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Original Article

The effect of metformin on prolactin levels in patients with drug-induced hyperprolactinemia

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ABSTRACT

Background: In bromocriptine-treated hyperprolactinemic patients with impaired glucose tolerance, metformin was found to reduce plasma levels of prolactin. No previous study has investigated its impact on plasma prolactin in patients with drug-induced hyperprolactinemia.

Methods: The study included 20 women with antipsychotic-induced hyperprolactinemia and 12 normoprolactinemic women, who, because of coexisting glucose metabolism abnormalities, were treated for 6 months with metformin. Hyperprolactinemic patients with prediabetes received moderate doses of metformin (1.7 g daily), while hyperprolactinemic and normoprolactinemic patients with type 2 diabetes were treated with high-dose metformin (2.55–3 g daily). Fasting plasma glucose levels, the homeostatic model assessment 1 of insulin resistance ratio (HOMA1-IR), glycated hemoglobin, as well as plasma levels of prolactin, thyrotropin, adrenocorticotropic hormone and insulin-like growth factor-1 were assessed at baseline and after 6 months of treatment.

Results: Despite reducing plasma glucose, HOMA1-IR, and glycated hemoglobin in all treatment groups, metformin decreased prolactin levels only if given at high doses to patients with elevated prolactin levels. No changes in thyrotropin, adrenocorticotropic hormone, and insulin-like growth factor-1 were observed in any treatment groups.

Conclusions: The obtained results suggest that the effect of metformin on plasma prolactin depends on its dose and is observed only in patients with elevated levels of this hormone.

1. Introduction

Long-term prolactin excess is often complicated by impaired glucose tolerance, hyperinsulinemia, insulin resistance, atherogenic dyslipidemia, subclinical atherosclerosis, endothelial dysfunction, and weight gain [1–8]. Dopamine agonists not only normalize elevated prolactin levels but also decrease body weight, insulin resistance, and hepatic glucose production through an increase in dopaminergic neurotransmission, which can reset the hypothalamus and improve insulin sensitivity [2,7,9,10]. Therefore, a quick-release form of bromocriptine has recently been approved by the United States Food and Drug Administration for use in type 2 diabetes [11]. Although dopamine receptor agonists are considered the drugs of choice in the treatment of symptomatic hyperprolactinemia, not all patients with elevated prolactin levels may be treated with these agents. An important group of patients in whom dopamine agonists are contraindicated are patients with antipsychotic-induced hyperprolactinemia, caused mainly by the use of the typical antipsychotics (phenothiazines, haloperidol, and thioxanthenes) and by some of the atypical agents (amisulpride, risperidone, and paliperidone) [12,13]. Although a reduction in dose or switching to a prolactin sparing antipsychotic may be effective for decreasing prolactin levels, these treatment strategies may carry the risk of an exacerbation or relapse of psychotic symptoms [14,15].

To the best of our knowledge, no previous study has examined the effect of metformin in patients with drug-induced hyperprolactinemia. This agent is, together with lifestyle adjustments, the first-line treatment for type 2 diabetes mellitus and is often used in other insulin resistance states [16,17]. Metformin reduces the risk of the development of long-term complications of diabetes, including macrovascular disease [18], as well as was found to reduce the progression of prediabetes to diabetes [19]. In recent years, some studies revealed that chronic metformin treatment may have an impact on pituitary function. Metformin content was found to be higher in the pituitary than in other brain structures [20]. In patients with hypothyroidism, metformin therapy decreased circulating levels of thyrotropin, often below the lower limit of the normal range, which was not accompanied by the changes in total and free thyroxine and triiodothyronine [21–25]. In women with

Abbreviations: ACTH, Adrenocorticotropic hormone; 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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polycystic ovary syndrome, this drug decreased plasma levels of luteinizing hormone and the luteinizing hormone/follicle stimulating hormone ratio [26–28]. Finally, metformin was found to reduce elevated prolactin levels. This effect, previously reported by other investigators in women with polycystic ovary syndrome [28–30], has been recently reported by our research team if metformin was administered to patients with microprolactinoma, traumatic brain injury, and primary empty sella syndrome, in whom hyperprolactinemia was insufficiently treated with bromocriptine [31].

Taking into account the high prevalence of drug-induced hyperprolactinemia and its treatment limitations, as well as the association of elevated prolactin levels with glucose metabolism disturbances, the aim of our study was to assess the effect of metformin on plasma levels of prolactin in patients with antipsychotic-induced hyperprolactinemia. The study also investigated whether this effect, if present, depends on metformin dose and on a type of glucose metabolism disturbance.

2. Materials and methods

The participants of the study (n = 20) were recruited among adult women (30–65 years old) with symptomatic hyperprolactinemia induced by chronic treatment with psychotropic agents. To be included, they had to be diagnosed with either prediabetes (fasting plasma glucose more than 100 mg/dL, and/or plasma glucose concentration 2 h after a 75-g oral glucose load at least 140 mg/dL but less than 200 mg/dL) (n = 10) or diabetes (fasting plasma glucose at least 126 mg/dL and/or plasma glucose concentration 2 h after a glucose load at least 200 mg/dL) (n = 10) within 3 months before the beginning of the study. The exclusion criteria were as follows: type 1 diabetes, glycated hemoglobin levels above 9.5%, prolactinoma, mixed pituitary tumors (secreting prolactin and other pituitary hormones), other hormonally active and non-functioning pituitary adenomas, hypothyroidism, primary hypogonadism, impaired renal or hepatic function, thyroid disorders, polycystic ovary syndrome, pregnancy or lactation, empty sella syndrome, and macroprolactinemia. No patient had been receiving hypoglycemic agents, drugs affecting circulating prolactin levels, and drugs known to interact with metformin or psychotropic agents.

