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Original research article

The effect of metformin on the hypothalamic-pituitary-thyroid axis in patients with type 2 diabetes and amiodarone-induced hypothyroidism

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ABSTRACT

Background: Chronic metformin treatment was found to reduce elevated thyrotropin levels. Amiodarone treatment is associated with a range of effects in thyroid function from mild derangements to overt thyroid dysfunction. No previous study has investigated the effect of metformin on hypothalamic-pituitary-thyroid axis activity in patients with amiodarone-induced hypothyroidism.
Methods: The study included three age-, sex- and weight-matched groups of amiodarone-treated patients with type 2 diabetes: patients with treated overt hypothyroidism (group I, $n = 15$), patients with untreated subclinical hypothyroidism (group II, $n = 15$), and subjects without thyroid disorders (group III, $n = 18$). The lipid profile, fasting plasma glucose levels, the homeostatic model assessment 1 of insulin resistance ratio (HOMA1-IR), glycated hemoglobin, the estimated glomerular filtration rate, as well as serum levels of thyrotropin, thyroid hormones, prolactin, insulin and insulin-like growth factor-1 (IGF-1) were assessed at baseline and after 6 months of metformin treatment (2.55–3 g daily).
Results: In all groups of patients, metformin reduced plasma glucose and triglycerides, serum insulin, glycated hemoglobin as well as HOMA1-IR. The estimated glomerular filtration rate, thyroid hormones, prolactin and IGF-1 remained at a similar level throughout the study. In patients with untreated amiodarone-induced hypothyroidism, but not in the other groups of patients, metformin reduced serum levels of thyrotropin and this effect correlated weakly with its action on insulin sensitivity.
Conclusions: The obtained results indicate that the effect of metformin on hypothalamic-pituitary-thyroid axis activity is partially related to thyroid function. Metformin treatment may bring clinical benefits to patients with amiodarone-induced hypothyroidism and poor tolerance of exogenous L-thyroxine.
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Introduction

Metformin is the first-line oral agent in the treatment of type 2 diabetes [1], which has been found to reduce the long-term complications of diabetes, including macrovascular disease [2]. Moreover, metformin reduces the risk of progression to type 2 diabetes from impaired glucose tolerance [3], as well as is used in polycystic ovary syndrome, non-alcoholic steatohepatitis and human immunodeficiency virus lipodystrophy syndrome [4]. In some studies, the use of metformin was associated with a reduction in serum thyrotropin levels, often to subnormal levels, which was not accompanied by changes in total and free thyroid hormone levels [5–10]. In contrast, the drug did not change thyrotropin levels in subjects with normal thyroid function [6,9,11], and its effect was negligible in patients with hyperthyroidism [12]. The impact of metformin on thyrotrope function is in part associated with the changes in dopaminergic regulation of thyrotropin secretion and is less pronounced in patients receiving bromocriptine treatment [10]. The possible alternative mechanisms include: changes in the affinity and/or number of thyroid hormone receptors, changes in thyroid hormone protein binding, enhanced gastrointestinal absorption of L-thyroxine, altered thyroid hormone metabolism, as well as and interference with the thyrotropin assay [5,6,13]. Despite a reduction in thyrotropin,

Abbreviations: AMPK, adenosine 5′-monophosphate-activated protein kinase; HOMA1-IR, the homeostatic model assessment 1 of insulin resistance ratio; IGF-1, insulin-like growth factor-1; SD, standard deviation.

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metformin-treated patients did not develop clinical symptoms of hyperthyroidism [14]. Taking into account that diabetic patients have a higher prevalence of thyroid disorders, particularly hypothyroidism, compared with the normal population [15], the effect of metformin on the hypothalamic-pituitary-thyroid axis may be clinically relevant.

Amiodarone is a class III antiarrhythmic drug used in the treatment of recurrent severe ventricular arrhythmias, paroxysmal atrial tachycardia, atrial fibrillation and maintenance of sinus rhythm after cardioversion of atrial fibrillation [16], which are often present in patients with type 2 diabetes [17]. The use of this agent, being a benzofuran-derived compound, containing 37% iodine by weight and having some structural similarity to thyroxine, is complicated in 15–20% of cases by the occurrence of thyroid dysfunction, either hypothyroidism or thyrotoxicosis [18,19]. Amiodarone-induced hypothyroidism occurs more frequently in women than men, in iodine-sufficient than in iodine-deficient areas, as well as in patients with preexistent thyroid dysfunction [18,19]. Most patients do not require discontinuation of amiodarone but are usually additionally treated with L-thyroxine [20]. However, in some patients, L-thyroxine supplementation, often at higher doses than in spontaneous hypothyroidism, may be poorly tolerated and/or may result in adverse effects [20].

To the best of our knowledge, no previous study has investigated the safety and effectiveness of amiodarone–metformin combination therapy. Therefore, the aim of our study was to determine whether metformin treatment affects hypothalamic-pituitary-thyroid axis activity in patients with hypothyroidism induced by chronic amiodarone treatment.

