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Sub-clinical hypothyroidism in diabetes and effect of metformin on thyroid stimulating hormone

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Abstract

Introduction: Patients with type 2 diabetes mellitus (DM) are associated with elevated thyroid stimulating hormone (TSH)level. Metformin is considered as standard therapy in type 2 DM and it alters TSH levels.

Objective: To see the effect of metformin treatment on thyroid function in patients with type 2 diabetes mellitus.

Design: Interventional Clinical Trial using convenience sampling

Place and Study Duration:The study was conducted in Dallah Hospital, Riyadh, Kingdom of Saudia Arabia. It lasted for an year (from April 2014 to June 2015).

Material and Methods: Two hundred and seventy one patients with type 2 DM were given metformin 2000 mg/day for approximately 24 weeks. The thyroid function [TSH, free thyroxin (FT4) and total thyroxin (TT4)] done at baseline, after 12 weeks and 24 weeks of metformintherapy. Two groups, the euthyroid group and SHT group were analyzed and compared.

Results: Among 271 patients, 15.5% (42) were classified in SHT group, whereas 84.5% (229) in euthyroid group. There were no significant differences of age and lipid levels between two groups whereas the high BMI, female gender, high FBS and HbA1c were associated with SHT group.The mean baseline TSH was 2.94+2.36 mIU/L in all subjects, 7.54+2.69 mIU in SHT group whereas 2.10+0.83 in euthyroid group. There was significant reduction in TSH level noted in SHT group after 3 months(p=0.017) and 6 months(p<0.001) of metformin therapy.The mean baseline TT4 was 9.13+1.59 in all subjects, 8.57+2.10 in SHT group whereas 9.24+1.40 in euthyroid group. The mean baseline FT4 was 1.08+0.24 in all subjects, 1.07+0.35 in SHT group whereas 1.08+0.22 in euthyroid group.

Conclusions: The study revealed close association of SHT with type 2 DM. The TSH lowering effect of metformin therapy only evident with SHT. There was no significant change seen in FT4 and TT4 levels.

Keywords: Sub-clinical hypothyroidism, metformin therapy, type 2 diabetes mellitus

Introduction:

Diabetes Mellitus (DM) and hypothyroidism are two endocrine disorders which are closely related. Almost 10 to 15 percentage of type 2 DM patients are found to have hypothyroidism. Some of the patients have overt hypothyroidism (OHT) while others have subclinical hypothyroidism (SHT).[1]

Metformin, an oral hypoglycemic, is the first line therapy for type 2 DM with a good drug safety profile.[2,3] The main side effect is gastrointestinal (GI) intolerance, including diarrhea, nausea, dyspepsia, and abdominal pain. Although GI symptoms may be observed in up to 28% of patients but only lead to discontinuation of therapy in less than 2% of patients.[4,5,6] Serious side effects like lactic acidosis are rare and mostly

associated with other comorbidities other than the use of metformin.[7]

Metformin's main effect is to lower serum-glucose levels by improving hepatic insulin resistance and reducing glucose production. Metformin mainly acts via activation of Adenosine[5] monophosphate activated protein kinase (AMPK), which is an intracellular sensor of nutrient availability and regulator of energy homeostasis.[8] These proteins are involved in different cellular functions and have several metabolic effects including increased fatty acid oxidation, decreased hepatic gluconeogenesis, improved insulin sensitivity and decreased blood glucose levels.[9] Besides these metabolic effects, metformin induces modulation of AMPK which modulates iodine uptake through thyroidal sodium-iodide symporter.[10]

Some studies suggest that therapy with metformin is associated with a reduction in serum TSH concentrations, without relevant changes in thyroxine (T4) and triiodothyronine (T3) levels. These results have been found in patients with patients with type 2 DM plus concomitant OHT or SHT.[11-17] In contrast, metformin was not causing any changes in TSH levels in euthyroid patients.[18]

The aim of this clinical trial was toscreen the previously undiagnosed cases of SHT in type 2 DM patients and to assess the effect of metformin therapy on TSH, FT4, and TT4 levels in patients with SHT or euthyroid status.

