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Clinical assessment of glycated hemoglobin in diabetic hypothyroid patients: A comparison with Euthyroid non diabetic subjects

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Abstract

Background: Thyroid disease and diabetes mellitus (DM) are the two most common heterogeneous endocrine disorders in the general population. Both hypothyroidism and type 2 DM are closely involved in cellular metabolism and affect the malfunction of various organ systems. HbA1c was studied for its correlation with thyroid hormones and used for screening, diagnosis, and control of glycemic status.

Objective: To evaluate the validity of HbA1c as a screening and useful test to diagnose hypothyroid patients with pre-diabetes and diabetes.

Methods: The current study was conducted in the Specialized Center for Endocrinology and Diabetes/Baghdad, Iraq from October 2021 to May 2022. The present study was carried out on 115 hypothyroidism patients (92 females and 23 males), and one hundred individuals with normal thyroid function were chosen as a control group. Each patient and individual was investigated for thyroid profile using Vitek immunodiagnostic assay system (VIDAS), while HbA1c was assessed on whole blood by automated chemistry analysis (Analyticom).

Results: The results showed that most hypothyroid patients were within the age group (24-70) years, which represented 20% ≤(30), 32.2% ≤(40), and 28.7% ≤(50) years. Most hypothyroidism patients were females constituting 80% compared with 20% for males. Most hypothyroidism patients were obese BMI≥30Kg/m² represented 42.7% and overweight ≥ 25Kg/m² represented 40% compared with 15.7 who were normal weight. The prevalence of diabetes mellitus represented more than two times among the hypothyroidism individuals compared with the control sample, which indicated a highly significant relationship at Pvalue<0.01. The results also showed that meaningful significant differences were revealed between the two independent groups with highly significant differences at Pvalue<0.01 within the following parameters (HbA1c, Glucose, Thyroid stimulating hormones (TSH), Thyroxine (TT4), Triiodothyronine (TT3).

Conclusion: The present study conclude that the frequency of diabetic patients was significantly increased in hypothyroid population when compared with general population. The use of HbA1c for screening and supported diagnosis assay is necessary to detect and control diabetic patients.

Keywords: Hypothyroidism, Thyroid hormones glycemic status, HbA1c.

Introduction

The two endocrinopathies thyroid disorder (TD) and type 2 Diabetes mellitus (DM) are significantly coexisting and excess and defect of any one result in systemic derangements in metabolic processes [1]. Thyroid hormones are correlated with insulin action, both insulin and thyroid hormones play crucial roles in the regulation of cellular metabolism [2]. In an underactive thyroid (hypothyroidism), there is reduced in the degree of glucose homeostasis, compared with euthyroid subjects. Liver gluconeogenesis, liver glucose output, glycogen synthesis, and deterioration lead to increased glycogen levels. Besides that, Beta cells produce the biological hormone insulin in the blood the half-life will be prolonged with an elevated level and decrease in insulin synthesis. Type 2 DM is a heterogeneous multifactorial disease caused by relative insulin inadequacy, condition of insulin resistance, and insulin receptor irregularities. In type 2 diabetes mellitus death of beta cell apoptosis is blocked caused by infections or chemicals induced [3,4]. The diagnosis of diabetes mellitus is classically based on blood glucose levels either fasting or 2-h plasma glucose (2hpG) after an oral glucose tolerance test (OGTT) using 75g anhydrous glucose [5]. The investigative standards of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have released new guidelines on the management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). The criteria consist of either fasting plasma glucose (FPG) 126 mg/dl (7mmol/L) or more or 2hpG 200 mg/dl (11.1mmol/L) or greater [6, 7]. Using HbAc1 as a diagnostic test with a threshold of ≥6.5% because the HbA1c has several advantages to the FPG and OGTT including glycemic status over the past 2-3 months and it is not affected by the biological variability, lifestyle measures, and pre-analytical variability like FPG or OGTT [8]. The main disadvantages are affected by hemoglobinopathies and recent hemolysis. Testing to detect type2 diabetes and pre diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2) and who have one or more additional risk factors for diabetes [9,10]. Therefore, diabetic patients need to be screened for thyroid dysfunction and assess the hyperglycemic effect by correlating fasting serum glucose and thyroid profile parameters [11-12]. The present study aims to examine the frequency of diabetes mellitus in patients with hypothyroidism and to assess the effect of diabetes on thyroid hormone levels and other biochemical variables in some Iraqi populations. In addition, a thyroid function test was studied for correlation with HbA1c.

