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Effect of Metformin on Hypothalamic-Pituitary-Thyroid Axis Activity in Elderly Antipsychotic-Treated Women With Type 2 Diabetes and Subclinical Hypothyroidism: A Preliminary Study

Robert Krysiak, MD, PhD, Witold Szkróbka, MD, and Bogusław Okopień, MD, PhD

Abstract

Metformin was found to reduce elevated serum thyrotropin levels, and this effect was partially determined by endogenous dopaminergic tone. The aim of this study was to compare the effect of metformin treatment on hypothalamic-pituitary-thyroid axis activity in elderly women with subclinical hypothyroidism treated with antipsychotic agents and not receiving this drug. The study population consisted of 34 elderly women with subclinical hypothyroidism, 16 of whom received antipsychotic drugs. Because of coexistent type 2 diabetes, these women were treated with metformin (2.55–3 g daily). Glucose homeostasis markers as well as serum levels of thyrotropin, free thyroid hormones and prolactin were measured at the beginning of the study and 6 months later. Thirty women completed the study. With the exception of prolactin, baseline serum levels of the assessed hormones were comparable in both study groups. Although metformin reduced serum thyrotropin levels in both groups, this effect was more pronounced in the antipsychotic-treated than in the antipsychotic-naive patients. The effect on serum prolactin was observed only in antipsychotic-treated patients. The impact on serum thyrotropin levels correlated with improvement in insulin sensitivity and with a reduction in prolactin levels. Free thyroxine and free triiodothyronine remained at a similar level throughout the study. The obtained results indicate that metformin reduces serum thyrotropin levels in elderly women, and this effect is particularly pronounced in women with diminished dopaminergic transmission.

Keywords

antipsychotics, diabetes mellitus, hypothalamic-pituitary-thyroid axis, metformin, thyroiditi

In light of recent research, it seems that metformin affects secretory function of pituitary cells, mainly of thyrotropes and lactotrophs. Metformin reduces elevated levels of thyrotropin, secondary to primary hypothyroidism[1–7] or resistance to thyroid hormone,[8] as well as decreases elevated prolactin levels induced by prolactin-secreting tumors, primary empty sella syndrome, traumatic brain injury, and antipsychotic drugs.[9–11] Metformin-induced changes in thyrotropin levels are not observed in patients with hyperthyroidism[12] and with normal thyrotropin levels.[1,2,13] In turn, the drug produces a neutral effect on circulating prolactin levels in patients with normal concentrations of this hormone.[9–11] These findings taken together suggest that metformin reduces the secretory function only of overactive, but not of normal, pituitary cells. Some studies indicate that the impact of metformin on pituitary cell function is in part associated with the changes in dopaminergic regulation of thyrotropin secretion.[1,2,14,15] This may explain why bromocriptine partially prevented the thyrotropin-lowering effect of metformin,[9] and why metformin-induced changes in serum levels of prolactin were more pronounced in patients receiving bromocriptine than cabergoline.[14] Moreover, dopamine plays a key role in the regulation of prolactin synthesis and secretion.[15,16] Sexual dimorphism in dopamine levels in pituitary stalk plasma and the rate of dopamine synthesis in the median eminence[17] and in the distribution of D_2/D_3 receptor binding in the pituitary[18] may explain why the effect of metformin on hypothalamic-pituitary-thyroid axis activity was stronger in women than in men with subclinical hypothyroidism,[19] whereas the effect on prolactin was more pronounced in women

Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland

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Corresponding Author:
Robert Krysiak, MD, PhD, Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Medyków 18, 40–752 Katowice, Poland
Email: r.krysiak@interia.pl

than in men with hyperprolactinemia (Krysiak et al, unpublished data).

