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EVALUATION OF THYROID FUNCTION MARKERS IN TYPE 2 DIABETIC PATIENTS IN RELATION TO INSULIN RESISTANCE

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ABSTRACT: Diabetes mellitus (DM) and thyroid disorders are both caused by endocrine abnormalities, and both have been shown to have a reciprocal influence and frequently coexist. Hence, the current study aims to detect the thyroid functions markers among patients with Type 2 diabetes (T2DM). In this research study, 90 enrolled participants aged 40 to 60 years were taken as samples for the study. There were 66 with T2DM and 24 who were non diabetic healthy individual. All individuals were investigated in terms of age, gender, diabetes duration, glycemic control (HbA1c), fasting blood glucose (FBG), diabetic complications, Body mass index (BMI), waist circumference (WC), and family history of DM. Samples were to assess serum thyroid hormones (TSH, FT3 and FT4), HbA1c, FBG, and insulin levels. The study's findings showed higher glucose incidence, hyperinsulinemia and higher insulin resistance (IR) in diabetic patients. Additionally, it has been noted that T2DM patients have low TSH concentrations and elevated blood concentrations of FT4 and FT3 than controls. Moreover, there was a highly significant correlation between serum FT4 and FT3 with values of FBG, insulin and IR. Also, a significant association between WC with insulin and Homa – Ir was noted. In conclusion, the diabetic patients showed significant relations with thyroid functions status.

KEYWORDS: Type 2 Diabetes, Insulin Resistance, Thyroid Related Hormones, HOMA-IR, HbA1c.

1. INTRODUCTION

Diabetes and thyroid problems are the two most frequent endocrine disorders caused by endocrine abnormalities, and both have been found to have a mutual impact on each other. DM and thyroid problems frequently coexist, often noticed in clinical practice; they have a close connection and bidirectional influence upon each other (Li *et al.*, 2022). Thyroid disorders are more likely to emerge in T2DM over time, with rates ranging from 9.9% to 48%. Furthermore, investigations have revealed a significant frequency of thyroid issue in the 13.4% diabetic population, with a larger prevalence (31.4%) among females with T2DM than males with T2DM (6.9%) (Hussein & AbdElmageed, 2021). According to a study, thyroid, kidney, and pancreas are all functionally associated to diabetes (Khidir & Kakey, 2013).

Recent studies have demonstrated that people with diabetes mellitus also have greater rates of thyroid disorders, and vice versa (Shah *et al.*). Thyroxine (T4) is not properly converted to triiodothyronine (T3) in peripheral tissues in T2DM, which also lowers the levels of thyroid-stimulating hormone (Kalra *et al.*, 2021). Researchers have shown that carbohydrate metabolism and pancreatic functions are regulated by thyroid hormones (THs) (Shehzad *et al.*, 2022). (T3) regulates cell activity physiologically by influencing how much glucose is taken in by pancreatic cells, which in turn regulates the release of insulin. Additionally, THs influence the metabolism of glucose in tissues that respond to insulin such as liver, adipose tissue and skeletal muscle (Al-bayati & Al-Khateeb, 2021). Besides above findings also a study reported high TSH level and low free thyroxine (FT4) level in diabetic patients, with a positive impact of thyroid hormones on hyperglycemia and insulin resistance (Rong *et al.*, 2021). Thyroid hormones (FT4) and (FT3) have been shown to have both agonistic and antagonistic effects on insulin in various organs (Spira *et al.*, 2022). Decreased tissue response to insulin is the definition of insulin resistance. Hyperinsulinemia develops in the body tissues due to how tissues respond to insulin (Demiral Sezer & Erdoğan Yücel, 2021). Based on fasting plasma glucose (FPG) and insulin, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) method is used for evaluating function of Pancreatic beta cell (β-cells) and IR. The (HOMA-IR) is a formula which estimates insulin sensitivity using FPG and insulin serum concentrations. Therefore, it frequently used to diagnose insulin resistance and metabolic state (Ha *et al.*, 2021). Obesity, particularly abdominal obesity, may be linked to T2DM via increasing IR. Obesity may be measured using the (BMI), and abdominal obesity can be examined by measuring the WC (Alkhalidy *et al.*, 2021). The current study was done to investigate the functional association between T2DM and thyroid disorders.