Subjects and Methods

This comparison study was conducted on a group of 115 hypothyroid patients (92 females and 23 males), whose ages ranged between (24-70) years in Baghdad city. Patient samples and control subjects were collected at the Department of Specialized Center for Endocrinology and Diabetes, for the duration period from October 2021 to May 2022. All participants in this study were recruited and went through an examination for thyroid function; [total thyroxin (TT4), total triiodothyronine (TT3), and thyroid-stimulating hormone (TSH)].

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One hundred euthyroid individuals with no history of thyroid dysfunction detected or any other disease were observed and selected as a control group. Age and gender were statistically matched for patient group control. Personal biodata collection, record clinical history, and medical examination were collected and designed on pro-forma assessment for this study.

Fasting venous blood glucose (FBG) samples were aspirated with period a of 12-hour fasting for analysis of glucose level and lipid profile. Estimation of glucose levels was carried out by enzymatic colorimetric assay (GOD-PAP) test kit supplied by Biomaghreb [13]. About 5 ml of venous blood was drowned by a vacuum disposable syringe, (2 ml) of this blood was mixed with an anticoagulant EDTA vial tube, then mixed gently using a blood shaker to avoid clotting of the blood. Whole venous blood was obtained for estimation of HbA1c using an automated clinical chemistry analyzer [14]. Blood serum was isolated by centrifuging at 3000 R.P.M, for 10 minutes and transferred into a clean tube, and frozen at(-20c°) For analysis of thyroid profile, serum thyroxine (TT4), triiodothyronine (TT3) and thyroid stimulating hormone (TSH) was measured by using VIDAS analyzer, which depends on enzyme-linked fluorescent assay (ELFA) [15,16].

Results and Discussion

Table (1): Statically distribution of the studied samples according to Gender and Age variables with Comparison of Significance

Variable	Groups	Samples		C.S. (*) P-value
		Study	Control	
Age (years)	20 -	10.4%	18%	Chi-Sq. test P=0.092 NS
	30 -	20%	13%	
	40 -	32.2%	31%	
	50 -	28.7%	21%	
	60 -70	8.7%	17%	
44.01 ∓ 10.7	**44.7 ∓ 13.0**	**t = 0.412 P=0.680 NS**		
Gender	Male	20%	25%	F.E.P. test P=0.237 NS
	Female	80%	75%	
Female / Male (1 : 1.33)				

(*) **Non significant at P>0.05**

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Table (1) displayed the relationship between the two groups according to age, the result indicated that there were non-significant differences at P>0.05 for the distribution of age groups between the two samples. In this study, 115 patients were diagnosed with hypothyroidism, their ages ranged between (24 and 70) years, as well a control group was obtained, whose ages ranged between (24–and 70) years. These results were in agreement with other studies [17,18,19]. The two most clinically significant changes in endocrine activity during the elderly comprised the pancreas and thyroid gland. Approximately 40% of individuals aged 65 to 74 years and 50% of those older than 80 years have impaired glucose tolerance or diabetes mellitus [20]. Age-related thyroid dysfunction is also common, lowered T4 and increased thyrotropin concentration occurs in 5% to 10% of elderly women [21]. These abnormalities are mainly caused by Autoimmune disease [22].

Relation between gender & hypothyroidism

Table (1) shows the association between the two groups according to gender, the outcome presented that there was a non-significant difference at P>0.05 for the distribution of gender between the two samples rather than (Female / Male) reported (1: 1.33) times at the (study/control) samples respectively. In the study group, males were (n=23) 20%, and female were (n=92) 80%, while in the control group, males were (n=25) 25% and female were (n=75) 75%. These results were extremely reliable for the studied groups since gender variable had corresponding similar distributions at each group. These results agreed with other studies [23,24]. Hypothyroidism is more common among women due to disturbance in reproductive hormones, mainly estrogen and progesterone [25].

