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Thyroid Dysfunction in Type 2 Diabetic Patients and the Effect of Diabetes Duration and Anti-glycemic Medications on Mean TSH and A1c levels: A Retrospective study

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ABSTRACT

Background: *The association between type 2 diabetes mellitus and thyroid disorder is a well-recognized one, necessitating checking diabetic patient for the presence of thyroid abnormality.* ***Objective:*** *To check the presence of hypo or hyperthyroidism in a sample of type 2 diabetic patients and to see whether anti-glycemic medications have any effect on mean TSH and A1c levels.* ***Methods:*** *This is a retrospective study on records of 1341 type 2 diabetic patients in the Specialized Center for Endocrinology and Diabetes, Baghdad for a period of 3 months in 2019, data were taken from patient records software and analyzed the presence of hypo or hyperthyroidism.* ***Results:*** *Out of 1341 type 2 diabetic patients 108 have thyroid dysfunction (8%), 7% for hypothyroidism and 1% for hyperthyroidism. Mean TSH levels were significantly lower with diabetes duration>5 years in hypothyroid patients (p=0.032) and lower when metformin was included in the treatment of hypothyroidism (p=0.036). No such an effect was present in hyperthyroid patients.* ***Conclusion:*** *Thyroid disorders among type 2 diabetic patients are under-estimated in our country, mean TSH levels are lower in hypothyroid patients when their treatment included metformin and lower with diabetes duration more than 5 years.*

Keywords: Type 2 diabetes mellitus, Hypothyroidism, Hyperthyroidism, Metformin

INTRODUCTION

Diabetes and thyroid diseases are the most common endocrine disorders encountered in medical practice [1]. The association between diabetes and thyroid disorders was first described in 1979 and a number of studies had estimated the prevalence of thyroid dysfunction among type 2 diabetic patients to the range between 2.2-17% [2,3]. Higher levels of HbA1c (A1c) are found in type 2 diabetic patients with thyroid dysfunction, and diabetes seems to influence thyroid function at two sites: first at the hypothalamic control of TSH by TRH, and second, at the peripheral tissues by converting T4 to T3.

Hyperglycemia leads to a reduction in concentrations of T4, 5-deiodinase, low concentrations of serum T3, raised levels of reverse T3 and low, normal or high levels of T4. Thyroid hormone regulates metabolism, while diabetes alters the metabolism of a number of materials, including glucose, fatty acids, triglycerides and lipoproteins. Thyroid hormones, also, can help in the regulation of carbohydrate metabolism and pancreatic metabolism, whereas diabetes also affects thyroid function tests to a variable extent. It is also worthy to mention that the underlying thyroid problem may go undiagnosed because of the similarities between signs and symptoms of thyroid disorders and diabetes [4].

Hyperthyroidism refers to a hypermetabolic state characterized by excessively released energy at rest, weight loss, reduced cholesterol levels and increased lipolysis and gluconeogenesis, while hypothyroidism leads to reduced energy release, weight gain, increased cholesterol levels, and reduced lipolysis and gluconeogenesis. It is also mentioned that euthyroid individuals may have fluctuations in the concentrations of thyroid hormone in the plasma, correlating to changes in the secretion and sensibility of insulin [5]. It had been noticed that hyperthyroidism may worsen glycemic control and make insulin requirement more than expected. It seems important to check thyroid function in type 2 diabetic patients, although this is not recommended in the guidelines [6]. Thyroid dysfunction in diabetics seems to be more prevalent in elderly people when compared to those below sixty [7].

The prevalence of thyroid dysfunction in type 2 diabetics in both sexes varies between males and females and it is not clear whether there is male or female preponderance, although in a study in Saudi Arabia it was found that there is male predominance of primary hypothyroidism, but this depends on patient number and selection, as it is well-known that females outnumber males in non-diabetic population, and it is well-known, also that this depends on a number of factors including ethnicity, geographic and environmental factors including iodine intake status and probably other undiscovered factors [8,9].