2. MATERIALS AND METHODOLOGY

A case control design was used in this study to investigate thyroid hormones and insulin resistance in T2DM patients. The study includes 66 diabetic patients (33 males and 33 females) at ages range from (40-60) years, and are on the metformin treatment. 24 subjects (12 males and 12 females) of age and sex matched with individuals free from signs and symptoms of DM disease were included as control group. The personal information and history of both patients and healthy individuals were recorded in a questionnaire. The interview concluded, participants information such as the patient's name, age, gender, address, duration of diabetes, diabetes complications, BMI, occupation, marital status, waist circumference and family history for DM.

The waist circumference is used to measure central obesity, while BMI is used to establish if a person is overweight or obese. BMI was determined using the conventional method as follows: BMI = weight (in kg) / height^2 (in m2)(Strings *et al.*, 2023).

For biochemical analysis, an overnight fasting blood samples (10-12 hrs.) were collected from the cases and controls attending the shahedan Qaladze teaching hospital in the Iraqi Kurdistan region from October 2021 to January 2022 by using disposable syringes and needles about 10 ml of blood was taken from each subject. Blood samples were put in two different types of tubes, one of them is Lavender Top Tube contains EDTA as the

anticoagulant and is used for HbA1c test (Abdullateef & Saleh, 2021). The other part was a 5ml of blood used for serum separation by centrifugation. After that, serum samples were obtained, then serum transferred into Eppendorf and tubes stored at deep-freezing point of (-20 °C) for biochemical analysis.

The measurement of serum fasting glucose and Hba1c was performed using Giesse diagnostics kit (Italy) on Geno TEK Chemistry analyzer 150 (Aflo Company - USA), Thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) insulin levels were measured using the Roche Diagnostic GmbH Kit (Germany) by Cobas e 411 Roche Company (Germany). (HOMA-IR) is a widely used method for measuring insulin resistance. It was derived from the following formula: HOMA-IR = [fasting glucose] (mg/dl) × [fasting insulin] (μU/ml)/405 (Abdullah & Salih, 2023).

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Statistical Analyses

The statistical analysis was done using Prism 8.0.1., SPSS version 24.0 and Microsoft excel program (2019) for Independent Samples T test and correlation coefficient calculations. The variables were summarized as mean and standard error. Probability (p) value < 0.05 was accepted as statistically significant (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NS not significant).

3. RESULTS

In the current study, the glucose incidence analysis revealed, the levels of FPG, Hba1c, and HOMA-IR in the diabetes group were significantly higher than in the healthy control group. In addition, serum insulin levels in DM patients were higher but not different statistically when compared with control group (Male and female), as illustrated in the table (1).

Table 1.Glucose incidence parameters in diabetic patients compared to controls

Parameters	Sex	Diabetic group	Normal group	P value
Fasting glucose mg/dL	male	174.8 ± 10.17	98.85 ± 2.9	0.001 ***
	female	207.1 ± 12.31	98.17 ± 2.631	0.001 ***
Hba1c (%)	male	8.841 ± 0.324	5.274 ± 0.071	0.001 ***
	female	8.491 ± 0.224	5.465 ± 0.09	0.001 ***
Insulin uU/ml	male	12.07 ± 1.160	9.392 ±0.9254	0.068 NS
	female	13.63 ±1.153	9.761 ± 1.261	0.223 NS
HOMA-IR	male	4.571 ± 0.381	3.139 ± 0.394	0.0318 *
	female	6.018 ± 0.590	2.572 ± 0.373	0.001 ***

The thyroid functions test parameters of the studied participants are shown in table (2), the levels of serum T3 and T4 were significantly high while serum TSH levels was significantly low in T2D group, compared to control group. The study of the thyroid status showed, that there is no significant difference in Ft3/Ft4 ratio levels among females in the T2D group compared to the control group.

Table 2. Thyroid functions test parameters in diabetic patients compared to controls

Parameters	sex	Diabetic group	Normal group	P value
TSH ng\ml	male	1.499 ± 0.160	2.124 ± 0.165	0.060 *
	female	1.545 ± 0.208	2.365 ± 0.278	0.039 *
FT4 pg/ml	male	18.03 ± 0.459	15.76 ± 0.380	0.0052 **
	female	17.37 ± 0.472	14.38 ± 0.659	0.0017 **
FT3 pg/ml	male	5.439 ± 0.096	5.049 ± 0.103	0.0263 *
	female	5.688 ± 0.181	4.647 ± 0.144	0.0022 **
Ft3/Ft4 Ratio	male	0.2824 ± 0.006	0.322 ± 0.011	0.0025 **
	female	0.3264 ± 0.011	0.317 ± 0.010	0.6739 NS

As seen in Table (3) and figure (1), in diabetic patients, there were highly significant negative correlation between serum Ft4 and values of FPG, insulin, and HOMA-IR.

