ORIGINAL ARTICLE

EFFECT OF METFORMIN ON THYROID STIMULATING HORMONE IN EUTHYROID TYPE 2 DIABETES MELLITUS PATIENTS
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ABSTRACT: BACKGROUND AND RATIONALE: Metformin use is reported to be associated with reduction in serum thyroid stimulating hormone (TSH) levels. However, recent reports suggest that the effect of metformin on TSH is seen only in those who have hypothyroidism and not in those who are euthyroid. OBJECTIVES: The objective of this study was to compare the difference in TSH levels between euthyroid type 2 diabetes mellitus (T2DM) patients on metformin versus those not on metformin. RESEARCH DESIGN AND METHODS: Using a cross sectional study design subjects with type 2 diabetes mellitus (N=150) were recruited from a rural community using simple random sampling. Individuals with known thyroid dysfunction were excluded. Data on socio-demographic variables, medications being used and duration of use were collected using structured questionnaire. Laboratory measurements included thyroid function tests, complete blood count, hepatic function tests, renal function tests and HbA1c estimation. RESULTS: The median TSH levels in patients with T2DM on metformin was 1.98 mIU/L (Q1=1.24mIU/L, Q3=2.76 mIU/L), whereas in patients with T2DM not on metformin the median TSH levels was 2.12mIU/L (Q1=1.30mIU/L, Q3=2.87mIU/L.)There was no statistically significant difference in the median TSH levels between patients with type 2 diabetes mellitus on metformin and those not on metformin (p=0.23).Further, there was no correlation between metformin dose and serum TSH levels (p=0.36). CONCLUSIONS: Metformin use did not affect serum TSH levels in euthyroid patients with T2DM.

KEYWORDS: Metformin Thyroid Stimulating Hormone Type 2 Diabetes Thyroid dysfunction.

INTRODUCTION: Metformin is a first line drug in the treatment of type 2 diabetes mellitus.¹ It is shown to protect against long term cardiovascular morbidity and mortality, apart from controlling blood glucose in patients with type 2 diabetes mellitus.²,³ Metformin is reported to reduce thyroid stimulating hormone levels (TSH). Some reports suggest lowering of TSH by metformin only in hypothyroid individuals.⁴,⁵,⁶,⁷ However, it is also reported that metformin may lower thyroid stimulating hormone levels both in hypothyroid as well as euthyroid individuals.⁸ In view of conflicting reports on the relationship between metformin use and TSH levels, we performed a cross sectional analysis of serum TSH levels in patients with type two diabetes mellitus (T2DM) that were receiving metformin and compared them with serum TSH levels of those individuals with T2DM that were not receiving metformin.

About 65 million people in India are reported to have diabetes.⁹ Metformin being a first line drug in the treatment of type 2 diabetes, it is pertinent that the relationship between thyroid function and metformin use are evaluated not only to ensure efficient, safe and rational use of metformin, but also to explore options for metformin use in conditions where TSH is elevated.
MATERIALS AND METHODS: Study population and sampling: Study subjects were selected from among people residing in 40 villages in a South Indian district (Ranga Reddy district) adjoining Hyderabad, India with a cumulative population of about 46,000. A list of subjects with T2DM residing in each of the 40 villages was generated in a survey conducted by SHARE India-MediCiti Institute of Medical Sciences, Hyderabad, in the year 2009. The list was subsequently updated two months prior to the commencement of the study. The data in this study was collected during the two month period between March-April 2014. Participants were selected by simple random sampling technique.

SAMPLE SIZE: 75 subjects with T2DM on metformin and 75 subjects with T2DM receiving non metformin based therapy were included in the study.

An IRB approval was obtained from MediCiti ethics committee, Hyderabad, India. Informed 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.

INCLUSION CRITERIA:
1. Male and female subjects >18 years of age with a physician diagnosis of T2DM.
2. All subjects who had at least a single thyroid profile test result available before they commenced antidiabetic therapy.

EXCLUSION CRITERIA:
1. Individuals known to have thyroid dysfunction before commencing anti-diabetic treatment,
2. Individuals who reported acute illness or hospitalization in the three months prior to recruitment,
3. Individuals with elevated hepatic enzymes (AST and ALT elevated beyond the upper limit of normal),
4. Individuals with eGFR <60 ml/min per 1.73m²,
5. Pregnant and lactating women.

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. Estimated GFR (eGFR) was calculated using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) calculator. Blood samples for complete blood picture were analysed on an auto analyser (Mindray BC 3000plus). 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 2010 and exported to STATA version 10 for analysis. Data were assessed for normality using the Shapiro Wilk test. Normally distributed continuous data were summarized as mean and standard deviation (Mean±SD). Serum TSH values, metformin dose and metformin duration were not normally distributed. Therefore, they were summarized as median and interquartile ranges (Q1, Q3). Comparison of TSH levels in patients with diabetes on metformin and those not on metformin was done using the Wilcoxon rank sum test. A Spearman correlation test was performed to assess the correlation between metformin dose and serum TSH. 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 are presented in Table 1. The median daily metformin dose was 1gram (Q1=0.5gram, Q3=1.5gram). The minimum and maximum daily dose of metformin were 0.5 gram and 2 gram respectively. The median duration of metformin use was 2.4years (Q1=1year, Q3=3 years). The minimum and maximum duration of metformin use were 6 months and 4 years respectively. Out of the total subjects with type 2 diabetes on metformin, 80% were on metformin mono-therapy and the remaining 20% 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 90% and the remaining 10 % were receiving only Insulin. The median duration of medication use in those not on metformin was 2.5 years (Q1=1.2years, Q3=2.75 years). The minimum duration of therapy in the non-metformin group was 8 months and the maximum was 3.5 years.

| Variable                  | NOT ON METFORMIN (N=75) | ON METFORMIN (N=75) | 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%       | 0.15    |
| Serum T4 in mcg/dl (Mean ±SD) | 6.98±1.12              | 7.12±0.98           | 0.42    |
| Serum T3 in ng/dl (Mean ±SD) | 109.98±8.61             | 108.67±7.87         | 0.33    |
| HbA1c % (Mean±SD)         | 8.2 ±2.                 | 8.3±1.9             | 0.76    |

Table 1: Characteristics of the study population
DISCUSSION: We specifically intended to study the influence of metformin on TSH levels in euthyroid individuals as there are limited data in this regard. 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. Similarly, another study conducted by Fournier et al. showed that metformin use was associated with an increased incidence of low TSH levels in patients receiving treatment for hypothyroidism, but not in euthyroid patients. Further, Dragan et al. reported that Metformin had no effect on TSH levels in euthyroid diabetic patients. 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. It is also stated that the biochemical lowering of TSH that was observed in some studies was not associated with biochemical or clinical features of hyperthyroidism.

Apart, from a single study that noted reduction in serum TSH associated with metformin use in both hypothyroid and euthyroid individuals with type 2 diabetes mellitus, there are no studies that report suppressive effects of metformin on TSH in euthyroid individuals.

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. Indeed, some investigators suggest that metformin can be explored as a therapeutic option to lower TSH in patients with thyroid cancer. Clearly, more research is needed before such avenues for using metformin can be explored.

CONCLUSIONS: Metformin use is not associated with changes in serum thyroid stimulating hormone levels in euthyroid type 2 diabetes mellitus patients.
The strengths of our study are, random sampling of study subjects and exclusion of study subjects with known confounders that could potentially affect thyroid function interpretation. Further, the presence of a comparative group of type 2 diabetes individuals not receiving metformin adds to the analytical value of the study design. The limitations are that the study design being cross sectional the temporal sequence of cause and effect cannot be evaluated.

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