Table (2): Statically distribution of the studied samples according to BMI and with Comparison of Significance

Variable	Groups	Samples		C.S. (*) P-value
		Study	Control	
BMI	**Underweight < 18.5**	**0.90%**	**1.00%**	**Chi-Sq. test P=0.143 NS**
	Normal weight 18.5 - 24	**15.70%**	**27.00%**	
	Overweight 25 - 29	**40.9%**	**26%**	
	Obese-1 30 - 34	**27.0%**	**34%**	
	Obese-2 35 - 39	**7%**	**6%**	
	Obese-3 ≥ 40	**8.7%**	**6%**	
29.5∓6.8	**28.8∓6.04**		**t = 0.404 P=0.880 NS**	

(*) **Non significant at P>0.05**

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Table (2) shows the association between the different groups according to BMI, the result revealed that there was a non-significant difference at P>0.05 for the distribution of BMI groups between the two samples. In the study group, BMI ranged between (17.0 and 57.0), whereas the control BMI ranged between (18.0 and 46.0).

The current study confirmed previous findings by different studies [26, 27]. Body mass index depends on the stability between food intake and total energy consumption. Energy consumption is processed mainly by physical activity and (REE) represents resting energy expenditure. The life span depends on the equilibrium of these factors [28,29].

Table (3): Descriptive statistics of the studied parameters for the two independent groups (Study and Control)

Parameters	Samples	No.	Mean	Std. Dev.	Std. Error	95% C.I. for Mean		Min.	Max.
						L. B.	U. B.		
HbA1c	Study	115	7.37	1.80	0.17	7.04	7.71	4.6	12.7
	Control	100	5.87	0.71	0.07	5.73	6.01	4.3	7.5
Glucose	Study	115	6.61	2.92	0.27	6.07	7.15	3.7	21
	Control	100	5.79	0.92	0.09	5.60	5.97	4	10
TSH	Study	115	22.34	19.35	1.80	18.77	25.92	5.4	60
	Control	100	2.24	1.23	0.12	2.00	2.49	0.3	4.9
T4	Study	115	71.31	24.18	2.25	66.85	75.78	61	115
	Control	100	84.10	12.10	1.21	81.70	86.50	56	108
T3	Study	115	1.36	0.49	0.05	1.27	1.45	0.3	2.3
	Control	100	1.56	0.38	0.04	1.48	1.63	0.9	2.3

Table (3) shows the descriptive statistics of the studied parameters for the two independent groups (study and control) as follows:

1- HbA1c parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls outside the normal range (4.5 – 7.0) % at the upstairs bound, and however that some of the original readings were normal. With respect of the control group, the mean value and 95% C.I. of the population mean value fall inside the normal range.

2- The glucose parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls outside the normal range (3.6 – 6.3) mmol/L at the upstairs bound, however, some of the original readings were normal. With respect to the control group, the mean value and 95% CI of the population mean value are fully inside the normal range.

3- TSH parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls outside the normal range (0.25 – 5.0) µIU/ml at the upstairs bound, however, some of the original readings were normal. With respect to the control group, the mean value and 95% CI of the population mean value are fully inside the normal range.

4- The T4 parameter showed that with the study group, the mean value and 95% C.I. of the population mean value fall inside the normal range (60 – 120) nmol/ml at the upstairs bound. With respect of the control group, the same results were reported as in the study group.

5- T3 parameter showed that with the study group, the mean value and 95% C.I. of the population mean value falls inside the normal range (0.92 – 2.33) nmol/ml at the upstairs bound. With respect of the control group, the same results were reported as in the study group.

Table (4): Outcomes of testing differences between the two independent groups (study and control) at the studied parameters

Parameters	Levene's Test for Equality of Variances		t-test for Equality of Means			C.S. P-value
	F	Sig.	t	d.f.	Sig. (2-tailed)	
HbA1c	59.4	0.000	8.2	153.8	0.000	HS
Glucose	28.9	0.000	2.9	139.3	0.005	HS
TSH	238.3	0.000	11.1	115.1	0.000	HS
T4	28.6	0.000	-5.0	172.6	0.000	HS
T3	8.10	0.005	-3.4	210.1	0.001	HS

HS: Highly Significant at P<0.01; NS: Non Significant at P>0.05

Table (4) shows the results of testing hypotheses according to equality of variances and equality of mean values. The results of testing indicated that there was a highly significant difference at P<0.01 within the following parameters: (HbA1c, Glucose, TSH, T4, T3).