Table 3.Correlation between serum free thyroxine levels with fasting glucose, insulin and Homeostatic Model Assessment for Insulin Resistance

Parameters	Patients group	
	R	P values
Ft4 and fasting glucose	-0.439	0.0004 ***
Ft4 and Insulin	-0.418	0.0006 ***
Ft4 and HOMA-IR	-0.445	0.0002 ***

The data analysis of the current results of correlation evaluation showed negative correlations between Ft3 and HOMA-IR, FPG and insulin. However, there were positive associations between Ft3 and Hba1c. HOMA-IR and the Ft3 / Ft4 ratio also have a significant and positive correlation (Table 4).

Table 4.Correlation between serum free triiodothyronine levels with Homeostatic Model Assessment for Insulin Resistance, fasting glucose, insulin, and hemoglobin A1C and free triiodothyronine / free thyroxine ratio with Homeostatic Model Assessment for Insulin Resistance

Parameters	Patients group	
	R	P values
Ft3 and fasting glucose	-0.459	0.0003 ***
Ft3 and Insulin	-0.337	0.0083 **
Ft3 and HOMA-IR	-0.255	0.046 *
Ft3/ Ft4 ratio and HOMA IR	0.351	0.0055 **
Ft3 and Hba1c	0.347	0.0065 **

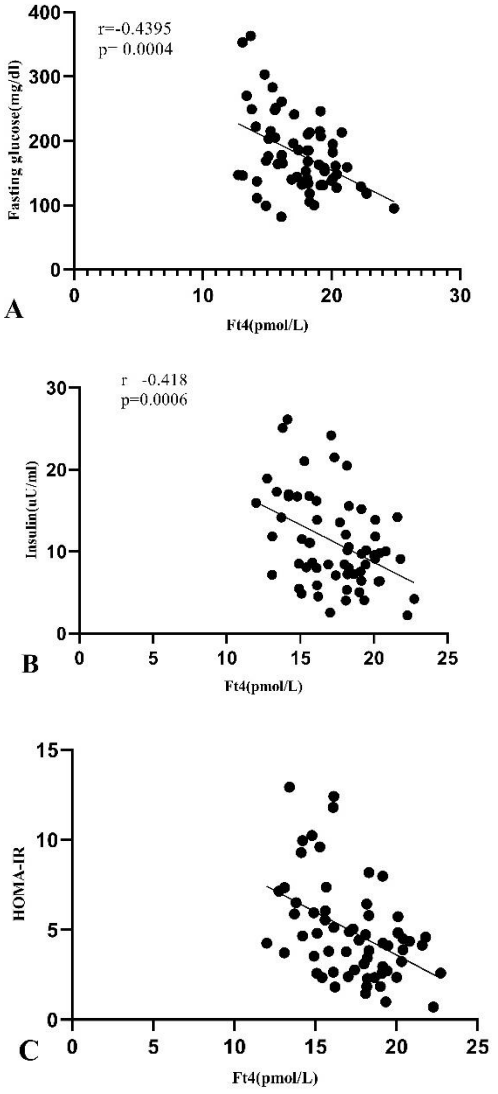

Figure 1*:* Correlation between **A**. free thyroxine levels with Fasting glucose **B**. free thyroxine levels with Insulin **C**. free thyroxine levels with Homeostatic Model Assessment for Insulin Resistance

In this study, as showed in Table (5) there were noted a significant association between WC with insulin and Homa Ir.

Table 5.Correlations between waist circumference with insulin and Homeostatic Model Assessment for Insulin Resistance.

Parameters	Patients group	
	R	P values
WC and insulin	0.588	0.0001 ***
WC and Homa Ir	0.565	0.0001 ***

