Research Paper

Hypothyroidism and the Risk of Occurrence of Type 2 Diabetes Mellitus

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ABSTRACT:

BACKGROUND:

Hypothyroidism is a syndrome resulting from deficiency of thyroid hormones leading to general slowdown of many metabolic processes

OBJECTIVE:

This study was designed for investigating the occurrence of type 2 diabetes mellitus among sample of patients with hypothyroidism, as well as investigate the relationship between fasting serum glucose and glycated hemoglobin levels with thyroid stimulating hormone, free triiodothyronine and free thyroxine

PATIENTS AND METHODS:

This is a comparative cross section study include 80 subjects was taken, 40 of them as patients diagnosed with clinical hypothyroidism who are on treatment. The remaining 40 apparently healthy individuals who served as a control group. The diagnosis of clinical hypothyroidism was depending on serum thyroid stimulating hormone level of more than 4.2 Ulu /ml with low levels of free thyroxine and free tri-iodothyronine.

RESULTS:

The mean values for the TSH levels of patients group (4.10 ± 3.25 µIU/ml) which was significantly higher than values of controls (1.74 ± 1.14, p µIU/ml < 0.001). Also, mean values for fasting serum glucose (103.68 ± 21.06 mg/dl, p < 0.001) and HbA1c (6.27 ± 1.18 %, p < 0.001) of hypothyroidism patients were significantly increased in comparison to these of control (86.23 ± 9.32 mg/dl, 5.28 ± 0.35 %, respectively).

CONCLUSION:

Overt hypothyroidism is related with an increased risk of type 2 diabetes mellitus and measurement of glucose indices needed to be included in hypothyroid investigations. Progression the prediabetes to diabetes seems more prominent in presence of uncontrolled hypothyroidism.

KEYWORDS: fasting serum sugar, free thyroxine, glycated hemoglobin, hypothyroidism, type 2 diabetes mellitus.

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INTRODUCTION:

The thyroid is an endocrine gland that control secretion of thyroid hormones thyroxine (T4) and triiodothyronine (T3) which affect normal growth, tissue differentiation, and metabolism. The production of thyroid hormones is controlled by thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland. The most common diseases affecting thyroid functions and cause decrease production is autoimmune thyroiditis (Hashimoto thyroiditis) (1) Around twelve percent of the adult has subclinical hypothyroidism (2,3).

The clinical features of hypothyroidism are general and non-specific, symptoms include: fatigue, menorrhagia and concentration lack, cold intolerance, change in bowel habit, and loss of hair. The spectrum of the symptoms reflects the degree of thyroid dysfunction, signs of hypothyroidism include edema, increase weight, enlargement of thyroid gland, mental impairment and delayed relaxation phase of deep tendon reflexes (4).

Diabetes mellitus (DM) is a metabolic disorder represented by sustained high blood glucose levels. Hyperglycemia caused by defect in either the insulin secretion or the insulin action or both of them. Which might lead to polyuria, polydipsia and polyphagia, with time, hyperglycemia may lead to hypertension, heart disease, blindness, renal failure, neuropathy, amputation, and stroke the implication of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins [5]. Type 2 diabetes mellitus (T2DM) represents about ninety percent of the cases of diabetes [6]; Checking of glycated hemoglobin levels (HbA1c) in the blood gives a clue about an individual's average blood level of glucose during the earlier 2-3 months. [7].

Hypothyroidism and diabetes are both common chronic metabolic disorders, a higher occurrence of the thyroid disorders was seen in patients with T2DM in comparison to the population. Also, a higher prevalence of DM is noted in patients with thyroid disorders. Both type two DM and hypothyroidism necessitates lifelong treatment [8].

Thyroid hormones stimulate insulin secretion in direct way by pancreatic β-cells the relation between hypothyroidism and DM is characterized by a complicated interaction. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and extra and shortage of any can lead to functional discrepancy of the other. Thyroid hormones apply concentrated effects in the regulation of glucose homeostasis. These effects consist of alterations of circulating insulin levels and counter-regulatory hormones, intestinal absorption, hepatic production and peripheral tissues uptake of glucose [9].

Insulin is a hormone of anabolism known to increase Thyroid Stimulating Hormone turnover, which is protein in nature. Newly, C-peptide has been shown to rise Na^+/K^+- ATPase activity, an action that also rise protein synthesis. Such activity would aggravate increased Turnover of TSH, which is a protein hormone (10).

So, the study was designed to explore the occurrence of T2DM among sample of Iraqi patients with hypothyroidism.

