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Study of Insulin Resistance in Patients with Hypothyroidism as a Risk Factor of Diabetes Mellitus

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ABSTRACT

Background: Thyroid disease is considered frequent in the population. Regarding diabetes mellitus (DM), hypothyroidism and subclinical hypothyroidism are considered common, and risk factors for DM development.

Objective: This work aimed to early prediction of diabetes mellitus among hypothyroidism patients and to correlate the serum FT3, FT4, and TSH with insulin resistance indexes and plasma insulin in cases with patients sub- and clinical hypothyroidism.

Patients and methods: At the Endocrine out-patient clinic at the Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals a total of 162 adult participants, 54 cases of overt hypothyroidism, and 54 patients with subclinical hypothyroidism (SCH) were studied in this case-control study. The cases were aliquoted into three groups: Group (A): 54 subjects euthyroid (control), Group (B): 54 cases with SCH, and Group (C): 54 cases with Overt hypothyroidism.

Results: The results showed that FT3 was significantly negatively correlated with cholesterol, HDL, FBG, and HbA1C. FT4 was significantly negatively correlated with TPO antibody and HbA1C but significantly positively correlated with cholesterol. TSH was significantly negatively correlated with TAG but significantly positively correlated with TPO antibody and regard FBG, F.INS and HOMA_IR were significantly high among sub- and clinical hypothyroidism groups than the control group.

Conclusion: The current study concluded a significant correlation between thyroid hormones and IR (HOMA-IR). The evaluation of IR is crucial in clinical events, and for the settlement of insulin sensitivity. To predict type2 DM in hypothyroid patients.

Keywords: Hypothyroidism, Diabetes, Insulin, FT3, FT4, TSH.

INTRODUCTION

The thyroid gland secretes hormones that are potential metabolic agents in controlling lipid and carbohydrate metabolism and energy homeostasis **(1).**

Hyper and hypothyroidism cause altered metabolic rate that affects lipid profile, body weight, and insulin resistance **(2).**

Insulin resistance is considered significantly strongly associated with obesity, metabolic syndrome, and DM **(3).** The thyroid axis is considered an example of the endocrine loop of feedback. To aid in thyroid hormone synthesis and secretion, hypothalamic Thyrotropin Releasing Hormone (TRH) may act as a regulator of the thyroid-hypothalamus-pituitary-thyroid axis **(4)**.

The reduced T3, and T4 levels and elevated TSH were correlated with hypothyroidism, resulting in increased lipoproteins and plasma lipids, and higher body weight. It has been reported that hypothyroidism causes an increased lipid profile **(2,5).**

The hypothyroidism hallmarks include decreased glucose absorption, decreased hepatic output of glucose, gluconeogenesis, and decreased glucose disposal **(6).** Dyslipidemia causes oxidative stress and insulin resistance by vice vicious cycle **(1,7).**

Insulin resistance, oxidative stress, hypertension, dyslipidemia, and coagulation defects were promoted by thyroid disease. Thyroid disease associated with dyslipidemia had a significant role in atherosclerosis **(8,9)**.

This work aimed to early prediction of diabetes mellitus among hypothyroidism patients and to correlate the serum FT3, FT4, and TSH with insulin resistance indexes in cases with patients sub- and clinical hypothyroidism.

PATIENTS AND METHODS

At the Endocrine out-patient clinic at the Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals a total of 162 adult participants, 54 cases of overt hypothyroidism, and 54 patients with subclinical hypothyroidism (SCH) were studied in this case-control study from March 2021 to October 2021, and another group of 54 euthyroid individuals was enrolled as a control group. The patients were divided into three groups: Group (A): 54 subjects euthyroid (control), Group (B): 54 cases with SCH, and Group (C): 54 cases with Overt hypothyroidism.

Ethical consent:

Approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed informed written consent for the acceptance of the operation. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

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Inclusion Criteria: Patients (within the age group 15-65 years) diagnosed according to ATA with Overt hypothyroidism will be included in the study group. Patients diagnosed with SCH. SCH is defined as TSH levels above the upper defined limits with FT3 and FT4 in the reference ranges(0.35-5.5mIU/ml)/FT3(2.8-7.1)/FT4(12-22) pmoL/L. age and gender-matched healthy individuals will be taken as controls.