Thyroid hypofunction is more common in older persons than in younger individuals, especially among women.[20] Unlike younger age groups, in the oldest population, subclinical hypothyroidism is not associated with a poor quality of life and any other adverse effects and may even favor a prolonged life span.[21] Therefore, subclinical hypothyroidism in this age group does not have to require levothyroxine treatment.[21] Elderly patients often require metformin therapy,[22] being the drug of choice not only in the treatment of type 2 diabetes,[23] but also of other insulin-resistance states.[24]

Taking into account the high prevalence and incidence of hypothyroidism[20] and type 2 diabetes[22] in elderly subjects, the common use of metformin[23,24] and antipsychotic drugs[25] in elderly patients, and no data concerning metformin action on thyrotropin and prolactin levels in this age group, the aim of our study was to compare the effect of metformin on hypothalamic-pituitary-thyroid axis activity in women treated with antipsychotic drugs and women not receiving these agents.

Methods

The study protocol was approved by our institutional review board (the Bioethical Committee of the Medical University of Silesia), and all women included in the study signed informed consent after careful explanation of the study procedures.

Patients

The participants in the study (n = 34) were recruited among elderly women (65–80 years old) with untreated subclinical hypothyroidism, defined as serum thyrotropin levels between 4.5 and 10.0 mU/L and free thyroid hormone levels within the reference range. Sixteen women had been receiving antipsychotic drugs for at least 6 months before the beginning of the study, whereas the remaining ones (n = 18) were antipsychotic drug–naive. To be included in the study, the participants were required to be diagnosed with type 2 diabetes (fasting plasma glucose at least 126 mg/dL and/or plasma glucose concentration 2 hours after a glucose load at least 200 mg/dL).

Exclusion criteria were: type 1 diabetes, glycated hemoglobin > 9%, acute coronary syndrome, stroke or cardiac surgery within 6 months preceding the study, New York Heart Association functional classes III and IV heart failure, elevated liver enzyme levels, serum creatinine > 2 mg/dL, and treatment with levothyroxine or other drugs known to affect hypothalamic-pituitary-thyroid axis activity or to interact with metformin or psychotropic agents.

Study Design

Metformin was administered at a starting dose of 500 μg once daily and gradually (over 2–4 weeks) titrated. The final dose (2.55–3 g/daily in 3 divided doses) was administered for the following 6 months. Throughout the entire study period, the participants complied with these dietary recommendations (the goals of which were a reduction in weight of 7% or more if necessary, total fat intake < 30% of total energy intake, saturated fat intake < 7% of energy consumed, cholesterol intake < 200 mg per day, an increase in fiber intake to 15 g per 1000 kcal, and moderate to vigorous exercise for at least 30 minutes per day). No changes in dosage of other drugs were allowed during this time. The investigation of possible drug-induced side effects was performed every 2 weeks. Compliance was assessed during each visit by tablet counts.

Laboratory Assays

Venous blood samples were drawn from the antecubital vein between 8:00 and 9:00 AM, at least 12 hours after the last meal, at the beginning of the study, and after 6 months of metformin treatment. Plasma lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides) and glucose and creatinine were measured with standard methods using commercial kits purchased from Roche Diagnostics (Basel, Switzerland). To avoid any error resulting from the Friedewald formula, LDL cholesterol was determined directly. Serum levels of thyrotropin, free thyroxine, free triiodothyronine, prolactin, and insulin were determined by direct chemiluminescence using acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Baseline glucose levels were also measured 2 hours after the oral ingestion of 75 g of glucose. All measurements were performed in duplicate, and final results were averaged. The homeostatic model assessment 1 of insulin resistance (HOMA1-IR) was calculated using the equation: HOMA1-IR = fasting insulin (mU/L) × fasting glucose (mg/dL)/405. The estimated glomerular filtration rate was calculated using the Modification Diet in Renal Disease Study equation.