Materials and Methods:

This clinical trial was done at Dallah Hospital, a tertiary care hospital in Riyadh, Kingdom of Saudi Arabia for a duration of one year (April 2014 to June 2015). Three hundred patients with type 2 DM were selected. The diagnosis of type 2 DM was done according to American Diabetic Association criteria.[2]

Patients less than 18 years of age, with creatinine >1.5mg/dl, known cases of hypothyroidism, users of medications like amiodarone, lithium, corticosteroids, oral contraceptive pills, heparin, propranolol, aspirin, warfarin or thyroxine, patients with cardiac, hepatic and renal failure, those already taking metformin > 2000mg/day or those allergic to metformin were excluded.

All patients, after informed consent and approval from ethical committee, went through history taking (demographic data collection), examination (specially neurological and fundus examination) and laboratory investigations like fasting blood sugar (FBS), Glycosylated hemoglobin (HbA1c), lipid profile, liver function test, creatinine, x ray chest, electro-cardiography, Thyroid stimulating hormone (TSH), Total T4 (TT4) and free T4 (FT4).

TSH (normal range 0.4-4.2 mIU/L) was done by immuno metric assay[19] by Turbo TSH urging IRMA kit. FT4 (normal range 0.8-1.7 ng/dl) and TT4 (normal range 5.4-11.5 mcg/dl) were assessed by chemiluminescent method,[19] using analyzer and kits of Siemens (ADIVA Centaur CP).

Baseline TSH, TT4 and FT4 were noted before execution of metformin therapy. All patients were divided into two groups according to baseline TSH. Group I with TSH level > 4.2 mIU/L were labeled as subclinical hypothyroidism and Group II with normal TSH level labeled as euthyroid.

All patients were given metformin 500mg twice daily in first week and then three times daily in second week and 1000mg twice daily for next 22 weeks. Patients already on metformin dose less than 2000mg/day were escalated in such a way that they ended up receiving metformin 2000mg/day at least for 22 weeks.

The measurement of TSH, TT4, and FT4 were done again after 12 weeks and 24 weeks after the start of metformin therapy. Six patients in SHT group and twenty three patients in euthyroid group were excluded from the study due to a loss of follow up or due to gastrointestinal side effects secondary to metformin therapy.

Table-1: Proportion of Age, Gestational Age, Gravidity, Parity and Efficacy (n=554)

Variables		Subclinical hypothyroid	Euthyroid	Total	df	p value
Age						
	<50 years	29	153	182	1	0.464
	>50 years	13	76	89		
Total		42	229	271		
Gender						
	Male	16	126	142	1	0.032
	Female	26	103	129		
Total		42	229	271		
BMI						
	Normal	0	29	29		
	Overweight	0	68	68		
	Obesity I	6	79	85	4	<0.001
	Obesity II	13	40	53		
	Obesity III	23	13	36		
Total		42	229	271		
Complication						
	Present	26	77	103	1	0.001
	Absent	16	152	168		
Total		42	229	271		

