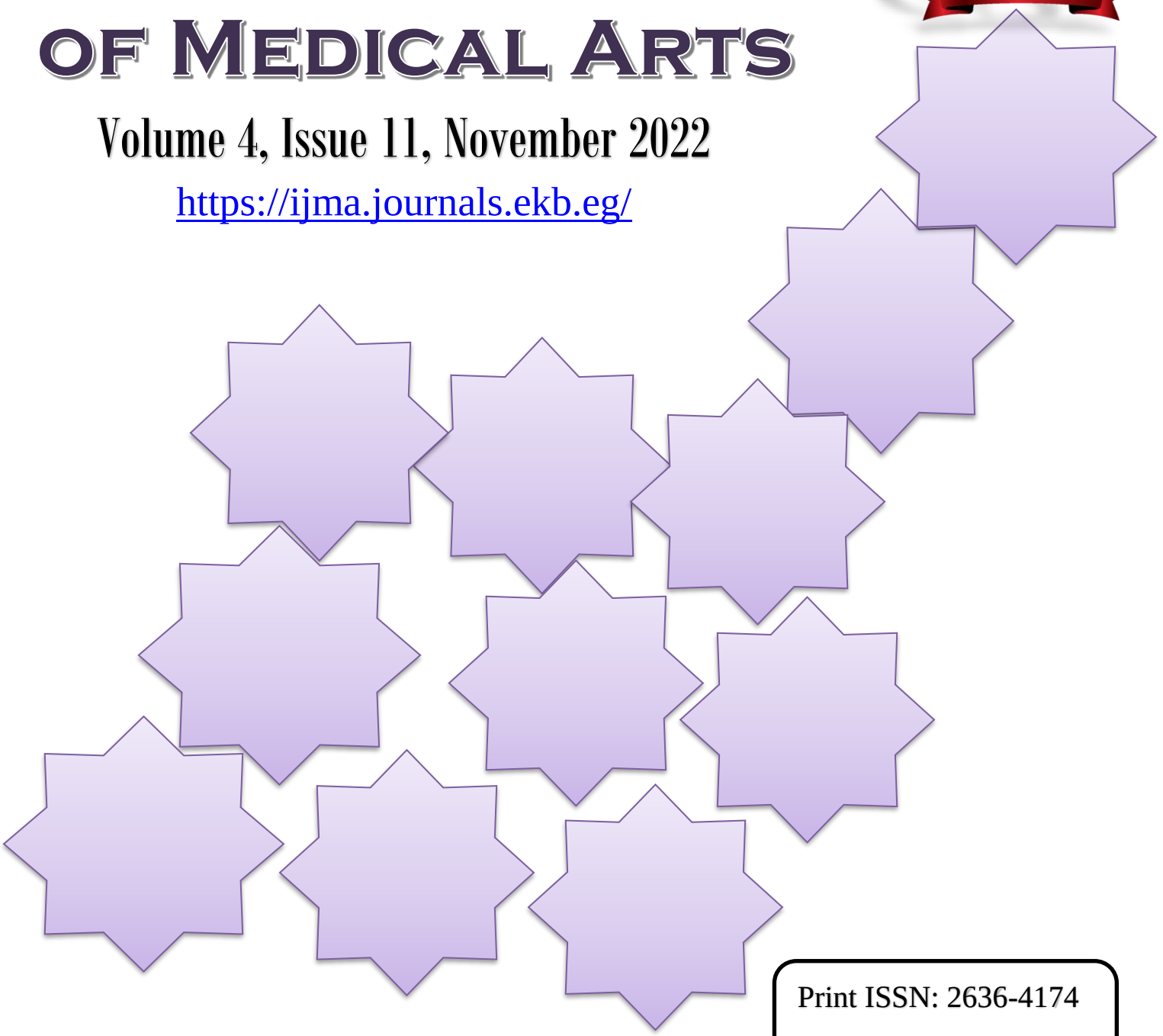

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Original Article

Study of Insulin Resistance in Patients with Subclinical Hypothyroidism

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ABSTRACT

Background: Subclinical hypothyroidism [SCH] is frequently encountered. Likewise, the prevalence of insulin resistance [IR] and its complications is increasing worldwide. The link between IR and overt hypothyroidism is well recognized, but the evidence is conflicting regarding SCH.

