ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A COMPARATIVE STUDY OF METFORMIN ON THYROID STIMULATING HORMONES IN PATIENTS WITH EUTHYROID TYPE 2 DIABETES MELLITUS

Pharmacology

Dr. Braj Nandan Kumar Sah* Tutor, Department of Pharmacology, Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India. *Corresponding Author

Dr. Sara Sultana Tutor, Department of Pharmacology, Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India.

ABSTRACT

Objectives: This present study was to compare the effect of metformin on thyroid stimulating hormones of euthyroid type 2 diabetes mellitus patients.

Methods: A detail history, clinical examinations and relevant investigations were performed to all cases of euthyroid type 2 diabetes mellitus. Collected blood sample was centrifuged and serum obtained was used for estimation of glucose and thyroid levels. Glucose was estimated by glucose oxidase peroxidase test. T3, T4 and TSH levels were estimated by immunoassay. Glycosylated hemoglobin (HbA1c) was determined by ion-exchange chromatography.

Results: Data was analysed with the help of SPSS (Version 26) software. Paired sample statistics was used. Mean ± Standard deviation were observed. P value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

Conclusions: This present study concluded that the metformin was not significantly affected the levels of serum thyroid stimulating hormones in euthyroid type 2 diabetes mellitus patients. Hence, in the primary prevention of diabetes, use of metformin is proven to be effective and safe.

KEYWORDS

Euthyroid, type 2 diabetes mellitus, T3, T4, TSH, HbA1C.

INTRODUCTION

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances in carbohydrate, fat and protein metabolism associated with absolute or relative deficiency of insulin secretion and / or insulin action [1]. The World Health Organization (WHO) has projected that the global prevalence of diabetes will increase to 300 million (7.8%) by 2030 [2]. Various endocrine and non endocrine organs except for pancreas influence diabetes mellitus [3]. Diabetes mellitus and thyroid disorders are one of the most commonly seen conditions in clinical practice. Diabetes is the commonest endocrine disorder worldwide [4]. Thyroid hormones are essential for metabolism and energy homeostasis and participate in insulin action and glucose regulation [5]. Previous studies reported higher prevalence rates of thyroid disorders in diabetic patients compared with nondiabetic individuals, and overt hypothyroidism was frequently observed in type 2 diabetes mellitus(T2DM) [6, 7]. This increase in prevalence is due to change in lifestyle habits like consumption of fermentable carbohydrates and sedentary habits. Thyroid disorders are also commonly occurring conditions amongst general population [8]. Metformin is a biguanide that has been in use for decades to treat diabetes. Efficacy and safety of metformin in the management of T2DM is well established [9]. It has the advantage that it is rarely associated with hypoglycaemia unless used in conjunction with insulin secretagogues such as sulphonylureas or insulin. Metformin has beneficial effects on body mass index (BMI) and lipid concentrations and has been proven to be safe showing no serious adverse effects [10]. Besides acting as an oral hypoglycaemic agent, it has been used with diet and physical activity to prevent diabetes in people at high risk [10].

In this present study, we had enrolled euthyroid type 2 diabetes mellitus patients. Objectives of this study was to evaluate the various parameters like T3, T4,TSH and HbA1c level of type 2 diabetes mellitus patients with or without receiving metformin.

MATERIALS AND METHODS

This present study was conducted in Department of Pharmacology with the collaboration of Department of Medicine and Department of Pathology of Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India during a period from February 2019 to June 2019. Entire subjects signed an informed consent approved by institutional ethical committee of Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India was sought.

METHODS:

A total of 100 euthyroid cases of type 2 diabetes mellitus were enrolled in this study. These total cases were categorized into two groups (group A and group B). Group A had 50 euthyroid cases of type 2 diabetes mellitus without on metformin. Group B had 50 euthyroid patients of type 2 diabetes mellitus on metformin.

A detail history, clinical examinations and relevant investigations were performed to all cases of diabetes mellitus.

Inclusion criteria

of this study were the patients of type 2 diabetes mellitus aged more than 40 years with irrespective of glucose control and with irrespective of treatment of OHA/insulin.

Exclusion criteria

were the patients of type 1 diabetes mellitus, and patients with gestational diabetes mellitus, pancreatitis, steroid induced diabetes and those who had proven thyroid disorder and on treatment, Patients suffering from hemoglobinopathies and anemia and patients on amiodarone therapy.

Procedures:

4ml of blood was withdrawn from anticubital vein of patients by a disposable syringe. Patients were kept fasting overnight. Collected blood sample was centrifuged and serum thus obtained was used for estimation of glucose and thyroid levels. Glucose was estimated by glucose oxidase peroxidase test. T3, T4 and TSH levels were estimated by immunoassay. Glycosylated hemoglobin (HbA1c) determined by ion-exchange chromatography.

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 was analysed with the help of SPSS (Version 26) software. Paired sample statistics was used. Mean ± Standard deviation were observed. P value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

OBSERVATIONS

This present study was enrolled a total of 100 euthyroid patients with type 2 diabetes mellitus with age group 40 to 70 years. Out of 100 patients, male and female ratio was 3:1.

