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Effect of metformin use on thyroid function in euthyroid type 2 diabetes mellitus patients

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ABSTRACT

Studies have shown that there is an association between type 2 diabetes mellitus and thyroid dysfunction although, the mechanism is poorly understood. This study assessed the thyroid function in euthyroid T2DM patients on metformin and its possible relationship with duration of metformin use. Thirty-five euthyroid T2DM patients who have been on metformin for ≥5 years, 10 euthyroid T2DM patients who have been on non-metformin oral antidiabeteic drugs for ≥5 years and 19 apparently healthy euthyroid controls were individuals served as controls. Serum levels of thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were determined using ELISA. Levels of TSH, FT3 and FT4 were similar in patients on metformin, non-metformin and the controls. The median level of TSH was insignificantly lower in patients who have taken metformin for ≥10 years compared with patients who have taken metformin for <10 years. Mean levels of FT3 and FT4 were similar between the 2 groups. Metformin use does not alter thyroid function in euthyroid T2DM patients. Also, prolonged use of metformin does not have significant effect on the levels of thyroid stimulating hormone and thyroid hormones in euthyroid T2DM patients.

Key words: Euthyroid, Metformin, Thyroid stimulating hormone, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus and thyroid dysfunction are common conditions of the endocrine system which appear to be closely linked [1]. The mechanism of interaction between these conditions is complex and unclear as it cannot be simply explained via shortage or excess of thyroid hormone [2]. In fact, relatively low but clinically normal thyroid function has been associated with adverse effects in patients with type 2 diabetes mellitus (T2DM) [3].

Reports have shown that thyroid dysfunctions especially, subclinical forms of hyperthyroidism and hypothyroidism, are frequently observed in patients with T2DM [4, 5].

The management of T2DM requires a comprehensive approach to achieve tight glycaemic control and cardiovascular risk reduction. These are achieved with the use of efficient hypoglyacemic drugs such as metformin. Metformin is the most commonly prescribed hypoglycaemic biguanide with significant effect on mortality reduction in patients with T2DM [6, 7]. It improves peripheral and liver sensitivity to insulin, reduces gluconeogenesis, increases insulin stimulated uptake and utilization of glucose by peripheral tissues, decreases appetite and causes weight reduction [8].

Despite the clinical benefits of metformin, several retrospective and prospective studies have associated metformin therapy with significant reduction in thyroid stimulating hormone (TSH) level [9, 10, 11, 12]. It has been reported that metformin may change the affinity and number of thyroid hormone receptors, and may act directly on TSH regulation, thus enhancing the effect of thyroid hormones on the pituitary. Additionally, metformin may upregulate gastrointestinal absorption of thyroxine, and may produce subtle changes in thyroid hormone protein-binding [9, 13].

Although clinical benefits of metformin are numerous in T2DM management, its relationship with thyroid function still needs further assessment. This study therefore, determined the levels of TSH, free thyroxine (FT4) and free triiodothyronine (FT3) in euthyroid type 2 diabetes patients on long-term metformin use.

MATERIALS AND METHODS

Thirty-five patients with T2DM who have been on metformin for ≥5 years and 10 patients with T2DM who have been on non-metformin oral antidiabeteic drugs for ≥5 years were recruited from the Endocrinology Unit of the Medical Outpatient Department (MOP) of the University College Hospital, Ibadan, Nigeria. Nineteen apparently healthy euthyroid individuals served as controls.

Exclusion criteria
Type 2 diabetes mellitus (T2DM) patients with established retinopathy, nephropathy, neuropathy, microangiopathy, ischemic heart disease and cerebrovascular disease were excluded from the study. Also, T2DM patients with pregnancy, apparent thyroid disease and those on corticosteroid, radioiodine, amiodarone and levothyroxine were excluded from the study. Additionally, patients who are older than 60 years were excluded from the study.

Informed Consent and Ethical Approval
Participants were enrolled into this study after obtaining a written informed consent from each of them. Also, an ethical approval (UI/EC/14/0120) was obtained from the University of Ibadan/University College Hospital Joint Ethical Committee.

Data and Sample collection
Information on duration of diabetes, thyroid disease, hypertension, hyperlipidaemia, diabetic retinopathy, nephropathy, neuropathy, ischemic heart disease, cerebrovascular disease and peripheral artery disease, type of treatment for diabetes (diet, oral agents and insulin) and the use of corticosteroid, radioiodine, amiodarone and levothyroxine were obtained through clinical history, patients' case files and physical examination.

About 10 ml of venous blood was collected from each participant to obtain serum which was stored at -20^0C until analysed.