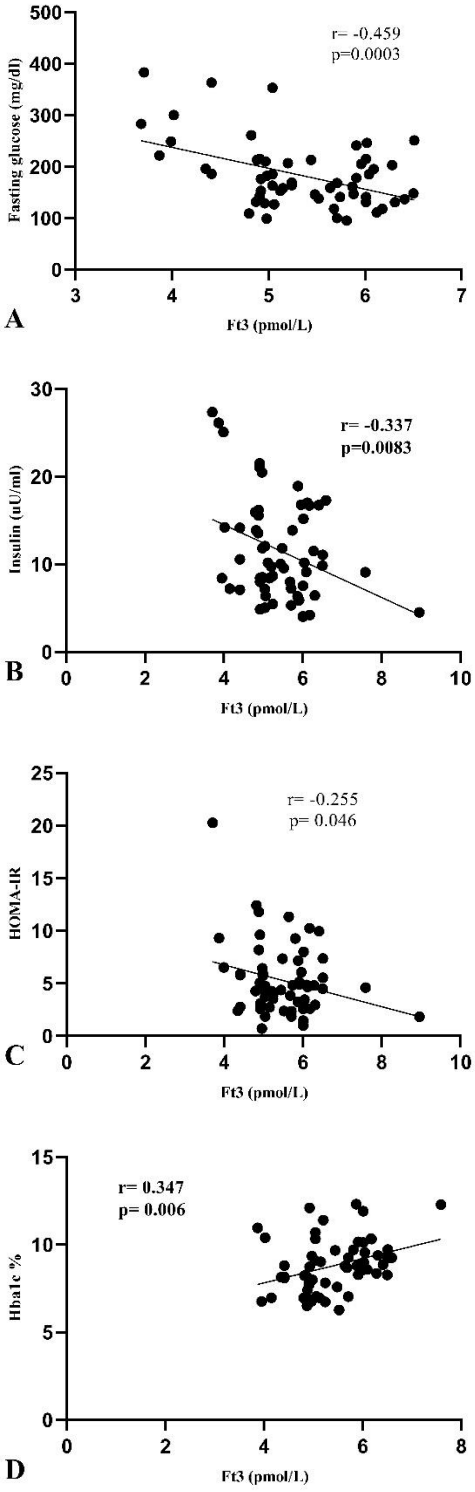

Figure 2:Correlation between **A**. free triiodothyronine with fasting glucose **B**. free triiodothyronine with Insulin **C**. free triiodothyronine with Homeostatic Model Assessment for Insulin Resistance **D**. free triiodothyronine with hemoglobin A1C.

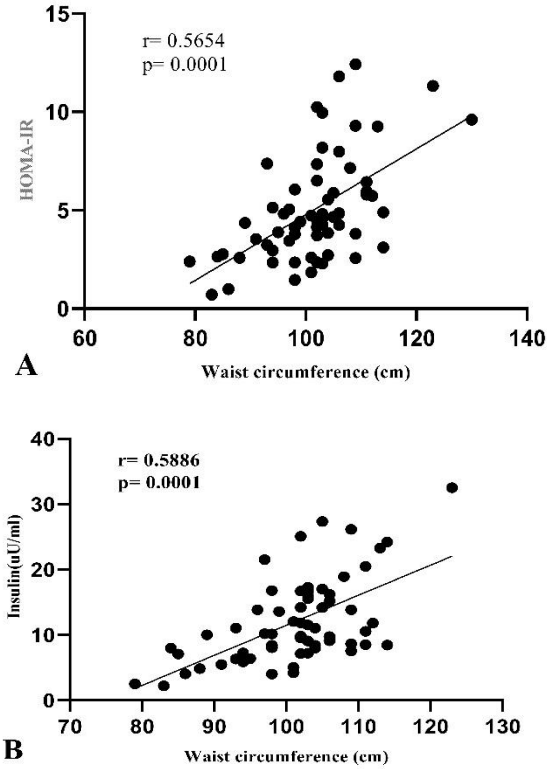

Figure 3: Correlations between **A**. waist circumference with insulin **B**. waist circumference with Homeostatic Model Assessment for Insulin Resistance.

Fasting glucose has a significant positive correlation with Hba1c and insulin, as illustrated in table (6). However, as shown in the table (7), HbA1c and fasting glucose are considerably and strongly linked with the duration of diabetes.

Table 6. Correlations between fasting glucose with hemoglobin A1C and insulin.

Parameters	Patients group	
	R	P values
Fasting glucose and Hba1c	0.4947	0.0001***
Fasting glucose and insulin	0.357	0.0051 **

Table 7. Correlations between duration of diabetes with hemoglobin A1C and fasting glucose.