Table-2: Data analysis by using student t test for unpaired samples

Variables	Conditions	N	Mean	Std. Deviation	Std. Error Mean	p Value
Age	sub clinical hypothyroid	42	52.29	7.806	1.205	0.682
	Euthyroid	229	51.71	10.647	0.704	
BMI	sub clinical hypothyroid	42	39.07	4.105	0.633	<0.001
	euthyroid	229	30.95	5.289	0.349	
TSH	sub clinical hypothyroid	42	7.548	2.6973	0.4162	<0.001
	euthyroid	229	2.102	.8327	0.0550	
FT4	sub clinical hypothyroid	42	1.079	.3510	0.0542	0.948
	euthyroid	229	1.082	.2236	0.0148	
TT4	sub clinical hypothyroid	42	8.575	2.1092	0.3255	0.056
	euthyroid	229	9.240	1.4606	0.0965	
FBS	sub clinical hypothyroid	42	154.50	19.068	2.942	0.004
	euthyroid	229	144.59	22.713	1.501	
HbA1c	sub clinical hypothyroid	42	9.979	.9699	0.1497	0.007
	euthyroid	229	9.510	1.0447	0.0690	
Cholesterol	sub clinical hypothyroid	42	268.62	18.523	2.858	0.669
	euthyroid	229	267.26	20.522	1.356	
Triglyceride	sub clinical hypothyroid	42	260.52	31.414	4.847	0.379
	euthyroid	229	265.17	30.165	1.993	
LDL	sub clinical hypothyroid	42	173.14	19.462	3.003	0.078
	euthyroid	229	167.19	21.322	1.409	

Two hundred and seventy one patients were analyzed using software SPSS v 22 (IBM). The chi square was applied where applicable and student t test for unpaired samples and paired samples were applied to compare the results of TSH, FT4 and TT4. The p value <0.05 was considered significant.

Results:

Among two hundred and seventy one patients, 42 patients (15.5%) were classified in SHT group, whereas 229 (84.5%) in euthyroid group. The mean age of all subjects was 51.80+10.24 yearsand there was no statistical difference between SHT and euthyroid group regarding age (p=0.464).

The male to female ratio was 1.1:1 overall but in SHT group it was 0.6:1 which revealed a significant increase of female SHT cases (p=0.032). [table 1]

The mean Body mass index (BMI) was 32.21+5.90 and increased BMI was closely associated with SHT group (p<0.001). [table 1&2] Mean FBS was 146.12+22.44mg/dl with increased FBS associated with SHT group (p=0.004). [table 2] Mean HbA1c was 9.58+1.04 in all subjects, 9.97+0.96in subclinical hypothyroid group whereas 9.51+1.04% in euthyroid group so, with a significant difference of HBA1c existing between the euthyroid and hypothyroid groups. (p=0.004). [table 2]

The mean cholesterol 267.47+20.19 mg/dl, triglycerides 264.45+30.34 mg/dl and LDL was 168.11+21.12 mg/dl. There was no statistically significant difference between the two groups regarding these parameters. [table 2]

The mean baseline TSH was 2.94+2.36 mIU/L in all subjects, 7.54+2.69 mIU in SHT group whereas 2.10+0.83 in euthyroid group. The mean TSH in SHT after 3 months of metformin therapy were 7.49+2.68 (p=0.017) whereas in euthyroid group was 2.056+0.89 (p=0.222) so there was a significant reduction of TSH seen in sub-clinical hypothyroid group after 3 months

Table-3: Paired Samples Statistics effect of metformin on subclinical hypothyroid group

		Mean	N	Std. Deviation	Std. Error Mean	p Value
Pair 1	TSH baseline	7.548	42	2.6973	.4162	0.017
	TSH after 3 months	7.490	42	2.6883	.4148	
Pair 2	TSH baseline	7.548	42	2.6973	.4162	<0.001
	TSH after 6 months	6.519	42	2.4978	.3854	
Pair 3	TT4 baseline	8.575	42	2.1092	.3255	0.056
	TT4 after 3 months	8.55	42	2.116	.327	
Pair 4	TT4 baseline	8.575	42	2.1092	.3255	0.228
	TT4 after 6 months	8.557	42	2.1132	.3261	
Pair 5	FT4 baseline	1.079	42	.3510	.0542	0.486
	FT4 after 3 months	1.074	42	.3513	.0542	
Pair 6	FT4 baseline	1.079	42	.3510	.0542	0.132
	FT4 after 6 months	1.060	42	.3465	.0535	