Hypothyroidism is the most prevalent problem encountered in type 2 diabetic patients, compared to hyperthyroidism. Insulin and thyroid hormones are intimately involved in cellular metabolism, thus an excess or deficit of either one of these hormones leads to a functional derangement of the others [10-13]. Metformin is the most commonly used anti-glycemic drug in type 2 diabetics and it was found that diabetic patients treated with metformin had smaller thyroid volume and a lower risk of nodule formation compared to control. It was also found that metformin has an isolated effect on reducing TSH levels in hypothyroid patients without changes in T3 and T4 levels. Metformin lower gluconeogenesis, reduces insulin resistance which was found to be more prevalent in hypothyroid patients, it is also thought that this drug changes the affinity and/or quantity of thyroid hormone receptors and increases the central dopaminergic tone or leads to activation of TSH receptors and by this way it enhances the effects of thyroid hormone in the pituitary [14,15]. In this study we tried to estimate the prevalence of both hypothyroidism and hyperthyroidism in a sample of type 2 diabetic patients and to find the effect of anti-glycemic agents on mean TSH and A1c levels.

MATERIALS AND METHODS

This is a retrospective study on records of type 2 diabetics attending the Specialized Center for Endocrinology and Diabetes-Baghdad over a period of 3 months, from January 2019 to April 2019. The data collected included age, gender, duration of DM, TSH level, presence or absence of goiter, type of anti-glycemic therapy, HbA1c level from the data available in the records, unfortunately we could not have an evidence to label patient as hypothyroid or subclinical hypothyroid, so the total number included both hypothyroid and subclinical hypothyroid patients, the same was applied on those with hyperthyroidism.

There was no evidence for the duration of thyroid dysfunction in the records but only the duration of type 2 diabetes was available. The record included 1341 type 2 diabetic patients 666 females (49.66%) and 675 males (50.34%), so the sex distribution was nearly equal. The age range was from 32-60 for hypothyroidism and 30-50 for hyperthyroidism. Pearson Chi square test was used for statistical analysis.

RESULTS

Table 1 showed the gender, age and disease prevalence among the studied sample. The age range was 30-75, and it was 32-60 for hypothyroid patients and 30-50 for hyperthyroid ones with female predominance. The number of hypothyroid patients was 94 (7%) and for hyperthyroid ones 14 (1%).

Table 1 shows some demographic data and disease prevalence (F=Female, M=Male)

Prevalence	No. and Percentage (%)	Gender (%)	Age range (year)
Total	1341	666 F (49.66%)	30-75
		675 M (50.34%)	
Hypothyroidism	94 (7%)	84 F (89.36%)	32-60
		10 M (10.64%)	
Hyperthyroidism	14 (1%)	11 F (78.57%)	30-50
		3 M (21.43%)	

Table 2 showed the thyroid status with diffuse goiter predominating 75.57% in hypothyroid patients, followed by thyroid atrophy 32.97%, while thyroidectomy was performed on 5.32% of hypothyroid patients. Regarding hyperthyroid patients, 11 (78.57%) had diffuse goiter, while the rest 3 (21.43%) had MNG.

Table 2 shows the thyroid status. (MNG= Multi Nodular Goiter)

Status	Hypothyroidism (%)	Hyperthyroidism (%)
Diffuse goiter	58 (61.7%)	11 (78.57%)
Atrophy	31 (32.97%)	-------
Thyroidectomy	5 (5.32%)	-------
MNG	-------	3 (21.43%)

Table 3 showed the relation between diabetes duration and both TSH and A1c levels. Regarding hypothyroidism, 48 patients have diabetes duration for 1-5 years with mean TSH of 13.1 while 46 patients have diabetes duration >5 years with mean TSH of 3.4 (p=0.032) and a mean A1c of 8.4% and 9.36% respectively (p=0.77). While in hyperthyroid patients mean TSH with diabetes duration for 1-5 years was 2.7 with TSH mean of 1.625 in those with diabetes at duration >5 years (p=0.845) with mean A1c with diabetes duration for 1-5 years was 9.6% and with duration >5 years 10.8% (p=0.56).