Statistical Analyses

All statistical analyses were performed using the Statistica 12.0 PL software package (StatSoft Polska, Kraków, Poland). Values for HOMA1-IR, triglycerides, prolactin, thyrotropin, and thyroid hormones were natural log-transformed to meet the assumptions of parametric tests. Antipsychotic-treated and antipsychotic-naive patients were compared using the *t* test for independent samples. The Student paired *t* test was used to compare differences between the means of

Table 1. Baseline Characteristics of Patients[a]

Variable	Antipsychotic-Treated Women	Antipsychotic-Naive Women	Difference (95%CI)
Number of patients	14	16	
Age (years), mean (SD)	72 (5)	72 (4)	0 (−0.91 to 0.91)
Smokers (%)	14	19	
Body mass index (kg/m^2), mean (SD)	26.4 (3.5)	25.9 (2.8)	0.5 (−0.135 to 1.135)
Autoimmune hypothyroidism (%)	71	75	
Metformin dose (g daily), mean (SD)	2.70 (0.20)	2.68 (0.18)	0.02 (−1.81 to 5.81)
Fasting glucose (mg/dL), mean (SD)	140 (17)	137 (15)	3 (−0.21 to 6.21)
HOMA1-IR, mean (SD)	5.31 (0.72)	4.83 (0.61)	0.48 (0.3463–0.6137)[b]
Total cholesterol (mg/dL), mean (SD)	205 (19)	207 (21)	2 (−2.01 to 6.01)
LDL-cholesterol (mg/dL), mean (SD)	120 (15)	118 (14)	2 (−0.91 to 4.91)
HDL-cholesterol (mg/dL), mean (SD)	49 (6)	50 (5)	1 (−0.11 to 2.11)
Triglycerides (mg/dL), mean (SD)	174 (25)	170 (21)	4 (−0.63 to 8.63)
Thyrotropin (mIU/L), mean (SD)	7.34 (1.40)	7.50 (1.23)	0.15 (−0.104 to 0.424)
Free thyroxine (pmol/L), mean (SD)	12.84 (1.52)	13.00 (1.82)	0.16 (−0.2456 to 0.5656)
Free triiodothyronine (pmol/L), mean (SD)	3.02 (0.52)	3.10 (0.64)	0.1 (−0.011 to 0.211)
Prolactin (ng/mL), mean (SD), 10–25[a]	49 (10)[a]	14 (7)	35 (33.27–36.73)[b]
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean (SD)	85 (18)	88 (14)	3 (−0.23 to 6.23)

CI, confidence interval; HOMA1-IR, homeostatic model assessment 1 of insulin resistance ratio; SD, standard deviation.

[a]Only data of individuals who completed the study were included in the final analyses.

[b]Statistically significant difference between groups.

variables within the same treatment group. The clinical importance of the result was assessed on the basis of the 95% confidence interval. A t statistic and 2 sample means were used to generate an interval estimate of the difference between 2 population means. Group differences of nominal data were calculated by the χ^2 test. Associations were calculated using Pearson's correlation coefficient (r). The results were considered statistically significant if 95% confidence intervals did not include the null value and/or 2-tailed $P < .05$.

Results

At the beginning of the study, both groups were comparable with respect to age, body weight relative to height, medical background, and clinical characteristics. Prolactin levels and HOMA1-IR were higher in antipsychotic-treated than in antipsychotic-naive women (Table 1).

Two antipsychotic-treated women were withdrawn from the study: one owing to nausea, vomiting, and dysgeusia and one because of abdominal distension, headaches, and dizziness. Among antipsychotic-naive women, one dropped out because of loss of appetite and diarrhea, whereas another woman declined to participate further in the study. No adverse events were observed in the remaining women who completed the study protocol and were included in the final analyses.

In both groups of women, metformin reduced plasma levels of glucose and triglycerides, and decreased HOMA1-IR. Metformin did not affect the estimated glomerular filtration rate, HDL cholesterol levels, and total and LDL cholesterol levels. In both groups of women, metformin reduced serum levels of thyrotropin but did not change serum levels of free thyroxine and free triiodothyronine. In antipsychotic-treated women, but not in antipsychotic-naive women, the drug decreased serum levels of prolactin. The effect of metformin on serum levels of thyrotropin and prolactin was stronger in antipsychotic-treated than in antipsychotic-naive women. Posttreatment levels of thyrotropin were lower, whereas posttreatment prolactin levels were higher in antipsychotic-treated than in antipsychotic-naive women (Table 2). The drug did not change the body mass index.