Parameters	Patients group	
	R	P values
duration of diabetes and Hba1c	0.472	0.0001 ***
duration of diabetes and fasting	0.493	0.0001 ***

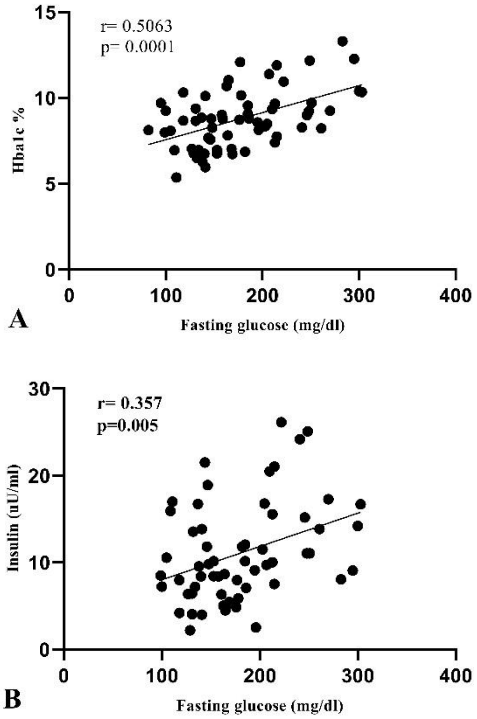

Figure 4: Correlations between **A**. fasting glucose with Hba1c **B**. fasting glucose with insulin

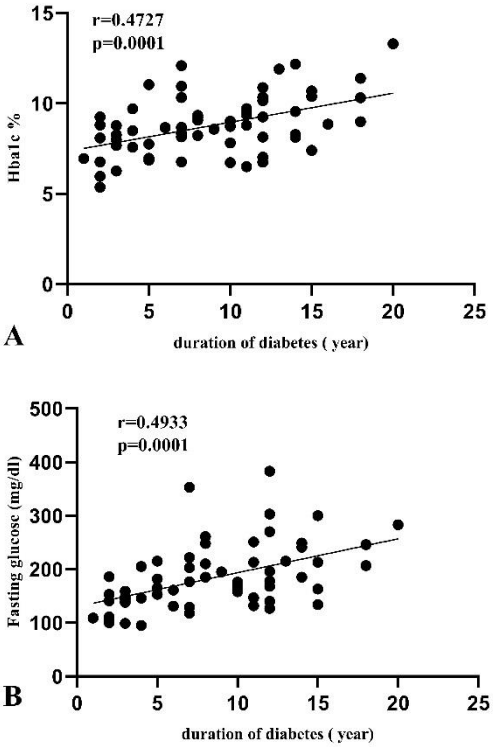

Figure 5: Correlations between **A**. duration of diabetes with hemoglobin A1C **B**. duration of diabetes with fasting glucose.

4. Discussion

This study's findings revealed that hyperinsulinemia and insulin resistance is higher in diabetic patients. This result was in agreement with previous study reported that insulin resistance precedes the development of hyperinsulinemia (Nolan & Prentki, 2019). Insulin resistance, a condition in which the body does not respond well to the effects of insulin as it should, is linked to

hyperinsulinemia. In that case, the pancreas produces more insulin in an effort to overcome the resistance, which raises the blood levels of insulin (Janssen, 2021). On the other hand, insulin resistance contributes significantly to the development of thyroid disorders in T2DM patients (Mehalingam *et al.*, 2020). The effects of thyroid hormone (THs) on glucose homeostasis have long been recognized. It has been linked to β-cells formation and has been shown to alter glucose metabolism via several organs including the liver, gastrointestinal tract, pancreas, adipose tissue, skeletal muscles, and the central nervous system (Eom *et al.*, 2022). The thyroid hormones act as insulin agonists and antagonists, respectively, to maintain a delicate equilibrium of glucose homeostasis. This equilibrium can be upset by hypothyroidism, which can also change glucose metabolism and result in insulin resistance (Vyakaranam *et al.*, 2014).The majority of obese people with insulin resistance have metabolic liver disease, due to alterations in lipid and glucose metabolism brought on by hyperinsulinemia, which may affect hepatic T4 to T3 conversion and the feedback effect of free hormone fractions on TSH synthesis (Racataianu *et al.*, 2017). The current investigation found that serum TSH level was lower.