Table-4: Paired Samples Statistics effect of metformin on euthyroid group

		Mean	N	Std. Deviation	Std. Error Mean	p Value
Pair 1	TSH baseline	2.102	229	.8327	.0550	0.222
	TSH after 3 months	2.056	229	.8922	.0590	
Pair 2	TSH baseline	2.102	229	.8327	.0550	0.152
	TSH after 6 months	2.192	229	1.1691	.0773	
Pair 3	TT4 baseline	9.240	229	1.4606	.0965	0.355
	TT4 after 3 months	9.56	229	5.405	.357	
Pair 4	TT4 baseline	9.240	229	1.4606	.0965	0.363
	TT4 after 6 months	9.555	229	5.4106	.3575	
Pair 5	FT4 baseline	1.082	229	.2236	.0148	0.109
	FT4 after 3 months	1.074	229	.2208	.0146	
Pair 6	FT4 baseline	1.082	229	.2236	.0148	0.100
	FT4 after 6 months	1.076	229	.2207	.0146	

of metformin therapy.

The mean TSH in SHT after 6 months was 6.51+2.49 (p<0.001) whereas in euthyroid group was 2.19+1.16 (p=0.152). Again there was a statistically significant reduction of TSH seen in SHT group after 6 months of metformin therapy. [table 3& 4]

The mean baseline TT4 was 9.13+1.59 in all subjects, 8.57+2.10 in SHT group and 9.24+1.40 in euthyroid group.The mean baseline FT4 was 1.08+0.24 in all subjects, 1.07+0.35 in SHT group and 1.08+0.22 in euthyroid group. There was no significant difference found in T4 and FT4 levels between two groups after metformin therapy. (table 3 & 4)

Discussion:

In our study 15.5% (42) of all DM patients were found to have SHT which is almost similar with the previous studies done by Chubb et al.[1] The age and lipid profile were not significantly different in euthyroid and SHT group but BMI, gender and glycemic control were significantly different in both groups.

Higher BMI (p<0.001), female gender (p=0.032), uncontrolled hyperglycemia (p=0.004) and complications of diabetes (p=0.001) were associated with subclinical hypothyroid group. We found significant reduction in TSH by metformin therapy SHT group in contrast to euthyroid group.

There was no effect of metformin therapy on total T4 and Free T4 in both groups. This is similar to the study by Cappelli et al[14] in which patients were divided into three groups. The first group had OHT and received thyroxin replacement therapy, the second group had SHT and were not on thyroxine replacement therapy while the last group was euthyroid. After metformin therapy for 12 months, TSH levels changed only in the first two groups. This TSH-lowering effect of metformin developed slowly and was detectable only after a few months of treatment. So the effect of metformin treatment on TSH level in SHT was related with duration of treatment. In our study the effect appeared in 90 days (p=0.017) and highest effect was seen after 180 days (p<0.001) following initiation of treatment. These findings are consistent with other studies that observed TSH lowering effects in 3 months13, 4 months 20 and 6 months 21 after metformin therapy initiation.

Our findings are supported by multiple other studies done in patients with high TSH with type 2 DM, which revealed that the initiation of metformin therapy was associated with a significant reduction in the serum levels of TSH in DM patients with SHT. TSH reduction was not associated with reciprocal changes in any other thyroid function parameters[12-15,20,21] and there was no effects in euthyroid patients.[11,14,15] The

lack of TSH level changes in euthyroid subjects with thyroid nodule is also reported by Rezzonico et al.[22]

As further confirmation, a strong correlation between baseline TSH value and the degree of its change during metformin treatment was reported in our study and by Isidro et al.[13] Evaluating the inter-relationship among TSH and thyroid hormone levels, it was found that treatment with metformin was not associated with any change in serum T4 levels.[13-15]

Patients with Sub-clinical or overt hypo-thyroidism who had concomitant co-morbids that required metformin therapy (e.g. patients of polycystic ovarian syndrome-PCOS) also noticed a decline in their TSH levels. Morteza et al[21] did a study in 2011 about SHT with polycystic ovarian syndrome in overweight female patients treated with metformin and noted significant reductions of TSH after metformin therapy.