Table 3 shows the relation between diabetes duration and both TSH and A1c

Disease	Duration of diabetes (years)	Patient No.	TSH	A1c	p-value
Hypo-thyroidism	1-5	48	13.1		0.032
	>5	46	3.4		
	1-5	48	-----	8.4	0.77
	>5	46	-----	9.36	
Hyper-thyroidism	1-5	8	2.7	-----	0.845
	>5	6	1.625	-----	
	1-5	8	-----	9.6	0.56
	>5	6	-----	10.8	

Table 4 showed the effect of metformin on mean TSH and A1c levels. It showed a significant effect of metformin on reducing mean TSH levels in hypothyroid patients (p=0.036) with no significant effect on mean A1c levels (p=0.2). Two patients out of 14 hyperthyroid patients (14.28%) were on metformin while the rest 12 (85.71) were on insulin. No significant effect on mean TSH levels (p=0.19) but significant effect on A1c levels (p=0.027). This means that although 2 patients were on metformin but reached similar values for mean A1c reached by those 12 who were on insulin.

Table 4 shows the effect of metformin on mean TSH and A1c levels

Disease	Patient No.	TSH	p-value	A1c	p-value
Hypo-thyroidism	With metformin (62)	4	0.036	10.7	0.2
	without (32)	7.6		10.317	
Hyper-thyroidism	with metformin (2)	1.3	0.19	10.7	0.027
	without (12)	1.39		10.317	

Table 5 showed the A1c levels in both hypothyroid and hyperthyroid diabetic patients. Collectively in both diseases those patients with A1c<7% were 22 out of 108 (20.37%), while 21 patients have A1c for 7-8 (19.44%) and those with poor control of diabetes (A1c>8%) were 65 (60.18%).

Table 5 shows the A1c level in both diseases

Disease	A1c<7% (Patient No.)	A1c=7-8% (Patient No.)	A1c>8% (Patient No.)
Hypothyroidism	20 (21.28%)	19 (20.21%)	55 (58.51%)
Hyperthyroidism	2 (14.29%)	2 (14.29%)	10 (71.42%)
Total	22 (20.37%)	21 (19.44%)	65 (60.18%)

DISCUSSION

From the data available from patients records we could not have a clue to the percentage of subclinical or clinical hypothyroid patients, so the percentage included the total number of cases, and it seems also that thyroid function was performed on those diabetic patients whom were suspected to have thyroid problem and it was not clear whether thyroid problem diagnosis was done on the first visit or before that but the duration of diabetes was evident in the records.

From the total number of type 2 diabetic patients (1341), 666 were females (49.66%) and 675 were males (50.34%) so the disease prevalence is nearly the same in both sexes, their age ranged from 30-75, 94 patients had hypothyroidism (7%) while 14 patients had hyperthyroidism (1%). This prevalence is much lower than in other studies which ranged between 22-56.82% for hypothyroidism (clinical+subclinical) and 6-8.15% for hyperthyroidism (clinical+ subclinical). In practice, little attention is directed toward thyroid problem in type 2 diabetes [16-22].

The low figure in our study reveals that thyroid dysfunction in type 2 diabetes is under-estimated, and this means that few fractions of type 2 diabetics are tested for thyroid problem. Fifty eight hypothyroid patients (61.7%) in our study have diffuse goiter while 31 (32.97%) have thyroid atrophy and only 5 (5.32%) have previous thyroidectomy. Regarding hyperthyroid patients 11 (78.57%) have diffuse goiter and 3 (21.43%) have MNG as shown in Table 2. This means that 69 patients (66.3%) of the total 108 patients have diffuse goiter which is most probably auto-immune.