Exclusion Criteria: Known cases of diabetes mellitus, hypertension, liver and renal disorders, congestive cardiac failure, any Patients with infection/illness. Patients' intake of medicines like statins, oral contraceptive pills, or Patients with a history of steroid use. Pregnant were excluded from the study. Alcoholics and smokers, and obese patients, BMI not more than 30.

All cases were subjected to:

1. Full medical history including; age, family history, educational level, structured questionnaire (current or previous diseases, use of medication, and smoking).
2. Complete clinical examination.
3. Anthropometric measurement (weight, height, and BMI).
4. Laboratory findings including FBG, HbA1C, Serum Fasting Insulin, Lipid profile, Thyroid hormones, Serum TSH, Free T3, FreeT4, Thyroid Peroxidase Antibody (TPO Ab), and Thyroglobulin Antibody (TG Ab)
5. Evaluation of Fasting Insulin Resistance Index (FIRI) was calculated by the Homeostasis Model Assessment (HOMA) [(10)].
   HOMA = Insulin (μU/ml) × Glucose (mmol/L)/22.5.

Statistical Analysis

Microsoft Excel software was used to code, enter, and analyze data obtained during the history, basic clinical examination, laboratory investigations, and outcome measures. To analyze data, they were entered into SPSS (SPSS version 20.0) Analytical software for the social sciences, SPSS. Quantitative data continues to group by mean, but qualitative data are represented as numbers and percentages, Differences and associations of qualitative variables were tested for significance using the Chi-square test (X^2). Multivariate analysis of variance or Kruskal-Wallis tests, and Pearson or Spearman's correlation coefficients can all be used to examine differences between quantitatively independent multiple groups. Significant findings required a P value of 0.05, whereas high significant findings required a P-value of 0.001.

RESULTS

Age was distributed as 41.96±14.62, 41.74±13.89, and 35.29±8.73 respectively with no significant difference among groups also there was no significant difference regard Weight or height or BMI but regard sex distribution female was significantly associated with Subclinical hypothyroidism Group (Table 1).

Table (1): Demographic data distribution among studied groups

			Control Group (A)	Subclinical hypothyroidism Group(B)	Overt hypothyroidism Group(C)	F	P
Age (years)			35.29±8.73	41.74±8.89	41.96±9.62	2.521	0.087
Weight (kg)			68.35±7.35	65.83±4.85	66.11±7.52	1.214	0.298
Height (cm^2)			167.48±7.66	159.20±32.28	165.03±8.71	1.289	0.255
BMI (kg/m2)			24.29±0.92	24.14±1.07	24.50±0.81	1.107	0.351
Sex	**Female**	**N**	32	50	36		
		%	59.3%	92.6%	66.7%		
	Male	**N**	22	4	18	11.36	0.011
		%	40.7%	7.4%	33.3%		
Total		**N**	54	54	54		
		%	100.0%	100.0%	100.0%		

#BMI=body mass index

TSH was significantly lower among the control group with no significant difference between the other two groups but regard FT3 and FT4 were significantly lower among the overt hypothyroidism Group with no significant difference between the other two groups. The control group was significantly lower than other groups regarding FBG, F.INS, and HOMA_IR, and no significant difference between group (B) and group(C) regarding them. Cholesterol and triglyceride were significantly higher at group (C) and significantly lower at group (A) but LDL was significantly higher in group (C) with no significant difference between the other two groups and there was no significant difference regarding HDL among studied groups (Table 2, Figure 1).

Table (2): Thyroid profile, HbA1C, F. INS, HOMA-IR, and lipid profile distribution among studied groups

	Control Group (A)	Subclinical hypothyroidism Group(B)	Overt hypothyroidism Group(C)	F	P
TSH (mIU/mL)	1.76±0.4*	7.18±1.78	7.28±1.63	37.012	**0.00****
FT3 (mIU/mL)	4.75±0.80	4.08±0.99	1.85±0.3*	85.36	**0.00****
FT4 (mIU/mL)	15.15±1.77	14.23±3.16	7.05±1.96*	62.31	**0.00****
FBG (mg/dL)	91.63±2.36*	101.69±7.98	104.63±10.58	3.90	0.041*
HbA1C (mmol/mol)	5.48±0.38	5.76±0.62	5.88±0.54	1.28	0.105
F.INS	11.51±1.23*	19.80±4.57	21.78±4.63	3.84	0.042*
HOMA-IR	3.87±0.18*	9.25±2.36	9.94±2.21	9.74	**0.00****
CHOL (mg/dL)	163.03±28.67#	183.96±38.67	206.74±51.04*	7.12	0.002*
HDL (mg/dL)	42.87±10.58	42.87±10.16	39.03±3.28	1.24	0.287
LDL (mg/dL)	113.33±18.6	115.78±21.39	135.17±26.02*	6.12	0.003*
TAG	112.37±5.69#	125.26±29.58	139.36±37.43*	4.52	0.028*