In addition, patients with T2DM had significantly greater serum FT4 and FT3 levels than controls. Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is defined by low (TSH) concentrations and increased blood concentrations of thyroid hormones T4, T3 or both. Additionally, subclinical hyperthyroidism is defined by normal T4 and T3 levels but low blood TSH levels (De Leo *et al.*, 2016). The findings of the current research detected a significantly negative association of FT4 with variables related to glucose homeostasis in diabetic male and female patients. Moreover, it has been noted that T2DM patients have higher rates of hyperthyroidism than control, our findings are in agreement with previous studies (US & Monika, 2022). Condorelli *et al.* (2022) showed that metformin therapy can dramatically lower TSH and raise FT4 and FT3 blood levels in those with healthy thyroid function. Metformin's ability to reduce TSH has been attributed to a number of molecular processes. Some researchers have proposed changes in thyroid hormone receptor affinity or expression, elevated central dopaminergic tone, and effects on TSH control as potential explanatory mechanisms (Cannarella *et al.*, 2021). Another significant finding from the study was that, fasting glucose, fasting insulin levels and HOMA-IR were decreased with increasing FT4. This study supports evidence from previous observations (Ha *et al.*, 2021).In addition , the current study found that FT3 was adversely linked with fasting glucose, insulin secretion, and IR in T2DM patients. Shi *et al.* (2021) reported the connection between FT3 and adverse metabolic conditions such obesity, mixed hyperlipidemia, and hyperglycemia. Moreover, it was noted in the study that high levels of FT3 were linked to the development of insulin resistance and that low levels of FT3 were directly linked to a reduction in HOMA-IR. Previously, it was discovered that high serum FT4 levels in individuals with T2DM were connected with glucose homeostasis parameters (Spira *et al.*, 2022). The correlations finding of glycemic status parameters, IR and thyroid hormones with BMI, and WC in T2DM patients. The results of this study show a correlation between greater BMI and higher HbA1c.This pattern of the association of T2DM and thyroid function may be caused by effect of BMI rising on HbA1C as previously mentioned (Boye *et al.*, 2021; Skogberg *et al.*, 2019). Obesity causes cells in the body to become less responsive to insulin generated by the pancreas, which can lead to insulin resistance. This indicates that the body's insulin is not efficiently lowering its sugar levels. Obesity, on the other hand, impairs adipose tissue function, resulting in decreased adipokine release into the circulation. Excess fat cells, over time, will cause fat cells to become resistant to insulin's antilipolytic actions, resulting in an increase in the process of lipolysis and free fatty acids in plasma. Free fatty acids boost gluconeogenesis resistance, which then triggers insulin in the liver and muscles (Sarnings *et al.*, 2022). However, in patients with type 2 diabetes mellitus, higher BMI and WC were linked to increased insulin resistance and lower insulin sensitivity (Deusdará *et al.*, 2022; Zhao *et al.*, 2017). The relationship and interaction between obesity and T2DM are mediated by a number of mechanisms, including increased lipolysis, higher levels of free fatty acid release from adipose tissue, decreased glucose uptake, and the increased secretion of pro-inflammatory signals, which may impair insulin sensitivity. Alterations in the release of adipokines and pro-inflammatory cytokines by adipose tissue have the potential to directly affect insulin signaling or to activate pro-inflammatory pathways in target tissues, which causes local and subsequently systemic insulin resistance (Blüher & Stumvoll, 2020).

We observed that the levels of FPG and Hba1c, were considerably higher in the diabetic group as compared to normal participants, this observation agrees with the results of various earlier researches. Studies of Shivaprasad *et al.* (2019), in diabetic patients showed significant correlation between HbA1c and duration of diabetes. The results of this study were similar to a previous study were done by Widyaningsih and Ahsani (2021). The development of diabetes from normal glucose tolerance is characterized by decreases in β-cells mass that result in reduced β-cells function. The resulting glucotoxicity may be a recognized factor for the stimulation of apoptosis, leading to proliferative abnormalities in β-cells. Therefore, it is possible that β-cells function might be compromised by having diabetes for a prolonged period of time, especially if glycemic control was inadequate (Hayashino *et al.*, 2017). Patients with diabetes for an extended period of time (more than 7 years) were more likely to have poor glycemic control. Recent research found that people with diabetes for more than ten years were more likely to have poor glycemic control than those with diabetes for three years. This might be attributed to ß-cell progressive impairment of insulin secretion over time, a rise in insulin resistance, and an abrupt drop in insulin secretion (Mamo *et al.*, 2019).

5. CONCLUSION

In the light of the results of this study which has been conducted for the first time in Qaladze City, we have reached the conclusion that the physiological correlations of hyperglycemic incidence with thyroid functions markers, and a significant contribution of insulin resistance development with developments of thyroid problems in people with type 2 diabetes.

6. Ethical Clearance

The project was approved by the local ethical committee at Koya University, Faculty of Health & Science. The project has also received approval from the Ministry of Health of the Kurdistan Regional Government to be conducted in the hospitals. Patients were asked to provide their informed permission. Data anonymity was protected at all levels of data processing.

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