At entry, serum thyrotropin levels correlated with serum prolactin levels and HOMA1-IR. The effect of metformin treatment on serum thyrotropin levels correlated with baseline thyrotropin levels, with baseline and treatment-induced changes in prolactin levels and baseline and treatment-induced changes in HOMA1-IR. In antipsychotic-treated women, baseline and treatment-induced changes in prolactin levels correlated with baseline and treatment-induced changes in HOMA1-IR. No other correlations between the investigated variables were observed in any group before and after metformin treatment (Table 3).

Discussion

In line with the results of the previous studies,[1–7] metformin decreased thyrotropin levels and produced a neutral effect on free thyroid hormone levels in elderly women with subclinical hypothyroidism. This effect correlated with baseline levels of thyrotropin, which indicates that the impact of metformin on thyrotrope secretory function depends on the degree of thyrotrope overactivity. The clinical significance of this

Table 2. Effect of Metformin on Glucose Homeostasis Markers and Thyroid Function Tests in Men and Women With Subclinical Hypothyroidism[a]

Variable	Antipsychotic-Treated Women	Antipsychotic-Naive Women	Difference (95%CI)
Fasting glucose (mg/dL),mean (SD)			
Baseline	140 (17)	137 (15)	3 (−0.21 to 6.21)
After 6 months	112 (11)[c]	110 (10)[c]	2 (−0.11 to 4.11)
Change	−28 (13)	−27 (12)	1 (−1.51 to 3.51)
HOMA1-IR, mean (SD)			
Baseline	5.31 (0.72)	4.83 (0.61)	0.48 (0.3463–0.6137)[b]
After 6 months	4.50 (0.82)[c]	4.11 (0.64)[c]	0.39 (0.2426–0.5374)[b]
Change	−0.81 (0.68)	−0.72 (0.64)	0.09 (−0.0423 to 0.2223)
Total cholesterol (mg/dL), mean (SD)			
Baseline	205 (19)	207 (21)	2 (−2.01 to 6.01)
After 6 months	200 (23)	201 (18)	1 (−3.14 to 5.14)
Change	−5 (8)	−6 (8)	1 (−0.6 to 2.6)
LDL-cholesterol (mg/dL), mean (SD)			
Baseline	120 (15)	118 (14)	2 (−0.91 to 4.91)
After 6 months	115 (13)	114 (16)	1 (−1.92 to 3.92)
Change	−5 (6)	−4 (4)	1 (−0.02 to 2.02)
HDL-cholesterol (mg/dL), mean (SD)			
Baseline	49 (6)	50 (5)	1 (−0.11 to 2.11)
After 6 months	53 (8)	54 (8)	1 (−0.6 to 2.6)
Change	4 (4)	4 (4)	0 (−0.8 to 0.8)
Triglycerides (mg/dL), mean (SD)			
Baseline	174 (25)	170 (21)	4 (−0.63 to 8.63)
After 6 months	149 (20)[c]	148 (18)[c]	1 (−2.81 to 4.81)
Change	−25 (18)	−22 (16)	3 (−0.41 to 6.41)
Thyrotropin (mIU/L), mean (SD)			
Baseline	7.34 (1.40)	7.50 (1.23)	0.15 (−0.104 to 0.424)
After 6 months	5.60 (1.12)[c]	6.41 (1.05)[c]	0.81 (0.5925–1.0275)[b]
Change	−1.74 (0.54)	−1.09 (0.62)	0.65 (0.5335–0.7665)[d]
Free thyroxine (pmol/L), mean (SD)			
Baseline	12.84 (1.52)	13.00 (1.82)	0.22 (−0.1159 to 0.5559)
After 6 months	13.46 (2.21)	13.54 (2.34)	0.08 (−0.376, 0.536)
Change	0.62 (0.43)	0.54 (0.44)	0.08 (−0.072 to 0.1672)
Free triiodothyronine (pmol/L), mean (SD)			
Baseline	3.02 (0.52)	3.10 (0.64)	0.08 (−0.0368 to 0.1968)
After 6 months	3.25 (0.60)	3.37 (0.71)	0.12 (−0.0117 to 0.2517)
Change	0.23 (0.48)	0.27 (0.35)	0.04 (−0.0442 to 0.1242)
Prolactin (ng/mL), mean (SD)			
Baseline	49 (10)	14 (7)	35 (33.27–36.73)[b]
After 6 months	38 (11)[c]	13 (7)	25 (23.15–26.85)[b]
Change	−11 (7)	−1 (6)	10 (8.69–11.31)[d]
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean (SD)			
Baseline	85 (18)	88 (14)	3 (−0.23 to 6.23)
After 6 months	83 (16)	86 (17)	3 (−0.31 to 6.31)
Change	−2 (6)	−2 (7)	0 (−1.31 to 1.31)