Determination of serum levels of thyroid hormones and thyroid stimulating hormone
Serum levels of thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were determined using ELISA (Monobind Inc., USA).

Statistical analysis
Data obtained were subjected to statistical analysis using SPSS version 20.0. Depending on the distribution of the variable, Analysis of variance (ANOVA), Kruskal-Wallis and Mann-Whitney *U* were used to determine the mean differences between the variables. $P<0.05$ was considered as statistically significant.

RESULTS

Table 1 shows the characteristics of the study participants. The mean body weight, body mass index and blood pressure were similar among patients on metformin only, non-metformin and the controls.

Similarly, patients on metformin only, non-metformin and the controls had similar serum levels of TSH, FT3 and FT4 (Table 2).

As shown in Table 3, the median level of TSH was slightly lower in patients who have taken metformin for ≥10 years compared with patients who have taken metformin for <10 years. However, mean levels of FT3 and FT4 were similar between the 2 groups.

Table 1: Characteristics of the study participants

	Metformin (n = 35)	Non-metformin (n = 10)	Control (n = 19)	*P*-value
Age (years)	59.2 ± 8.9	56.2 ± 8.0	54.4 ± 7.6	0.133
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.800
Body weight (kg)	72.3 ± 9.8	71.1 ± 6.8	69.6 ± 12.5	0.661
BMI (kg/m^2)	26.0 ± 3.4	25.3 ± 3.8	25.4 ± 4.3	0.803
Systolic BP (mmHg)	126.0 ± 15.0	120.0 ± 8.2	133.0 ± 25.8	0.189
Diastolic BP (mmHg)	83.6 ± 12.1	82.0 ± 7.9	85.8 ± 13.0	0.679

Table 2: Serum levels of thyroid stimulating hormone, free thyroxine and free triiodothyronine in the study participants

	Metformin (n = 35)	Non-metformin (n = 10)	Control (n = 19)	*P*-value
TSH (µIU/ml)	1.8 (1.1 - 2.5)	2.1 (1.6 - 2.3)	2.0 (1.4 - 3.0)	0.700
FT3 (pg/ml)	2.1 ± 0.3	2.2 ± 0.2	2.3 ± 0.2	0.127
FT4 (ng/dl)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.764

Table 3: Serum levels of thyroid stimulating hormone, free thyroxine and free triiodothyronine based on duration of metformin use

	<10 years (n = 22)	≥10 years (n = 13)	*P*-value
TSH (µIU/ml)	1.9 (1.4 – 2.5)	1.1 (0.9 – 2.8)	0.204
FT3 (pg/ml)	2.2 ± 0.3	2.1 ± 0.3	0.711
FT4 (ng/dl)	1.0 ± 0.1	1.0 ± 0.1	0.719

DISCUSSION

A number of uncertain biological mechanisms have been put forth to explain the TSH-lowering properties of metformin [14]. Cappelli et al. [15] hypothesized that metformin enhances the inhibitory modulation of thyroid hormones on central TSH secretion without modifying circulating FT3 or TSH levels in a normal functioning closed-loop control system.

The observed non-significant differences in TSH, FT3 and FT4 levels in patients on metformin compared with those on non-metformin antidiabetic drug is in line with the reports of Cappelli *et al.* [15, 16] and Fournier *et al.* [1]. Our observation further confirms the hypothesis that metformin has no effect on thyroid function in T2DM patients with intact pituitary-thyroidal axis. This hypothesis is further alluded to by the observed non-significant difference in the levels of TSH, FT3 and FT4 in patients on metformin compared with the controls.

Fournier et al. [1] showed that the use of metformin is not associated with an increased risk of low TSH levels and has no pattern with duration of use. The observed non-significantly lower TSH level in T2DM patients who have been on metformin for 10 years or more compared with patients with fewer years supports the report of Cappelli et al. [15] who reported non-significantly lower mean TSH level in euthyroid T2DM patients after 12 months of metformin use. Although our observed TSH levels were not significantly different between the 2 groups, studies with prolonged year of follow up (for example 20 years) may shed more light on the possible interplay between metformin use and TSH level in euthyroid T2DM patients as TSH level reduction could be gradual.

Small sample size was a major limitation in this study. Also, we were unable to do thyroid ultrasonography on the study participants.

It could be concluded from this study that metformin use does not alter thyroid function in euthyroid T2DM patients. Also, prolonged use of metformin does not have significant effect on the levels of thyroid stimulating hormone and thyroid hormones in euthyroid T2DM patients.

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