Aim of the work: To evaluate the IR in Egyptian female patients with SCH in the absence of diabetes mellitus [DM].

Patients and methods: A case-control study that included 30 female patients with SCH [case group], and [control group] included 30 healthy female subjects. All participants were free of DM. Clinical and laboratory evaluation were carried out including measurement of thyroid profile, serum insulin, plasma glucose levels, and lipid profile. IR was assessed by the homeostasis model assessment for insulin resistance [HOMA-IR].

Results: We found significant increase in HOMA-IR in the case group [P<0.001]. Thyroid stimulating hormone [TSH] was correlated with HOMA-IR. Patients with SCH exhibited disturbed lipid profile.

Conclusion: In the absence of DM and in the event of SCH, Egyptian female patients have higher HOMA-IR index with respect to control subjects. Dyslipidemia is characteristic in those patients. HOMA-IR was correlated with TSH levels in the study population.

Keywords: Insulin resistance; Subclinical hypothyroidism; Thyroid dysfunction.

INTRODUCTION

Thyroid hormones [TH] play an important role for energy balance, glucose metabolism, and lipid metabolism [1]. Subclinical hypothyroidism [SCH] is a condition associated with a raised thyroid stimulating hormone [TSH] but a normal free thyroxine [FT4] level [2]. On the other hand, insulin resistance [IR] is a hallmark characteristic of type 2 diabetes mellitus [T2DM] [3], where High blood pressure, abdominal obesity, and impaired glucose metabolism are all risk factors [4].

Thyroid diseases are much more common in patients with T2DM than in the general population, supporting possible relationship between thyroid disorders and IR [3].

The association between IR and overt hypothyroidism [OH] is well known, but still controversy exists whether this association is also present in SCH [2, 5, 6].

AIM OF THE WORK

The objective of this study was to assess IR in Egyptian female patients with SCH compared the healthy control subjects in the absence of diabetes mellitus.

PATIENTS AND METHODS

This was a case-control study that included thirty female patients with SCH [case group], and thirty healthy female subjects matched for age and body mass index [BMI] [control group]. Patients were recruited from the outpatient clinic, Al-Azhar University Hospital, New Damietta during the period from December 2020 to October 2021. The Al-Azhar University's local ethics committee accepted the study protocol, and every patient voluntarily agreed to participate after receiving full information.

Inclusion criteria: Female patients aged 18-60 y newly discovered with SCH who didn't receive replacement therapy before the study. Patients having TSH values above 4 Iu/L, and FT4 and free triiodothyronine [FT3] within the reference range [0.89-1.76 ng/dl and 2.3-4.2 pg/ml respectively] were assigned as SCH [7].

Exclusion criteria: the presence of diabetes mellitus, other endocrinal disorders, sever co-morbid diseases, pregnancy or lactation indicated the exclusion from the study. In addition, the use of drugs affecting the thyroid axis or metabolism, or the insulin sensitivity [e.g., insulin sensitizers, and corticosteroid] were all indications of exclusion.

All participants were subjected to the following:

1. Full history stressing on symptoms suggestive of thyroid diseases, symptoms suggestive of reactive hypoglycemia as well as history of allergic or other autoimmune diseases.

2. Clinical examination, with anthropometric measures including body weight, height, waist circumference [measured as per the WHO] [8, 9], and BMI {calculated by simple dividing weight [in kg] by square of height [in meters]}.

3. Laboratory investigations included: lipid profile, thyroid profile [TSH, FT4, and FT3], fasting serum insulin, fasting plasma glucose and 2-hour postprandial plasma glucose.