* Group significantly higher by LSD, # Group significantly lower by LSD

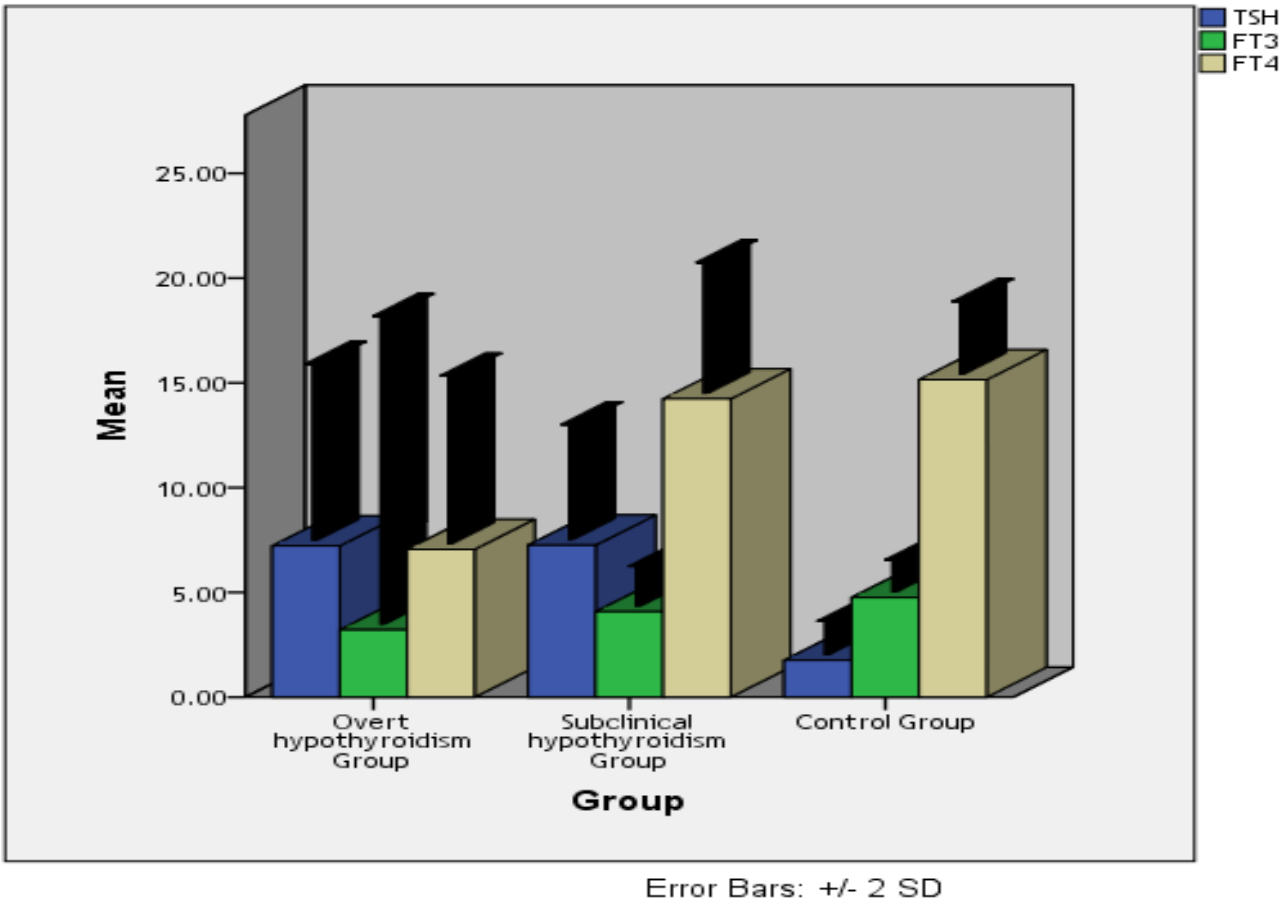

Figure (1): Mean of thyroid profile distribution among the studied groups

TSH had a significant positive correlation with TPO antibody, negative with FBG, Fasting Insulin and HOMA IR, FT3 had a significant negative correlation with cholesterol also FT4 had a significant negative correlation with cholesterol and also with FBS, HbA1C and F.INS (Table 3).

