

Original Research Article

Evaluation of thyroid hormone dysfunction in type - 2 diabetes patients on metformin therapy – A cross sectional study

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Abstract

Diabetes and thyroid diseases are two familiar endocrinopathies seen in the general population. Abnormal thyroid hormone levels can also be found in individuals with diabetes. Metformin may lower thyroid stimulating hormone levels both in hypothyroid as well as euthyroid individuals. To this purpose, we studied analysis of serum TSH levels in patients with type-2 DM who were receiving metformin and compared them with serum TSH levels of those individuals with T2DM that were not on metformin. Study participants were selected from the people residing in neighbouring villages in and adjoining Kadapa district of Andhra Pradesh. Study duration was 6 months between June-November 2008. Sample size was 80 subjects with T2DM on Metformin and 80 subjects with T2DM receiving non Metformin based therapy were included in the study. Data were entered in Microsoft Excel 2007 and data was expressed as mean and standard deviation (Mean±SD). Serum TSH values, metformin dose and metformin duration were not normally distributed. Comparison of difference in means between the two groups for normally distributed continuous variables namely, age, HbA1c,

serum T3 and T4 was done by unpaired student's t test. $P < 0.05$ was treated as significant. Metformin utilize was not associated with changes in serum thyroid stimulating hormone levels in euthyroid type-2 DM patients. The presence of a comparative group of type 2 diabetes individuals not receiving Metformin add to the analytical value of the study design.

Key words

Thyroid dysfunction, Thyroid Stimulating Hormone (TSH), Type-2 Diabetes, Metformin.

Introduction

Diabetes and thyroid diseases are two familiar endocrinopathies seen in the general population. Abnormal thyroid hormone levels can also be found in individuals with diabetes [1]. The World Health Organisation has projected that the global prevalence of diabetes will rise to 300 million (7.8%) by 2030 [2]. Metformin is the first line drug in the treatment of type-2 DM [3]. A number of reports suggest lowering of TSH by metformin only in hypothyroid individuals [4-8]. However, it is also reported that metformin may lower thyroid stimulating hormone levels both in hypothyroid as well as euthyroid individuals [9]. In view of differing reports in relation between metformin therapy and TSH levels, we studied analysis of serum TSH levels in patients with type-2 DM patients whom were receiving metformin and compared them with serum TSH levels of those individuals with T2DM that were not on metformin. Blood sugar HbA1c and thyroid functions like TSH, T3, and T4 were estimated. Out of the total subjects with type 2 diabetes on metformin, 81% were on metformin mono-therapy and the remaining 19% received sulfonylurea and/or Insulin in addition to metformin. In the non-metformin group the subjects receiving sulfonylurea alone or in addition to pioglitazone or Insulin comprised 89% and the remaining 11% were receiving only Insulin. The median duration of medication use in those not on metformin was 2.5 years ($Q1=1.2$ years, $Q3=2.75$ years). The minimum duration of therapy in the non-metformin group was 9 months and the maximum was 4.2 years.

Material and methods

Study participants were selected from the people residing in neighbouring villages in and

adjoining Kadapa district of Andhra Pradesh. Study participants were selected by simple random sampling technique. Study centre was RIMS, Kadapa and study duration was 6 months between June-November 2008. Sample Size was 80 subjects with T2DM on Metformin and 80 subjects with T2DM receiving non Metformin based therapy were included in the study. Ethical Committee has approved the study protocol and informed patient consent was obtained from the study participants and the study subjects were screened using the inclusion and exclusion criteria listed below to assess eligibility for enrolment into the study.

All the patients included with age >18 years of age with established clinical and laboratory diagnosis of T2DM and subjects who had minimum one thyroid profile test result available before they commenced anti-diabetic treatment. Individuals known to have thyroid abnormality before starting the anti-diabetic therapy, subjects with whom were reported acute illness or medical treatment in three months prior to initiation of the study procedure, individuals with elevated hepatic enzymes (AST and ALT elevated beyond the upper limit of normal), individuals with $eGFR < 60$ ml/min per $1.73m^2$, pregnant and lactating women were excluded from the study. Study subjects were screened for eligibility according to the criteria listed above with the help of an interviewer administered structured questionnaire and/or clinical examination; and biochemical estimation appropriate for that particular condition. A pretested structured questionnaire was used to collect data on demographics, medications used and diet. Serum creatinine was estimated by modified Jaffe kinetic method [10]. Estimated

GFR (eGFR) was calculated using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) calculator [11]. Blood samples for complete blood picture were analysed with Mindray BC 3000 plus auto analyser and HbA1c estimation was done by high performance liquid chromatography (BioradD10). TSH, Triiodothyronine (T3) and Tetraiodothyronine (T4) were estimated by chemiluminescence assay. The normal range for TSH according to laboratory standard used in this study was 0.34 - 4.25 mIU/L. The normal ranges for T4 and T3 used in the study were 4.6-12 mcg/dl and 80-180 ng/dl respectively.