The study was performed in accordance with the 1964 Helsinki Declaration, and the protocol was accepted by the local ethics committee. All patients were fully informed of the purpose and the possible risks of the study and provided written informed consent. Women with diabetes were treated with phenothiazines (n = 3), haloperidol (n = 2), sulpiride (n = 2), and risperidone (n = 3), while prediabetic patients received phenothiazines (n = 3), haloperidol (n = 2), thioxanthenes (n = 2), sulpiride (n = 1), and risperidone (n = 2). All enrolled patients were informed regarding the principles of a healthy diet and instructed to stop smoking and to cease alcohol consumption, and they were encouraged to participate in either moderately or vigorously intensive physical activity at least five days of the week. All enrolled patients were treated with metformin, which 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 (1.7 g in patients with prediabetes and 2.55–3 g in patients with type 2 diabetes) was administered for the following 6 months. During the entire study, all included patients complied with lifestyle modification while a dose of the antipsychotic agents remained constant throughout the study period. Compliance was assessed during each visit by tablet counts and was considered satisfactory when the number of tablets taken by a patient ranged from 90% to 110%. The control group included 12 age- and weight-matched normoprolactinemic women with type 2 diabetes receiving 2.55–3 g of metformin.

Venous blood samples were collected from the antecubital vein at 8 a.m. (to avoid possible circadian fluctuations in the parameters studied) after an overnight 12-h fasting at baseline and at the end of the treatment period. Before blood collection, the participants had been resting in a quiet room for at least 30 min in the seated position. To minimize analytical errors, all assays were carried out in duplicate. Plasma fasting glucose and creatinine were assayed by routine laboratory techniques (Roche Diagnostics, Basel, Switzerland). Plasma insulin, prolactin, and insulin-like growth factor-1 (IGF-1) levels were determined by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany). Circulating levels of thyrotropin and adrenocorticotropic hormone (ACTH) were measured using an electrochemiluminescence immunoassay method (Roche Diagnostics, Lewes, UK). The estimated glomerular filtration rate was calculated using the Modification Diet in Renal Disease Study equation. The homeostasis model assessment 1 of insulin resistance index (HOMA1-IR), a surrogate index of insulin sensitivity, was calculated by the formula: [fasting insulinemia (mU/L) × glycemia (mg/dL)]/405. Glycated hemoglobin was determined using a commercially available kit obtained from Sigma (St. Louis, MO). Intra- and inter-assay coefficients of variation were less than 6.1 and 8.6%, respectively.

The obtained results were analyzed using the Kolmogorov–Smirnov test for data normality. Because of skewed distributions, values for HOMA-IR and hormones were natural-log transformed to satisfy assumptions of normality and equal variance. Between-group comparisons were performed using one-way analysis of covariance followed by the post-hoc Newman–Keuls test. Student's paired *t* test was used to compare differences between the means of variables within the same treatment group. In all statistical analyses, age, smoking, and body mass index were considered as potential confounders. The χ^2 test was employed to compare the proportional data. Correlations were calculated using Kendall's tau test. Statistical significance was assumed at $p < 0.05$.

3. Results

The baseline characteristics of the included patients are summarized in Table 1. No significant differences were observed in the age, weight, and medical backgrounds between the groups at the onset of the study. No serious adverse effects were reported during the entire study period, and all patients completed the study. Plasma levels of prolactin were higher in hyperprolactinemic women in comparison with normoprolactinemic ones, with no difference between patients with diabetes and prediabetes. As expected, metformin administered for 6 months to both groups of hyperprolactinemic patients and to normoprolactinemic patients with type 2 diabetes reduced fasting plasma glucose, HOMA1-IR, and glycated hemoglobin (Table 2). Metformin treatment did not affect the estimated glomerular filtration rate. In women with prediabetes and women with normal prolactin levels, metformin produced no effect on plasma levels of prolactin, thyrotropin, ACTH, and IGF-1. In hyperprolactinemic patients with diabetes, high-dose metformin decreased plasma prolactin by 23% ($p < 0.05$), but did not change plasma levels of the other hormones. Post-treatment levels of prolactin were higher in women with hyperprolactinemia than in women with normal prolactin levels (Table 2).

In all treatment groups, baseline prolactin levels correlated weakly with HOMA1-IR (r values between 0.28 [$p < 0.05$] and 0.37 [$p < 0.01$]. The effect of metformin treatment on prolactin in hyperprolactinemic women with type 2 diabetes correlated with baseline prolactin levels ($r = 0.51$, $p < 0.001$) and weakly with the impact on HOMA1-IR ($r = 0.31$, $p < 0.05$). No other correlations between the investigated variables were observed in any group before and after metformin treatment.

4. Discussion

The major finding of our study is that high-dose metformin moderately decreased plasma prolactin levels in women with antipsychotic-induced hyperprolactinemia but did not affect plasma levels of the other measured hormones. We can only hypothesize about the