CI, confidence interval; HOMA1-IR, homeostatic model assessment 1 of insulin resistance ratio; SD, standard deviation.

[a]Only data of individuals who completed the study were included in the final analyses.

[b]Statistically significant difference between groups.

[c]Statistically significant difference between posttreatment and baseline values in the same group.

[d]Statistically significant difference in the effect of metformin between groups.

finding remains unclear and requires further investigation. A thyrotropin threshold for the initiation of levothyroxine treatment in the elderly population with mild thyroid failure has not been defined, and in each case, the potential benefits of lowering thyrotropin levels must be weighed against the risks associated with overtreatment.[26] Another interesting finding of our study was that the effect of metformin differed between antipsychotic-treated and antipsychotic-naive patients, being more pronounced in the first group of women. It seems that the effect of metformin on dopaminergic pathways in the central nervous system is opposite that of antipsychotic drugs. In women in whom obesity and impaired insulin sensitivity resulted from polycystic ovary syndrome, metformin administration enhanced the endogenous hypothalamic dopaminergic tone.[27] Almost all antipsychotic drugs have the ability to reduce dopaminergic transmission

Table 3. Correlations Between Assessed Variables

Correlated Variables		Antipsychotic-Treated Women	Antipsychotic-Naive Women
Baseline thyrotropin	Baseline prolactin	0.53[a]	0.40[a]
Baseline thyrotropin	Baseline HOMA1-IR	0.34[a]	0.26[a]
ΔThyrotropin	Baseline thyrotropin	0.47[a]	0.39[a]
ΔThyrotropin	Baseline prolactin	0.41[a]	0.34[a]
ΔThyrotropin	Baseline HOMA1-IR	0.25[a]	0.28[a]
ΔThyrotropin	ΔProlactin	0.42[a]	0.36[a]
ΔThyrotropin	ΔHOMA1-IR	0.35[a]	0.28[a]
Baseline prolactin	Baseline HOMA1-IR	0.38[a]	0.08
ΔProlactin	Baseline HOMA1-IR	0.23[a]	0.05
ΔProlactin	ΔHOMA1-IR	0.31[a]	0.02

HOMA1-IR, homeostatic model assessment 1 of insulin resistance ratio.
Data represent the correlation coefficients (*r* values) at baseline and during treatment (Δ).
[a]Statistically significant.

in the tuberoinfundibular pathway.[28] On the basis of these studies, we may assume that a stimulatory effect of metformin on thyrotrope secretory function is more prominent in women in whom this function is markedly diminished than if this function is intact or slightly impaired. Although we did not determine pituitary levels of dopamine, the presence of correlations between treatment-induced changes in thyrotropin levels and baseline and treatment-induced changes in serum prolactin indirectly supports this hypothesis. Basal production of pituitary prolactin is mainly controlled by tonic inhibitory mechanisms mediated by dopamine in the tuberoinfundibular pathway,[28] and therefore serum prolactin levels may be regarded as a marker of dopaminergic transmission in this pathway. The stronger effect of metformin on dopaminergic transmission in the tuberoinfundibular pathway in antipsychotic-treated women than in antipsychotic-naive women may explain why the drug affected prolactin levels only in the first group of patients.