The homeostasis model assessment for insulin resistance [HOMA-IR] was calculated by using the formula [10]: HOMA-IR = [insulin mU/L × glucose [mg/dl] / 405

Blood samples were withdrawn after 12 to 14 h overnight fasting and centrifuged within 30 to 45 min of collection. Blood analyses were done at the Clinical Pathology Department, Al-Azhar University Hospital [New Damietta] on the day of blood collection. All reagents were brought to room temperature [18-25 ^{o}C] and mixed by gently inverting or swirling prior to use. Washing buffer was prepared by adding distilled or deionized water to 50x wash concentrate to a final volume of 750 ml. If reference standards are lyophilized, re-constitution each standard with 0.5 ml distilled water was done. The reconstituted material was allowed to stand for at least 20 minutes. Reconstituted standards are sealed and stored at 2-8 ^{o}C.

Statistical analysis: IBM SPSS version 22.0 [IBM Corporation, Armonk, NY, USA] was used to analyze computer-generated data. Continuous data were presented as the mean ± standard deviation [SD], and categorical data were presented as percentages. The Chi-Square test was used to compare two or more categorical groups. The Mann–Whitney U test

or Student's t test were used for continuous variables. We used the 0.05 significance threshold to detect significance of the findings. Pearson correlation was performed to evaluate the association between TSH and HOMA-IR.

RESULTS

The control group was matched with the case group regarding the age, weight, height and BMI [table 1, fig. 1].

Patients with SCH had a significantly higher total cholesterol [TC], low-density lipoprotein [LDL], triglycerides [TG], fasting plasma glucose [FPG], fasting Insulin and HOMA-IR, but with a significant decrease of high-density lipoprotein [HDL] compared to the control group [table 2].

Positive history of recurrent attacks of reactive hypoglycemia, followed by personal history of atopic or autoimmune diseases occurred more frequently in the SCH patients than the control group. Also, the presence of T2DM was the main positive finding in the family history of the case group [63.3%, P=0.004], followed by hypertension [HTN] [43.3%] then thyroid diseases [26.7%]. However, the last two items were not statistically significant [table 3].

Using Pearson correlation, a moderate positive correlation was reported between TSH and HOMA-IR [r=0.603] [figure 2].

Table [1]: Comparison between the two groups regarding the clinical and anthropometric data

	[Patients group]	[Control group]	Test	P value
	Mean ± SD	Mean ± SD		
Age [y]	35.93±10.19	35.30±7.91	t=0.269	0.789
Systolic blood pressure [mm Hg]	119.90±15.26	126.77±13.70	u=294.00	**0.016***
Diastolic blood pressure [mm Hg]	75.93±8.52	76.17±8.55	u=439.00	0.864
Pulse [beat/min]	74.63±7.57	79.47±9.94	u=322.50	0.058
Height [cm]	159.87±6.99	158.50±8.47	u=416.50	0.619
Weight [kg]	89.03±25.24	91.13±22.75	t=0.338	0.736
BMI [kg/m^2]	34.99±10.42	35.83±9.27	u=419.50	0.652

BMI: Body mass index, U: Mann–Whitney test, t: student t test

Table [2]: Comparison of laboratory investigations between the studied groups

	[Patients group]	[Control group]	Test of Sig.	P Value
	Mean ± SD	Mean ± SD		
TSH [Iu/L]	8.08±3.07	2.16±1.27	t=9.903	**<0.001***
Free T3 [pg/dl]	2.72±0.84	2.28±0.70	u=302.50	**0.029***
Free T4 [ng/dl]	1.12±0.24	1.12±0.31	u=434.50	0.818
Total cholesterol [mg/dl]	186.77±25.74	162.07±13.93	t=4.622	**<0.001***
Triglycerides [mg/dl]	136.43±32.15	109.57±32.66	t=3.210	**0.002***
LDL-C [mg/dl]	111.50±25.96	84.10±18.17	t=4.736	**<0.001***
HDL-C [mg/dl]	44.77±7.14	53.20±10.68	t=3.594	**0.001***
FPG [mg/dl]	95.03±7.43	79.90±7.96	t=7.611	**<0.001***
2-hPPPG [mg/dl]	128.10±8.06	133.67±11.94	t=2.116	**0.039***
Fasting insulin [mIU/L]	25.05±9.801	7.80±4.443	t=8.780	**<0.001***
HOMA-IR	5.84±2.30	1.47±0.83	t=9.774	**<0.001***