In this study mean TSH in hypothyroid patients with diabetes duration >5 years showed significantly lower results compared to those with diabetes duration >5 (TSH 6 *vs* 15.1) (p=0.032) while no statistically significant difference regarding mean A1c (p=0.77) and both groups have a high A1c but it is clear from Table 3 that those with diabetes durations >5 years have a higher mean A1c level compared to those with duration <5 years (9.36 *vs* 8.4%). This means that the longer duration of diabetes the higher the mean A1c but a lower mean TSH, so we can see that the longer duration of diabetes the higher mean A1c but the lower mean TSH levels, this means that as diabetes advances, the efforts to control it are disappointing, this is in contrary to TSH levels which means it is easier to reduce TSH levels as the duration advances probably because the easier metabolism in hypothyroidism compared to the complex glucose metabolism and the treatment is to replace thyroxin in hypothyroid patients compared to a very complicated course of hyperglycemia which has a large number of anti-glycemic drugs including insulin indicating the complexity of the syndrome while we have only one drug (thyroxin) to treat hypothyroidism.

This also declares that thyroid dysfunction in type 2 diabetics is associated with higher levels of A1c [4]. We did not come across studies that link between mean TSH levels and diabetes duration, but in a study performed by Madayaram, et al., it was found that thyroid dysfunction was more prevalent among type 2 diabetic patients with diabetes duration >5 years (7.9% below 5 years vs 33.4% above 5 years) [23]. There were no significant differences regarding mean TSH in hyperthyroid patients (p=0.845) and A1c (p=0.56) although still mean A1c is higher in those with diabetes duration >5 years compared to those below 5 years (10.8% *vs* 9.6%) as evident in Table 3 also.

Among the 94 hypothyroid patients in this study, 62 included metformin for treatment among other measures, 32 have no metformin included, the effect of metformin on reducing TSH levels is very clear (p=0.036), while A1c levels are nearly the same (p=0.2). This is clear in Table 4 which also shows that 2 patients out of the 14 hyperthyroid patients are on metformin while the other 12 are on insulin. This means that although the majority are on insulin but still metformin reached the same A1c level although it was used in the minority of patients (p=0.027) while no significant difference regarding mean TSH levels (p=0.19).

The excessive secretion of thyroxin in hyperthyroidism triggers a hypermetabolic state leading to weight loss, increased lipolysis and gluconeogenesis [5,24]. This explains why most of our hyperthyroid patients are on insulin therapy. The TSH lowering effect of metformin in hypothyroid patients was observed in other studies. Fournier, et al., found that the use of metformin in type 2 diabetic patients was associated with an increased incidence of low TSH levels [25].

On the other hand, Nurcheshmeh, et al. mentioned in his study that metformin can lower TSH levels even in patients with subclinical hypothyroidism and coexisting metabolic syndrome [26]. These findings were also present in other study performed by Karimifar, et al. [27]. In this study we also noticed that 20.37% of patients are at target regarding A1c level <7%, 19.44% have A1c between 7-8% while 60.18% have A1c >8%. This is better than the finding mentioned by Abdulqawi Almansari who found that those who achieved an A1c <7% were 2.2%, with A1c between 7-8% were 12.4% while the majority 85.4% had an A1c >8% [28]. Another study by Pablos, et al., showed that 37.4% of patients had A1c ≥ 7% while the range in the Netherlands was 25.9% and in Turkey 52% [29]. This reflects the wide variation of figures among different studies which depends on a number of factors like the use of insulin or oral drugs for diabetes, patient reluctance to treatment with insulin when required, etc.

CONCLUSION

This study showed that the prevalence of thyroid dysfunction in type 2 diabetic patients in our country (Iraq) is under-estimated, and metformin has a significant TSH lowering effect in hypothyroid patients. We encourage checking more type 2 diabetic patients for thyroid problem as much as it is feasible, as this is cost-effective.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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