Despite similar baseline levels of thyrotropin, both treatment groups differed in prolactin levels and insulin sensitivity. The presence of correlations between prolactin and HOMA1-IR in antipsychotic-treated women indicates that both biomarkers are reciprocally linked, and this finding is in line with chronic prolactin excess being frequently complicated by prediabetes, hyperinsulinemia, insulin resistance, weight gain, atherogenic dyslipidemia, and subclinical atherosclerosis.[29–34] That the thyrotropin-lowering effect of metformin depended on the degree of improvement in insulin sensitivity suggests its association with the metabolic effects of this agent. This finding may well be explained by an inhibitory effect of metformin on hypothalamic adenosine 5′-monophosphate-activated protein kinase,[35] an enzyme that plays a key role in cellular energy homeostasis.[36] The impact of metformin on its activity resembles the effect of triiodothyronine.[37] This similarity suggests that by affecting adenosine 5′-monophosphate-activated protein kinase, metformin may modify the feedback regulation of thyrotropin secretion by thyroid hormones.

Our study provides some new clinically relevant information concerning metformin use in the geriatric population. First, metformin is a safe and effective antidiabetic agent in elderly patients with mild thyroid hypofunction, and its impact on serum glucose and insulin sensitivity is not affected by concomitant treatment with antipsychotic drugs. Second, metformin seems to be an interesting alternative to levothyroxine in elderly women with glucose metabolism abnormalities and subclinical hypothyroidism, in whom levothyroxine treatment is poorly tolerated or contraindicated. The elderly population is particularly susceptible to the development of levothyroxine overtreatment-induced hyperthyroidism, adversely affecting cardiovascular and bone health.[38,39] The presence of correlations between the strength of the thyrotropin-lowering effect of metformin and baseline thyrotropin and our not observing any case of subnormal thyrotropin levels suggest that the risk of metformin-induced hyperthyroidism in geriatric patients is probably very low. The finding that metformin had a negligible effect on hypothalamic-pituitary-thyroid axis activity in patients with subclinical hyperthyroidism[12] and patients without glucose abnormalities[1,2,13] is in line with this view. Another argument justifying use in elderly women is the observation that metformin treatment results in a significant decrease in the size of benign thyroid nodules in insulin-resistant women.[40] It should be underlined that the geriatric population is characterized by the frequent occurrence of thyroid nodules.[39] Finally, metformin treatment may be particularly useful in elderly patients with thyroid hypofunction receiving antipsychotic drugs. Given the propensity of dopamine agonists to worsen psychotic symptoms, iatrogenic hyperprolactinemia in patients with psychiatric disorders should not be managed with these drugs.[41] In this population,

metformin both decreased circulating prolactin levels and produced the strongest thyrotropin-lowering effect.

Our study has several limitations worth noting. The major one is the small sample size that may have impacted the statistical significance of the quantitative findings. The study protocol did not allow us to answer the question of whether a similar effect on hypothalamic-pituitary-thyroid axis activity would be observed in patients with overt hypothyroidism who were not participants of the study. Because Poland is a country with a proper daily iodine intake,[42] it cannot be excluded that the effect of metformin on serum thyrotropin and free thyroid hormones may be different in iodine-deficient areas. Finally, we did not measure peripheral markers of thyroid hormone action.

Conclusions

In conclusion, although metformin reduced serum thyrotropin levels in both groups of elderly women, the impact of this drug was stronger in antipsychotic-treated than in antipsychotic-naive patients. The extent of reduction in serum thyrotropin levels depended on baseline thyrotropin and prolactin levels and correlated with treatment-induced changes in serum prolactin and HOMA1-IR. The obtained results indicate that metformin reduces thyrotropin in elderly patients partially by interacting with dopaminergic regulation of thyrotrope secretory function. Because of its limitations, our study should be regarded as a pilot one, and larger prospective studies including patients with and without thyroid dysfunction are needed to support our observations.

Declaration of Conflicting Interests

The authors declare no conflicts of interest.

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