T3: triiodothyronine, T4: thyroxine, FPG: fasting plasma glucose, 2-hPPPG: 2-hour postprandial plasma glucose, HOMA-IR: Homeostasis model assessment for insulin resistance, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, TSH: thyroid stimulating hormone, t: student t test. u: Mann-Whitney test. Fasting plasma glucose [n: 70-100 mg/dl], 2-hpp plasma glucose [n: 70-140 mg/dl], Fasting insulin [n: less than 25 mIU/L], TSH [n: 0.27-4 Iu/L], FT3 [n: 2.3-4.2 pg/dl], FT4 [n: 0.89-1.76 ng/dl].

Table [3]: Demographic and clinical characteristics of the two groups

		Patients group [no = 30]		Control group [no = 30]		P Value
		No.	%	No.	%	
Family history of	Diabetes mellitus	19	63.3	7	23.3	**0.004***
	Hypertension	13	43.3	8	26.7	0.279
	Thyroid diseases	8	26.7	2	6.7	0.080
Medical history of	Reactive hypoglycemic attacks	25	83.3	5	16.7	**<0.001***
	Atopic or autoimmune disease	15	50.0	5	16.7	**0.013***

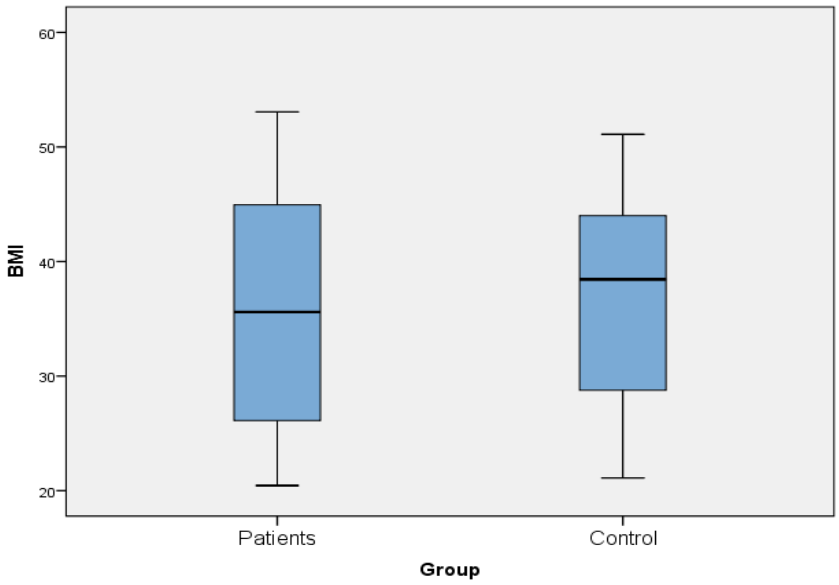

Figure [1]: Comparison between the two groups regarding the BMI [body mass index]