Table. 1. Comparison of parameters of euthyroid type 2 diabetes mellitus patients without receiving metfromin and with receiving metformin

Parameters	Not received metformin (N=50) (mean ± S.D.)	Received metformin (N=50) (mean ± S.D.)	Correlation (r)	P-value
Age	58.580±7.974	57.520±9.183	-.156	0.278
T3	108.800±5.696	105.940±5.036	0.010	0.948
T4	6.720±1.212	6.500±1.233	-.068	0.638
TSH	2.180±0.628	2.480±0.862	0.251	0.078
HbA1C	8.080±1.226	8.380±1.412	-.089	0.541

Here, when we had compared the mean age, mean free T3, mean free T4, TSH and HbA1C levels of euthyroid type 2 diabetes mellitus without or with metformin medication. P value was found to be greater than 0.05. Hence, it was not significant differences.

DISCUSSIONS

Diabetic Mellitus is an important health problem affecting major population worldwide. India has the dubious distinction of being home to the largest number of people suffering from diabetes in any country. The disease is responsible for significant mortality and morbidity due to the complications [11]. Metformin is first line recommended therapy for T2DM according to the International Diabetes Federation Global Guidelines for T2DM, in agreement with similar guidelines from the ADA, as well as the European Association for the Study of Diabetes (EASD) [12,13]. The ADA Consensus Conference also recommended that high-risk individuals (HbA1c $\geq$ 6.0%; body mass index $\geq$ 30 kg/m2; age $\leq$ 60 years) with IGT or Impaired Fasting Glucose (IFG) be treated with metformin [14].

In our present study, we had studied on euthyroid type 2 diabetes mellitus patients. And we had categorized the total patients into two groups (group A and group B). Group A had 50 euthyroid type 2 diabetes mellitus patients who did not receive metformin. And group B had also 50 euthyroid type 2 diabetes mellitus patients who received metformin. 58.580 ±7.974 years and 57.520 ± 9.183 years were the mean age of type 2 diabetes mellitus patients of group A and group B respectively and it was not significant differences (p=0.278).

In this present study, When we had compared mean free T3 levels of group A with group B, Pearson's correlation and p value were found to be 0.010 and 0.948 respectively. Hence it was not significant differences.

Diabetes mellitus is a complex multifactorial disease with varying aetiologies but in most of the cases there is genetic predisposition. It has been associated with various physiologic changes in different organ systems of human body [15]. Thyroid hormones i.e. T3 and T4 act as antagonist for insulin which also potentiates its action [16]. The synthesis of thyroid hormone releasing hormone generally decreases in patients with diabetes [17]. In a study conducted by Bharat et al, [18] the levels of TSH significantly increased amongst diabetic patients but T3 levels showed no significant change amongst diabetics and non diabetics.

In this present study, when we had compared the mean free T4 levels of euthyroid type 2 diabetes patients, who had not received metformin (group A) with who had received metformin (group B). Pearson's correlation and p value were found to be -0.068 and 0.638 respectively. It was not significant differences. Hence level of T4 was not greatly changed. Similarly, when we had compared the mean TSH levels of group A and group B. Pearson's correlation and p value were found to be 0.251 and 0.078 respectively. Hence, a level of TSH was also not significantly differences. In our study all cases were euthyroid. When we had compared the levels of HbA1C of group A with group B patients, Pearson's correlation and p value were found to be -.089 and 0.541 respectively. It was also not significant changed. Hence, this present study shows that the receiving of metformin as a medicine in euthyroid type 2 diabetes mellitus patients was not significantly affected the levels of T3, T4, TSH and HbA1C levels.

Thyroid hormones have profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels and counter regulatory hormones, intestinal absorption, hepatic production and peripheral tissues uptake of glucose. Thyroid hormones oppose the action of insulin and stimulate gluconegenesis and glycogenolysis [19].

In euthyroid individuals with DM the serum tri-iodothyronine (T3) levels, basal thyroid stimulating hormone (TSH) levels and TSH response to thyrotropin releasing hormone (TRH) are all subjected to alteration by the glycemic status. DM appears to influence thyroid function at two sites; firstly at the level of hypothalamic control of TSH release and secondly at peripheral tissue by converting T4 to T3. The nocturnal TSH peak is blunted or abolished in diabetic patients, and the TSH response to TRH is also impaired [20]. Reduced T3 levels have been observed in patients with uncontrolled diabetes. Possible explanation for this "low T3 state" could be impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycemic control. Higher levels of circulating insulin coupled with IR have shown a proliferative effect on thyroid tissue which may lead to larger thyroid size with increased nodule formations [21,22]. Obesity is the most important causal factor for progression of IGT to diabetes and is primarily responsible for the rising trend in T2DM. Weight loss achieved via lifestyle modification or pharmacologic intervention enhances insulin sensitivity thereby improving glucose tolerance in IGT individuals. Metformin reduces insulin resistance which is the underlying cause of both obesity and PCOS in non-diabetic persons. Improving insulin sensitivity may account for weight reduction under metformin therapy. Effect of metformin on weight loss has been reported in several trials [23,24].

Similar study was conducted by Shailendra D, et al. [25] in their study, metformin was not affected the levels of thyroid stimulating hormones of euthyroid type 2 diabetes mellitus patients. Thus, their study supported the findings of our study.

CONCLUSIONS

This present study concluded that the receiving of metformin in euthyroid type 2 diabetes mellitus patients were not significantly affected the levels of serum thyroid stimulating hormones. Hence, in the primary prevention of diabetes mellitus, use of metformin is proven to be effective and safe.

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