PATIENTS AND METHODS:

Study design:

This study is a comparative cross-sectional study design that conducted at Baghdad Teaching Hospital in Medical City and Department of biochemistry \College of Medicine \University of Baghdad through the period from. February 1st 2023 to July 2023.

Ethical consideration

The study protocol was approved by scientific council of pathology –Iraqi board for medical specialization at 8 -1.2023 .and Verbal consent from participants was taken after explaining the objective of this study.

Study population

It includes 80 subjects selected from endocrine outpatient clinic ,40 of them with prior diagnosis of hypothyroidism, and other 40 subjects act as control. with age range from 35 to 65 years old.

The occurrence of T2DM of the included patients with hypothyroidism was investigated based on American Diabetes Association Classification and diagnosis for DM [HbA1c ≥ 6.5% (≥48 mmol/mol)] . This, or FSG ≥126 mg/dL (≥7.0 mmol/L) [11] .

Exclusion criteria

Study eliminates patients with hyperthyroidism, history of type 1, type 2 DM, pregnancy, patients on drugs known to change thyroid hormone level (amiodarone, lithium), liver disease, renal disease, acute illness, fever, hemoglobinopathies, iron deficiency anemia .

Anthropometry:

Anthropometric measurements like waist circumference, height and weight and mass body mass index (BMI Kg/m^2) for each person included in this study. which calculated by equation: BMI (Kg/m2) = weight (Kg)/height2 (m2) [12].

Procedure and data collection

Five mL of peripheral venous blood were collected from median cubital vein from each participant using 5 ml disposable syringe, after an overnight 10-12 hour fasting state, divided into two parts; 2 mL was transferred into Ethylene diamine tetra acetic acid tube for measuring HbA1c, and the other 3 mL was transferred into gel tube allowed to clot for thirty minutes and then centrifuged for ten minutes at 2500 revolution per minute (rpm) to obtain serum. The separated serum was used for measuring fasting serum glucose FSG, TSH, FT4 and FT3.

Fasting serum glucose(FSG) is measured by Architect Abbott c40000 clinical chemistry analyzer by Hexokinase/G-6-Posphodehydrogenase G-6-PDH method ، while, Hemoglobin A1c was measured by using Tosoh automated Glycohemoglobin Analyzer HPLC-723®G8 by High Performance Liquid Chromatography (HPLC) ،and thyroid stimulating hormone (TSH) and free iodothyronine (FT3) and free Thyroid hormone (FT4) was measured by Tosoh AIA2000 immunoassay analyzer .

Statistical Analysis

The study was interrupted using version 25.0 software of statistical package of social sciences (SPSS) program. Chi-square test used to test association between qualitative variables, independent (t test) was used to evaluate difference of mean between two quantitative variables and ANOVA was used to assess difference of mean of more than two quantitative variables groups. P value regarded significant if ≤ 0.05.

RESULTS:

The study included 80 participants, 40 of them as patient (75% were females, 25% were males), and the other 40 as control (71% of participants were females and 29% were males), the Anthropometric measurements of both patients group and control group are showing in table1.

Table 1: Mean (±SD) of demographic parameters in hypothyroidism patient and control groups.

Parameter	Controls (n=40)	Hypothyroidism Patients (n=40)	p-value (calculated)
Age (years)	47.68 ± 8.75	44.75 ± 9.13	0.14 NS
Body Mass Index (BMI) Kg\m^2	29.64 ± 5.22	30.81 ± 6.85	0.39 NS
waste circumference (cm)	102.55 ± 15.18	98.48 ± 13.95	0.21 NS

NS:no-significant-difference

While, the biochemical parameters of both hypothyroidism patients and controls was measured, show non-significant differences in mean values of fT3 (4.02 ± 0.85 pmol/L) and fT4 (15.90 ± 3.86 pmol/L) in patients group in comparison to those of controls group (4.04 ± 0.64 pmol/L, 14.80 ± 2.67 pmol/L, respectively). mean values for the TSH levels of patients group (4.10 ± 3.25 µIU/ml) which was significantly higher than values of controls (1.74 ± 1.14, p µIU/ml < 0.001). Also, mean values for fasting serum glucose (103.68 ± 21.06 mg/dl, p < 0.001) and HbA1c (6.27 ± 1.18 %, p < 0.001) of hypothyroidism patients were significantly increased in comparison to these of control (86.23 ± 9.32 mg/dl, 5.28 ± 0.35 %, respectively), as illustrated in table 2.

Table 2: Mean (± SD) values of the measured biochemical parameters of hypothyroidism patients and controls.