In the past few years, several clinical observations have consistently shown a lowering of serum TSH levels in patients with newly diagnosed hypothyroidism following the administration of metformin.[11,12] In one study, thyroid-function parameters did not change in euthyroid patients with PCOS after starting metformin therapy, but decreased significantly in patients with hypothyroidism after a 4-month course of metformin treatment.[13]

The mechanism by which metformin lowers TSH level is still unclear but what is known is that metformin acts on the TRH/TSH/T4 axis in a complex and multifactorial manner. Metformin may change the affinity and/or number of thyroid hormone receptors; it may increase the central dopaminergic tone or may directly act on TSH regulation, thus enhancing the effect of thyroid hormones on the pituitary gland.[12,23] Although exact mechanisms are not completely known, central effects of metformin on TRH/TSH regulation might involve the AMPK system.[24] Although metformin acts as an activator of AMPK in the periphery, it inhibits AMPK activity in the hypothalamus and enhances the inhibitory modulation of thyroid hormones on TSH secretion.[24] These effects would not modify TSH levels when the feedback system is preserved, but they may explain the TSH reduction observed in subjects with impaired thyroid- hypophyseal feedback.

Another clinical subset that needs to be considered are euthyroid obese subjects. In our study high BMI was associated with raised TSH level as reported in a study by Fox et al[25] and the use of metformin might affect high BMI subject's basal metabolism by reducing TSH levels.

Other studies aimed to clarify the relationship between TSH levels and metformin treatment have been conducted[11,12,16,20,22] but their results were often conflicting, because of differences in their design and data collection. Most had a retrospective design, a small study sample and included patients with different indications for metformin treatment (i.e., insulin resistance, T2D or PCOS). In addition, most of the evaluated patients were affected by obesity, which may have effect on TSH levels.[26]

Lupoli et al[18] did a meta analysis in 2014 on populations from different studies for metformin effect on TSH levels using meta regression for confounders. This study revealed that BMI and other variables had no confounding effect on TSH levels. Although metformin-induced TSH changes seem to be slight, metformin could be used as treatment option in patients with hypothyroidism (OHT or SHT) who may need less thyroxine replacement or may not need thyroxin replacement at all. It could possibly be the best option for patients with a metabolic disorder and a slightly raised TSH.

Limitations of the study included not factoring in obesity as a confounding factor as multiple studies have should an association between high BMI and high TSH. Metformin also has an effect on obesity but no BMI data was collected by the authors following the initiation of metformin therapy. Another limitation was that we

excluded OHT patients from the study so the true effect of metformin on TSH may not be observed.

Despite these limitations, the study provided clear information about the relationship between metformin and TSH levels. Our study results further strengthen the clinical impact of previous reported findings. Since a vast majority of patients with both disorders are at a higher risk for cardio-vascular diseases, our study shows that a careful assessment of thyroid function is necessary in diabetic patients to detect the early development of SHT which can then be treated using only metformin.

Conclusion:
We conclude that the result of this study confirmed that metformin therapy is associated with decrease in TSH level when it is high in type 2 DM patients. This could be a treatment option for patients with SHT to reduce level of TSH, so that thyroxine replacement therapy can be delayed. The level of TSH should be monitored in all patients with type 2 DM specially those who are on metformin therapy. On the other hand as metformin therapy alters the TSH levels, therefore, patients with OHT on thyroxin replacement should do TSH function test frequently. However, additional properly designed (large sample size, homogeneous disease subsets, and adjustment for confounding conditions) prospective studies are needed to address these relevant issues.

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Role and contribution of authors:
Dr. Muhammad Farooq, collected the data, references and wrote the initial writeup.

Dr. Arshad Ali, collected the references, helped in the interpretation of the data

Dr. Nayyer ul Islam, critically went through the article, and made the final changes

Dr. Asad Qamar, helped in collecting the references, and critically went through the article and advised for necessary changes in the article

Dr. Mohammad Yousuf ul Islam, collected the data, references and helped in introduction writing.

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