Statistical Analysis

Data were entered in Microsoft Excel 2007 and data was expressed as mean and standard deviation (Mean±SD). Serum TSH values, metformin dose and metformin duration were not normally distributed. Comparison of difference in means between the two groups for normally distributed continuous variables namely, age, HbA1c, serum T3 and T4 was done by unpaired student's t test. P <0.05 was treated as significant.

Results

There were no significant differences between study subjects receiving metformin and those not receiving metformin. Characteristics of the study population were as per **Table - 1**. The median daily metformin dose was 1 gram (Q1=0.5 gram, Q3=1.5 gram). The minimum and maximum daily dose of metformin was 0.5 gram and 2 gram respectively. The median duration of metformin use was 2.5 years (Q1=1 year, Q3=3 years). The minimum and maximum duration of metformin use were 7 months and 5 years respectively. Out of the total subjects with type 2 diabetes on metformin, 81% were on metformin mono-therapy and the remaining 19% received sulfonylurea and/or Insulin in addition to metformin. In the non-metformin group the subjects receiving sulfonylurea alone or in addition to pioglitazone or Insulin comprised 89% and the remaining 11% were receiving only Insulin. The median duration of medication use in those not on metformin was 2.5 years (Q1=1.2 years, Q3=2.75 years). The minimum duration of therapy in the non-metformin group was 9 months and the maximum was 4.2 years. There was no significant difference between the median serum TSH in patients with diabetes on metformin and those not on metformin (*P=0.21) as per **Table - 2**.

Table – 1: Characteristics of the study population.

Variable	Not on-Metformin (n=80)	On-Metformin (n=80)	P value
Age in years (Mean ±SD)	54.58 ± 11.86	55.19±10.51	0.60
Gender (%) M=male; F=female	57.85 M: 42.62 F	50.32%:49.68%	0.16
Serum T4 in mcg/dl (Mean ±SD)	5.98±1.12	6.12±0.98	0.44
Serum T3 in ng/dl (Mean ±SD)	108.98±8.61	107.67±7.87	0.34
HbA1c % (Mean±SD)	8.0 ±2.	8.1±1.9	0.75

Table – 2: Comparison of serum TSH levels between those on metformin and not on metformin.

TSH IN SUBJECTS ON METFORMIN (mIU/L) (n=80)	TSH IN SUBJECTS NOT ON METFORMIN (mIU/L) (n=80)	P value (Wilcoxon's Rank Sum Test)
2.16 (Q1=1.38, Q3=2.76)	2.13 (Q1=1.48mIU/L, Q3=2.87.)	*P=0.21

Discussion

The use of oral hypoglycaemic medications in the treatment of patients with type 2 diabetes also has varying effects on thyroid hormone homeostasis. Cappelli, et al. in their study evaluated thyroid hormone profiles by studying the interaction between metformin and circulating thyroid function parameters in patients who were started on metformin [12]. We purposely studied influence of metformin on TSH levels in euthyroid individuals as there are partial data in this aspect. We did not find any significant difference in serum TSH levels between those receiving metformin and those not receiving metformin in euthyroid type 2 diabetes mellitus patients. This finding of ours is consistent with the findings of a meta-analysis conducted by Lupoli, et.al. They analysed the effects of treatment with metformin on TSH levels and concluded that there was no change in TSH levels in euthyroid patients [13].

Dragan, et al study found Metformin had no effect on TSH levels in euthyroid diabetic patients [14]. Our study also correlating with the study results of Shailendra et al. [15]. Therefore; it is reassuring to note that thyroid stimulating hormone is not influenced by metformin in euthyroid individuals. Though reports indicate that thyroid stimulating hormone levels are lowered by use of metformin in individuals with pre-existing hypothyroidism, the exact biochemical mechanisms underlying such a change in TSH are not clearly understood. More research is needed to thoroughly assess the mechanisms behind the lowering of TSH caused by metformin in individuals treated for hypothyroidism and to gauge the clinical implications of TSH lowering induced by Metformin.

Conclusion

Metformin utilize is not associated with changes in serum thyroid stimulating hormone levels in euthyroid type-2 DM patients. The presence of a comparative group of type 2 diabetes individuals

not receiving metformin add to the analytical value of the study design.

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