Materials and methods

Patients

Patients (45–75 years old) were eligible for the study if they met the following criteria: (1) at least 6 months' treatment with oral amiodarone at the daily dose of 200–400 mg together with adequate anticoagulation therapy (if recommended by American College of Cardiology Foundation/American Heart Association/European Society of Cardiology/Heart Rhythm Society guidelines [21]); and (2) recently diagnosed and previously untreated type 2 diabetes mellitus (fasting plasma glucose $\geq$126 mg/dL or plasma glucose concentration 2 h after a glucose load $\geq$200 mg/dL).

Patients were excluded if they had an uncorrected QT interval >440 ms, familial long QT syndrome, previous torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia, symptomatic bradycardia, known sick sinus syndrome, atrioventricular block or ventricular rate <50 beats/min; QRS interval >140 ms, New York Heart Association functional class IV heart failure, or heart failure requiring inotropes, or were hemodynamically unstable (systolic blood pressure <90 or >60 mm Hg and diastolic blood pressure >95 mm Hg). Patients with acute coronary syndrome, stroke or cardiac surgery within 6 months preceding the study, hypothyroidism diagnosed before amiodarone treatment, glycated hemoglobin >9%, elevated liver enzyme levels, serum creatinine >2 mg/dL, receiving one or more of the following medications: cimetidine, phenytoin, cholestyramine, and cyclosporine or drugs known to affect thyroid function or to interact with amiodarone and metformin were also not included in the study.

Study design

The study protocol was approved by our institutional review board, and subjects gave written, informed consent to participate in the study. Based on thyroid function test, the study populations consisted of three age-, sex- and weight-matched groups: (I) patients diagnosed previously with hypothyroidism and treated with L-thyroxine (50–150 μg daily) in whom thyrotropin levels were above 0.45 mIU/L but below 4.5 mIU/L (n = 15), (II) patients with untreated subclinical hypothyroidism (plasma thyrotropin levels more than 4.5 mU/L but below 10 mU/L) (n = 15), and (III) subjects without thyroid disorders (n = 18). The mean dose of L-thyroxine in group I was 95 μg daily. All included patients were then treated with metformin, as well as were given detailed advice about how to achieve the goals of lifestyle modification, which were a decrease in weight $\geq$7% if necessary, total fat intake <30% of total energy intake, saturated fat intake <7% of energy consumed, cholesterol intake <200 mg/day, an increase in fiber intake to 15 g/1000 kcal, and moderate to vigorous exercise for $\geq$30 min/day. Metformin was administered at a starting dose of 500 mg once daily and this dose was gradually (over a period of 4 weeks) titrated. The final daily dose of metformin (2.55–3 g) was administered for the following 6 months. Throughout the entire study period, the participants complied with these dietary recommendations and continued treatment with the same daily dose of amiodarone as before the study (200–400 mg). Patients who were already taking other drugs kept their pharmacologic schedule constant during the study. Compliance was assessed at each visit by interrogation and pill count.

Laboratory assays

Laboratory assays were performed at the beginning of the study and after 6 months of treatment. Venous blood samples were taken 12 h after the last meal from the antecubital vein in a temperature-controlled room (24–25 °C). To avoid possible circadian fluctuations in the parameters studied, samples were drawn during constant daily hours (between 8.00 and 9.00 a.m.), and to minimize analytical errors, all assays were carried out in duplicate. Plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), fasting glucose and creatinine, as well as serum insulin levels were measured with standard methods using commercial kits purchased from Roche Diagnostics (Basel, Switzerland) and DRG Instruments GmbH (Marburg, Germany). To avoid any error resulting from the Friedewald formula, LDL-cholesterol was determined directly. The homeostasis model assessment 1 of insulin resistance (HOMA1-IR) was calculated by dividing the product of insulin (mIU/L) and glucose (mg/dL) by 405). The estimated glomerular filtration rate was calculated using the Modification Diet in Renal Disease Study equation. Glycated hemoglobin was evaluated using a commercially available kit (Sigma, St. Louis, MO, USA). Serum levels of thyrotropin as well as total and free thyroid hormones were measured with electrochemiluminescence immunoassay (Roche Diagnostics, Lewes, UK). Serum prolactin and insulin-like growth factor-1 (IGF-1) were determined by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany). Serum levels of thyrotropin were measured using an electrochemiluminescence immunoassay method (Roche Diagnostics, Lewes, UK). Intra- and interassay coefficients of variation were less than 6.2 and 8.5%, respectively.

Statistical analysis

The Kolmogorov-Smirnov test was used as the first statistical analysis approach to verify data distribution normality. Because of skewed distributions, values for insulin, HOMA1-IR, triglycerides, prolactin, IGF-1, thyrotropin and thyroid hormones were natural-log transformed to meet the assumptions of parametric tests. Comparisons between the study groups were performed using one-way analysis of variance followed by the *post hoc* Bonferroni

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