Table (3): Correlations of variable data with Thyroid profile

		TSH	FT3	FT4
Cholesterol (mg/dL)	**R**	0.192	-0.249*	-0.233*
	P	0.086	0.0250	037
HDL (mg/dL)	**R**	0.027	-0.113	0.194
	P	0.814	0.316	0.083
LDL (mg/dL)	**R**	0.073	-0.066	-0.155
	P	0.547	0.587	0.200
TAG	**R**	-0.141	-0.011	-0.027
	P	0.230	0.928	0.822
FBG (mg/dL)	**R**	-0.372*	-0.031	-0.314*
	P	0.012	0.787	0.032
HbA1C (mmol/mol)	**R**	-0.188	0.042	-0.227*
	P	0.093	0.708	0.042
F.INS	**R**	-0.406*	-0.042	-0.228*
	P	0.005	0.712	0.041
HOMA_IR	**R**	-0.422*	-0.042	-0.090-
	P	0.002	0.707	0.424
TG Ab (IU/ml)	**R**	0.096	-0.26	-0.044
	P	0.394	0.819	0.695
TPO Ab (IU/ml)	**R**	0.305**	-0.075	-0.193
	P	0.006	0.505	0.084

A correlation between FT3 and cholesterol was found to be significant in group (c). There was a strong correlation between TAG, HDL, FBG, and HbA1C and FT4 in the group (b) of people who had high levels of TSH and low levels of FT3. TSH was significantly positively correlated with TPO antibody and FT4 was significantly positively correlated with cholesterol but negatively correlated with TPO antibody in group (a) (Table 4).

Table (4): Correlations of variable data with Thyroid profile

		Control group (A)			Subclinical group (B)			Overt group (C)		
Group		**TSH**	**FT3**	**FT4**	**TSH**	**FT3**	**FT4**	**TSH**	**FT3**	**FT4**
CHOLI	**r**	-.33	0.24	0.43*	-0.19	0.17	-0.18	0.16	-0.39*	0.11
	P	.09	0.23	0.02	0.33	0.39	0.38	0.42	0.04	0.57
HDL	**r**	-.03	0.35	0.20	0.08	-0.48*	-0.15	0.15	-0.195	0.26
	P	.87	0.08	0.32	0.71	0.01	0.44	0.44	0.331	0.18
LDL	**r**	-.24	0.21	0.34	0.03	0.06	0.38	-0.17	-0.08	0.04
	P	.29	0.32	0.1	0.90	0.79	0.07	0.42	0.715	0.86
TAG	**r**	-.03	-0.16	0.17	-0.45*	0.20	-0.01	-0.36	0.008	0.35
	P	.88	0.46	0.43	0.02	0.31	0.96	0.08	0.970	0.09
FBG	**r**	.14	-0.26	-0.05	0.02	-0.38*	-0.36	-0.34	0.056	0.13
	P	.49	0.2	0.80	0.91	0.04	0.06	0.08	0.781	0.51
HbA1C	**r**	-.25	-0.3	-0.22	-0.26	-0.5**	-0.40*	-0.34	0.195	-0.11
	P	.21	0.13	0.27	0.19	0.01	0.04	0.07	0.329	0.59
F.INS	**r**	-.30	-0.15	0.21	0.02	0.31	-0.29	-0.02	-0.075	-0.37
	P	.13	0.44	0.29	0.90	0.11	0.14	0.89	0.709	0.06
HOMA_I R	**R**	-.26	-0.17	0.2	-0.15	-0.13	-0.18	-0.03	-0.073	-0.38
	P	.19	0.4	0.32	0.47	0.52	0.38	0.88	0.717	0.05
TG Ab	**R**	.17	0.3	0.09	-0.36	-0.16	-0.35	0.143	-0.011	0.03
	P	.41	0.13	0.64	0.06	0.41	0.07	0.478	0.956	0.87
TPO	**R**	.61**	-0.34	.52**	-0.28	-.137-	-0.22	0.198	-0.014	0.15
	P	.001	0.08	.005	0.16	.496	0.27	0.322	0.944	0.45

#F.INS=FASTING INSULIN

DISCUSSION

As regards demographic data among the studied groups, we found that the mean age was distributed as 41.96±14.62, 41.74±13.89, and 35.29±8.73 respectively with no significant difference among groups also there was no significant difference regard Weight or height or BMI but regarding sex distribution females were significantly associated with Subclinical hypothyroidism Group.