Parameters	Control (n=40)	Hypothyroidism Patients (n=40)	p-value (calculated
TSH µIU/ml	1.74 ± 1.14	4.10 ± 3.25	< 0.001*
fT3 pmol/L	4.04 ± 0.64	4.02 ± 0.85	0.90 NS
fT4 pmol/L	14.80 ± 2.67	15.90 ± 3.86	0.14 NS
HbA1c %	5.28 ± 0.35	6.27 ± 1.18 %	< 0.001*
Fasting glucose mg\dl	86.23 ± 9.32	103.68 ± 21.06	< 0.001*

* means significant difference, NS: no-significant differences, P value regarded significant if ≤ 0.05.

The occurrence of diabetes mellitus and pre-diabetes as defined by fasting glucose and/ or HbA1c in patients and control groups, the results show that in patients group 6 out of 40 (15 %) had fasting glucose level ≥ 126 mg/dl in comparison to controls group (0.0 out of 40; 0.0 %) with significant difference (p < 0.0). In addition, 16 out of 40 patients (40 %) had HbA1c % equal or above 6.5 % compared to 0.0 out of 40 controls (0.0 %), with significant difference (p < 0.001). Moreover, 8 out of 40 patients (16 %) had HbA1c between (5.7-< 6.5 %) in comparison to 2 out of 40 controls (5 %) with significant difference (p < 0.001), as shown in table 3.

Table 3: Occurrence of diabetes mellitus and pre-diabetes as defined by fasting glucose and HbA1c in patient and control groups

Parameters		Groups		p-value
		Patients	control	
Fasting glucose (mg/dl)	< 126 mg/dl	34	40	0.02*
		85.0%	100.0%	
	≥ 126 g/dl	6	0	
		15.0%	0.0%	
HbA1c %	normal	16	38	<0.001*
		40.0%	95.0%	
	prediabetes	8	2	
		20.0%	5.0%	
	Diabetic	16	0	
		40.0%	0.0%	

* means significant in difference P value ≤ 0.05

DISCUSSION:

The study design included gender, age, and BMI -matched- of patients and healthy control group (table 1) in order to minimize biological variations and to be away from obesity effect on the obtained results.

Hypothyroidism, is a hormonal condition related to metabolism rate of the body. The ominous high levels of the TSH had been noticed in the cases as compared to the normal subjects in the study (table 2), this is in accordance with study by Ates *et al.* [13], that stated that increase could be as a result of the deregulation in the hypothalamus-pituitary axis producing endocrine dysfunction [14]. in addition, TSH and HbA1c values were detected high in non-diabetic hypothyroid subjects in comparison to normal controls according to Ismail *et al.* [15].

Depending on the thyroid hormone effects on metabolism of lipids, carbohydrates, and insulin secretion also, the relation between the thyroid gland function and type 2 diabetes has been assumed. Regarding thyroid dysfunction, hypothyroidism was related to resistance of insulin and changes in metabolism of glucose, which may lead to hypothyroidism increase the occurrence of T2DM. A recent review labelled that hypothyroid disease might lead to insulin resistance which might occur through a change of GLUT4 translocation and effect of leptin hormone, and an increase of free fatty acids [16]. Also, the mean values of HbA1c of hypothyroidism patients group were significantly increased compared to those of controls group (table 2) and this agreed with Bhattacharjee, et al. [17] who suggested that HbA1c level were found to be ominously higher in patients with hypothyroidism compared to control group and HbA1c levels reduced noticeably with treatment in hypothyroid patients and this influence was probably attributable to low red blood cells turnover in hypothyroid patient according to their study.

There was no significant correlation found between HbA1C and TSH in patient with hypothyroidism in this study and also there was no significant correlation found between fasting glucose level and TSH and this findings go in accordance with Christy *et al.* [18], and that was against finding of Ali, *et al.* [19] who found significant positive relationship between TSH and HbA1c % in the uncontrolled hypothyroidism group which may be the cause of this discrepancy with present study in which most hypothyroidism patients were in fair control state.

In this study, there is a direct correlation between hypothyroidism occurrence and elevation of glycated hemoglobin as well as FSG values between both study groups, which shows that there is a strong difference in between the hypothyroidism patient and the control groups in the values of both HbA1c with FSG which agree with Chaker *et. al.* [20], who showed that high Fasting Serum Glucose rate is more in patients with hypothyroidism, and agree with Gronich [21] who concluded that hypothyroidism is a risk factor for new onset diabetes based on HbA1c levels and that agree with the findings of Bhattacharjee, *et al.* [17]. The results of this study are also in accordance with results of Chen *et al.* [22] study who found that high TSH and low FT3, FT4 are related with a higher risk of evolving

Type 2 diabetes depend on measuring both FBG and HbA1c levels for all participants in the study.