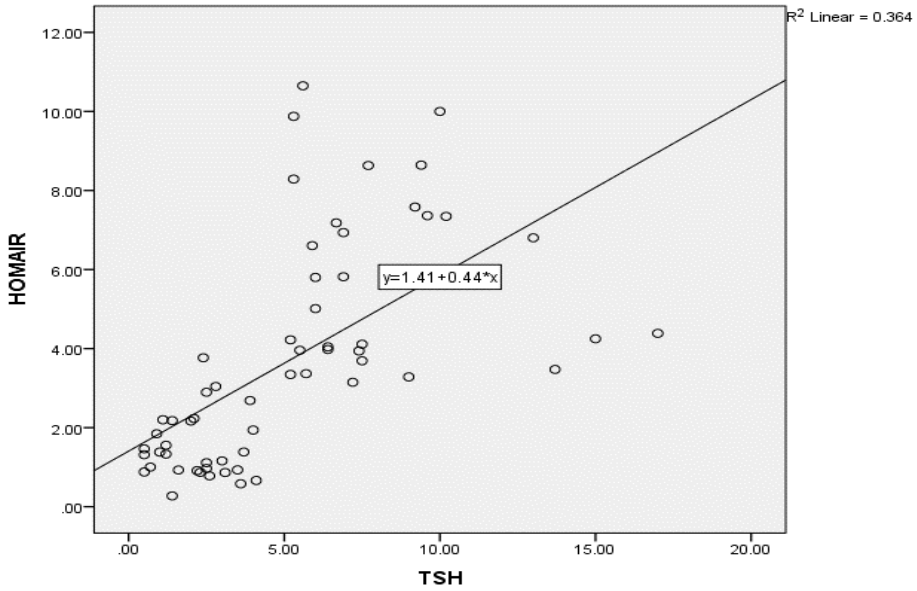

Figure [2]: Correlation between TSH [thyroid stimulating hormone] and HOMA-IR [homeostasis model assessment for insulin resistance] in the study population

DISCUSSION

It has been recognized that IR is linked to OH, but still controversy exists regarding the case of SCH [2, 5, 6]. In addition, research on this association targeting individuals without DM is lacking.

Maratou et al. [11] observed significantly higher HOMA-IR in patients with OH and SCH patients compared to euthyroid subjects. Furthermore, they found reduced GLUT4 level in the plasma membrane of monocytes in SCH and OH patients in comparison with the euthyroid group. This reduction may be responsible -at least partially- of the impaired insulin action. Interestingly, **Roos *et al.*** [12] observed increase in the levels of IR parameters even under minute drop in thyroid hormone levels. In addition, experimental data showed beneficial effect of thyroid hormones on glucose transporters [13, 14].

The present study was conducted to evaluate the IR in Egyptian female patients with SCH without the presence of DM.

By comparing the control and the case groups, our results showed increase in fasting insulin levels and HOMA-IR in patients with SCH, even they were matched for sex, age and

BMI. These findings support previous results obtained by Gen ***et al.*** [15]. On the contrary, Stoica et found the mean HOMA-IR for the SCH patients and that for the control group were of no significant differences [16].

This variability of results in IR in SCH patients with respect to the euthyroid control among the previous studies may be related to the demographic, design, or selection factors.

Our observation of positive correlation between both TSH and HOMA-IR has been recognized by several authors [5, 11, 17-20].

Not far from the IR, our results revealed higher plasma glucose levels [although still under the diabetic reference] within the case group of SCH.

Mahmoud *et al*. [21] showed that fasting plasma glucose for the euthyroid group was lower than the patients' group. In a comparable situation, patients with SCH had a 2.29-fold increased risk for diabetes compared with euthyroid subjects [22]. On the other hand, the association between serum lipid concentrations, thyroid dysfunction and IR has been recognized [23].

With respect to SCH, several reports have revealed an association with increased levels of total cholesterol [TC] and LDL-C [24-28]. In addition, some studies have shown that SCH may also be accompanied by increased TGs [29, 30] and decreased HDL-C levels [31]. Moreover, euthyroid subjects with high normal TSH levels [2-4 mIU/L], but with positive antithyroid antibodies may also exhibit elevated cholesterol levels [32].

In consistency with the previous reports, and by comparing the mean values of lipid profile between the case and control groups, our study demonstrated higher levels of total TC, LDL-C, TGs in the SCH group. Indeed, the mean HDL-C was lower in that group.

It has been known that hypothyroid subjects express less LDL receptor genes [33], while thyroxine replacement improved dyslipidemia linked to hypothyroidism within 4–6 weeks [34].

Despite the data above, there are some reports indicating no significant difference in lipid profile between SCH patients and controls [35-37].

The value of this work comes from its operation on patients without diabetes. Although, the study included a relatively small sample, it was carried on a homogenous group of Egyptian female individuals.

Conclusion: In the absence of DM, Egyptian female patients suffering from SCH have more IR scores as measured by the HOMA-IR index than the matched control. This index was correlated with TSH levels in our cohort. Dyslipidemia is a constant finding in patients with SCH.

Conflict of Interest and Financial Disclosure: None

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