The correlation between the two samples

Table (5): Statically distribution of the studied samples according to the Diabetics variables with Comparison of Significance

Variable	Groups	Freq. & Percents%	Samples		C.S. P-value
			Study	Control	
HbA1c	Normal	Freq.	17	30	F.E.P. test P=0.006 HS C.C.=0.181 P=0.007
		HbA1c	36.2%	63.8%	
		Samples	14.8	30.0%	
	Abnormal	Freq.	98	70	
		HbA1c	58.3%	41.7%	

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		Samples	85.2%	70.0%	HS
Odds Ratio			Control/Study (1: 0.405)		
Glucose	Normal	Freq.	75	81	F.E.P. test P=0.007 HS C.C.=0.174 P=0.010 HS
		Glucose	48.1%	51.9%	
		Samples	65.2%	81.0%	
	Abnormal L. b.	Freq.	40	19	
		Glucose	67.8%	32.2%	
		Samples	34.8%	19.0%	
Odds Ratio			Control/Study (1: 0.440)		

HS: Highly Significant at P<0.01

Table (5) shows the distribution of the two samples according to different diagnoses (normal and abnormal) towards Hypothyroidism disease and Diabetics Mellitus (HbA1c and Glucose) parameters. The results were corresponding non-proportionally distributed and indicated a highly significant relationship at P<0.01, which indicated that patients with Hypothyroidism disease have more chance of being diabetic. In addition to that, an odd ratio was reported, which indicates that the prevalence of Diabetes mellitus represented more than two times the Hypothyroidism individuals compared with the control sample.

The current work showed the prevalence of diagnostic diabetic patients among some Iraqi hypothyroid patients and that diabetic women were more frequently affected than men. These results were in agreement with a number of reports on hypothyroidism and type 2DM [30,31,32]. While other study by Swamy et al (2012) there was significant percentage emphasize that the diabetic patients to be followed up with thyroid profile. The presence of chronic diabetic directed to drift towards hypothyroidism [33]. The reason for this outcome is that the thyroid gland which produces thyroxine (T4) and triiodothyronine (T3) are insulin antagonists that also encourage the action of insulin indirectly [34].

Table (6): Statically distribution of the studied samples according to Hypothyroidism Functions and with Comparison of Significance

Variable	Groups	Samples		C.S. P-value
		Study	**Control**	
TSH	**Normal**	**0.0%**	**100%**	**F.E.P. test P=0.000 HS**
	Abnormal	**100%**	**0.0%**	
T4	**Normal**	**73%**	**98%**	**F.E.P. test**

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	Abnormal L. b.	**27%**	**2%**	**P=0.000 HS**
Control/Study (1: 18.2)				
T3	**Normal**	**74.8%**	**95%**	**F.E.P. test P=0.000 HS**
	Abnormal L. b.	**25.2%**	**5%**	
Control/Study (1: 6.5)				

Table (6) displays the study samples to elucidate the hypothyroidism functions (normal & abnormal). The results reported that TSH parameters revealed a high significant difference at P>0.01 compared with the control group, and high significant differences were reported at P<0.01 with T4 & T3 parameters. These results were in agreement with a number of recent studies [35,36,37]. Research by Singh et al (2011) found the serum levels of TT3 and TT4 were significantly lower in diabetic subjects, while level of serum TSH was significantly higher in diabetic subjects [38,39]. The present study reported various levels of abnormal thyroid hormones in study groups of some Iraqi populations. This alteration may be an outcome of the various medications received**,** by patients for example Levo-Thyroxine and Insulin [40, 41].

The HbA1c or glycosylated hemoglobin test provides a good picture of the average blood sugar levels over a few months, giving access to diagnosis and monitoring of type 2 diabetes. However, certain biological factors and analytical factors could prevent this test from giving accurate results. These several risk factors or conditions affect the result of the HbA1c being falsely lowered or falsely elevated [42].

Limitations

The main limitation of this current study are the need to increase of the sample sizes. Another limitation of the current study there are conditions in which the HbA1c test is not a dependable origin for diagnosing diabetes, including, anemia, Iron deficiency, kidney disease, HIV, thalassemia, sickle cell disease, hemolysis, pregnancy, and blood transfusion.

Conclusion

1- Patients with age range between (30-50) years showed a high prevalence of hypothyroidism when compared with other age group.

2- Primary hypothyroidism was more common in females than males.

3- The frequency of diabetic patients was significantly increased in the hypothyroid population when compared with the general population.

4- We conclude from this study that the use of HbA1c for screening and supported diagnosis assay is necessary to detect and control diabetic patients.

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