Eliminating the impact of age, sex, and comorbidities risk of Type 2 DM, its rate in hypothyroidism patients was still greater than the controls, which suggest that hypothyroidism intrusive with carbohydrates metabolism stimulated DM development. Possibly because insulin resistance and abnormal secretion and insulin clearance [22].

Significant difference also found in this study in the percentage of pre-diabetes and diabetes status between hypothyroidism patients and controls (table 3), that concluded that higher TSH levels is linked with an escalated risk of T2DM and evolution from prediabetes to diabetes. Findings were accordant with results of Chang *et al.* [23] which concluded that individuals with high serum thyroid-stimulating hormone levels are at greater risk of developing pre-DM.

The responsible mechanism for the relation between hypothyroidism and development of glucose intolerance is not clear. Initially, hypothyroidism may establish an insulin resistance linked to an increase in levels of lipids and decrease in glucose disposal in skeletal muscle and adipose tissue. Insulin resistant state, was provoked in euthyroid females who had undergone thyroidectomy by sharply stopping thyroxine replacement therapy. Also, impaired translocation of glucose transporters (e.g., GLUT4) may play a role in the impaired peripheral glucose disposal observed in hypothyroidism. Second, Type 2 DM and hypothyroidism might have some common genetic determinants. Third, hypothyroidism may indirectly effect glucose metabolism in indirect way by interacting with multiple humoral factors which involve adiponectin, ghrelin, glucagon, leptin, epinephrine and growth hormone (GH). Hypothyroidism can also decrease spending of energy, thermogenesis and metabolic rate. Hypothyroidism can also interfere with oxidative metabolism of mitochondria, which also might cause a rise in the prevalence of T2DM [23].

The clinical importance in this findings is the relation between thyroid gland function and the development from prediabetes state to diabetes state is prominent. Though, the individuals with a low-normal levels of the thyroid hormone, which involve large percentage of the population, are at a high risk for progression from the pre-diabetes stat to diabetes [20].

The results of this study disagree with the findings of Bos *et al.* [24] which found there is no relationship between TSH/FT4 with type 2 diabetes, suggesting that the relation reported by the traditional observational studies might be as a result of unmeasured confounding or reverse causation, In other hand, Bos and colleagues had been found that there is relation between genetic variants associated with thyroid metabolism and the insulin resistance which support a potential role of thyroid gland function in the pathogenesis of type 2 diabetes. Also more recent study by Kuś *et al.* [25] had found that there is no relation between thyroid gland hormones and T2DM in their main analyses.

CONCLUSION:

It seems that overt hypothyroidism may increase the risk of type 2 DM and measurement of b.suger indices (fasting or 2-hr post prandial glucose level and HbA1c). On the other hand, Progression of prediabetes stat to T2DM seems to be more prominent in presence of uncontrolled hypothyroidism.

Recommendation:

Depending on the findings of this study it recommended that for the future clinical tests must include the assessment of type 2 DM prevalence in subclinical hypothyroidism and hyperthyroidism. As well as, study association between insulin level and insulin resistance and occurrence of hypothyroidism. since that thyroid gland dysfunction is more commonly occur in women and T2DM is more commonly occur in men more attention must be directed toward the sex related factors.

Source of funding:

Nil.

Conflict of Interest:

Nil

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REFERENCES:

1. Ellervik C, Halsall DJ, Nygaard B. Thyroid disorders. In: Rifai N, ed**. Tietz Textbook of Laboratory Medicine. 7th ed. 2023**;806–45.
2. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement**. Thyroid.2014**;24(12):1670–751.doi: 10.1089/thy.2014.0028.
3. Cooper DS, Biondi B. Subclinical thyroid disease**. Lancet. 2012**;379(9821):1142–54. doi: 10.1016/S0140-6736(11)60276-6.