The present study can be supported by the study by **Choi *et al.* [11],** that conducted on 5727 cases for identification of the association between IR and thyroid disease. The cases were divided into five groups; overt hypothyroidism, SCH, subclinical hyperthyroidism, overt hyperthyroidism, and euthyroid. The mean age was 37.99 ± 0.23 years, females represented 47.93% of cases. Thyroid dysfunction was prominent in females. Euthyroid represented 92.32%. There was a significant difference regarding height, on the other hand, BMI did not show a significant difference.

As regard thyroid profile distribution among studied groups, we found that TSH was significantly lower among the control group with no significant difference between the other two groups but regard FT3 and FT4 were significantly lower among the Overt hypothyroidism Group with no significant difference between the other two groups.

In agreement with our results the study **Vyakaranam *et al.* [12],** revealed that the TSH was significantly elevated in SCH (14.2±5.23 μU/ml) when compared with euthyroids (2.24 ± 1.43 μU/ml). While the two groups as regard FT3 and FT4 were not significantly different.

While the study by **Upadya *et al.* [13],** found that the man T3, and T4 were decreased significantly ($p < 0.01$), TSH was elevated significantly ($p < 0.01$) in cases with hypothyroidism compared to controls. The T3 and T4 mean levels were reduced significantly, and TSH showed significant elevation ($p< 0.01$) in subclinical cases compared to clinical cases.

As regards the correlations with thyroid profile, we found that TSH was significantly positively correlated with TPO, negative with FBG, F.INS, and HOMA IR, FT3 was significantly negatively correlated with cholesterol also FT4 was significantly negatively correlated with cholesterol and also with HbA1C and F.INS. We also found that TG Ab and TPO were significantly positively correlated.

In the overt group, we found that FT3 was significantly negatively correlated with cholesterol. Also, in the Sub-clinical group, our results showed that TSH significantly negatively correlated with TG, FT3 significantly negatively correlated with HDL, FBG, and HA1C, and FT4 significantly negatively correlated with HbA1C.

In the control group, we found that TSH was significantly positively correlated with TPO, and FT4 was significantly positively correlated with cholesterol but negatively correlated with TPO.

The study by **Choi *et al.* [11],** revealed that in linear regression analysis, thyroid function was positively correlated with the TyG index. In Overt hypothyroidism, they found that there was a positive significant correlation between thyroid function and TyG index. They also found that in linear regression analysis, thyroid function was non significantly associated with the HOMA-IR index.

While **Yang *et al.* [14],** found in the SHO group, that HOMA-IR had negative relation to FT4 ($p<0.05$) and positive relation to LDL-C ($p<0.05$). Among the HO group, It was found that HOMA-IR was adversely associated with FT3 and FT4 ($p<0.01$) and positively associated with TSH ($p<0.05$). Both SHO and HO groups showed a substantial positive correlation between HOMA-IR and homocysteine ($p<0.05$ and $p<0.01$). Only Hcy and FT4 plasma levels were shown to be significant in patients with HO or SHO after adjustment for other variables such as age, body mass index (BMI), blood lipids, and thyroid function indexes (Hcy). (OR = 0.27 and -0.23, respectively, all $p<0.01$).

Furthermore, **Upadya *et al.* [13],** reported that Homa-IR was associated with TSH, whereas insulin did not associate with thyroid hormones in hypothyroid patients. TSH was positively associated with cholesterol and LDL, whereas T3 and T4 were not associated with lipid profiles in hypothyroid patients. T3, T4 levels were positively associated with cholesterol in the clinical group, whereas TSH was not associated.

CONCLUSION

The current study concluded a significant correlation between thyroid hormones and IR. The evaluation of IR is crucial in events clinical and subclinical hypothyroidism, and for settlement of insulin sensitivity. For reducing the risk, IR should be controlled.

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