4. Alzahrani AS, Al Mourad M, Hafez K, Almaghamsy AM, Alamri FA, Al Juhani NR, Alhazmi AS, Saeedi MY, Alsefri S, Alzahrani MDA, Al Ali N, Hussein WI, Ismail M, Adel A, El Bahtimy H, Abdelhamid E. Diagnosis and Management of Hypothyroidism in Gulf Cooperation Council (GCC) Countries. **Adv in Ther. 2020**;37(7):3097-111. doi: 10.1007/s12325-020-01382-2. Epub 2020 Jun 1. PMID: 32488658; PMCID: PMC7467410.
5. American Diabetes Association. Introduction: Standards of medical care in diabetes—2018**. Diabetes Care. 2018**;41:S1–2.
6. Goyal R, Jialal I. Type 2 diabetes. In: StatPearls. Treasure Island (FL): **StatPearls Publishing; 2023 Jan-**. Available from: StatPearls.
7. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. **Biomark Insights. 2016**;11:95–104. doi: 10.4137/BMI.S38440.
8. International Diabetes Federation. **IDF Diabetes Atlas. 2017**. Available from: IDF Diabetes Atlas.
9. A study of thyroid disorders among patients with type 2 diabetes mellitus. **IOSR J Biotechnol Biochem. 2016**;2(5):33–36.
10. Asmabi M, Sonagra AD, Imdad T, Shylaja TV. Correlation between glycemic control and thyroid status in patients with type 2 diabetes mellitus. **Int J Biotechnol Biochem. 2018**;14(2):85–93.
11. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes—2021**. Diabetes Care. 2021**;44(Supplement_1): S15–S33. doi: 10.2337/dc21-S002.
12. World Health Organization. ICD-10: International statistical classification of diseases and related health problems. Geneva: **WHO; 2004**;2nd ed., 10th revision, Vol. 2.
13. Ates I, Altay M, Topcuoglu C, Yılmaz FM. Circulating levels of irisin are elevated in hypothyroidism: a case-control study. ***Arch* Endocrinol Metab. 2015**;60(2):95–100. doi: 10.1590/2359-3997000000077.
14. Al-Fatlawi ACY. An evaluation of blood glucose and lipid profile in female hypothyroidism patients in Kerbala province, Iraq. **Biomedicine. 2022**;42(3):556–60.
15. Ismail M, Irfan AH, Rao V, Reddy MNL, Jagidar SA. Effects of thyroid hormone on glycated hemoglobin in non-diabetic subjects with overt hypothyroidism**. J Evol Med Dent Sci. 2017**;6(11):882–87.
16. Roa Dueñas OH, Van der Burgh AC, Ittermann T, Ligthart S, Ikram MA, Peeters R, Chaker L. Thyroid function and the risk of prediabetes and type 2 diabetes. **J Clin Endocrinol Metab. 2022**;107(6):1789–98. doi: 10.1210/clinem/dgac006.
17. Bhattacharjee R, Thukral A, Chakraborty PP, Roy A, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Effects of thyroid status on glycated hemoglobin**. Indian J Endocrinol Metab. 2017**;21(1):26
18. Christy AL, Manjrekar P, Babu RP, Rukmini MS, Hegde A. Elevation of HbA1C in non-diabetic hypothyroid individuals: is anemia the connecting link? A preliminary study**. J Clin Diagn Res. 2013**;7(11):2442–44.
19. Ali AY, Allehibi KI, Al-Juboori NA. Glycemic status in patients with primary hypothyroidism and its relation to disease severity**. Mustansiriya Med J. 2020;**19(1):20–24. doi: 10.4103/MJ.MJ_5_20.
20. Chaker L, Ligthart S, Korevaar TIM, Hofman A, Franco OH, Peeters R, Dehghan A. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study**. BMC Med. 2016**;14(150):1–8. doi: 10.1186/s12916-016-0693-4.
21. Gronich N. Hypothyroidism is a risk factor for new-onset diabetes: a cohort study. **Diabetes Care. 2015**;38(9):1657–64.
22. Chen RH, Chen HY, Man KM, Chen SJ, Chen W, Liu PL, Chen YH, Chen WC. Thyroid diseases increased the risk of type 2 diabetes mellitus: a nationwide cohort study. **Medicine (Baltimore). 2019**;98(20): e15631. doi: 10.1097/MD.0000000000015631.
23. Chang CH, Yeh YC, Shih SR, Lin JW, Chuang LM, Caffrey JL, Tu YK. Association between thyroid dysfunction and dysglycemia: a prospective cohort study. **Diabet Med.** 2017;34(11):1584–90.
24. Bos MM, Smit RAJ, Trompet S, van Heemst D, Noordam R. Thyroid signaling, insulin resistance, and type 2 diabetes mellitus: a Mendelian randomization study**. J Clin Endocrinol Metab. 2017**;102(6):1960–70.
25. Kuś A, Marouli E, Del Greco MF. Variation in normal range thyroid function affects serum cholesterol levels, blood pressure, and type 2 diabetes risk: a Mendelian randomizationstudy. **Thyroid. 2020**;31(5): 721–31.