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ORIGINAL ARTICLE

Thyroidal effect of metformin treatment in patients with polycystic ovary syndrome

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Summary

Objective Metformin is widely used for the treatment of type 2 diabetes. Growing evidence supports the beneficial effects of metformin also in patients with polycystic ovary syndrome (PCOS). It was recently reported that metformin has a TSH-lowering effect in hypothyroid patients with diabetes being treated with metformin.

Design Aim of this study was to evaluate the effect of metformin treatment on the thyroid hormone profile in patients with PCOS.

Patients and measurements Thirty-three patients with PCOS were specifically selected for being either treated with levothyroxine for a previous diagnosis of hypothyroidism ($n = 7$), untreated subclinically hypothyroid ($n = 2$) or euthyroid without levothyroxine treatment ($n = 24$) before the starting of metformin. The serum levels of TSH and FT_4 were measured before and after a 4-month period of metformin therapy.

Results Thyroid function parameters did not change after starting metformin therapy in euthyroid patients with PCOS. In the 9 hypothyroid patients with PCOS, the basal median serum levels of TSH (3·2 mIU/l, range = 0·4–7·1 mIU/l) significantly ($P < 0·05$) decreased after a 4-month course of metformin treatment (1·7 mIU/l, range = 0·5–5·2 mIU/l). No significant change in the serum levels of FT4 was observed in these patients. The TSH-lowering effect of metformin was not related to the administered dose of the drug, which was similar in euthyroid as compared with hypothyroid patients with PCOS (1406 ± 589 *vs* 1322 ± 402 mg/day, respectively; NS).

Conclusions These results indicate that metformin treatment has a TSH-lowering effect in hypothyroid patients with PCOS, both treated with L-thyroxine and untreated.

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Introduction

Metformin is a widely used drug for the treatment of type 2 diabetes. Metformin is commonly regarded as safe drug, because no clinically relevant pharmacologic interaction was described with most of the commonly used drugs, with the exception of folate and vitamin B12.[1–3] With specific regard to polycystic ovary syndrome (PCOS), metformin is not licensed for the treatment of this condition in any country to date.[4] Nevertheless, in the last few years, growing evidence supported beneficial effects of metformin in PCOS.[5,6] These studies prompted consensus statements and recommendations for the use of metformin in patients with PCOS.[7–10]

Despite the fact that metformin was introduced nearly 50 years ago in the clinical practice for the treatment of diabetes, only recently has this drug was reported to modify the thyroid hormone profile,[11–13] producing a significant decrease in the serum levels of TSH. Vigersky *et al.*[11] described four patients with primary hypothyroidism, being euthyroid on L-thyroxine (LT4), in whom the administration of metformin led to a significant fall in the serum levels of TSH. In these patients, the serum levels of FT4 were unchanged, and no clinical sign of thyrotoxicosis was observed. The effect of metformin was found to be reversible, because drug withdrawal was accompanied by a significant rise in serum TSH levels, which returned to the premetformin serum concentration.[11] More recently, it was demonstrated that the TSH-lowering effect of metformin is also observed in primary hypothyroid patients with diabetes and primary hypothyroidism, who are not treated with L-T4 replacement therapy.[13]

Despite the clinical relevance of these findings, the mechanisms by which metformin produces a TSH-lowering effect remain largely unknown. To further characterise the effect of metformin treatment on circulating thyroid function parameters, we investigated the impact of metformin treatment on the serum levels of

thyroid hormones and TSH in a cohort of patients with PCOS, both euthyroid or hypothyroid.

Patients and methods

Patients

The original study group included 35 patients with PCOS being treated with metformin. Among them, seven patients were specifically selected from the computerized database of our outpatient clinic for being hypothyroid on L-thyroxine substitution treatment. They were affected by chronic autoimmune thyroiditis, and their L-thyroxine substitution dose was stable since at least 6 months. Twenty-eight more patients with PCOS were consecutively recruited from our outpatient clinic. Two of them had subclinical hypothyroidism because of chronic autoimmune thyroiditis and were left untreated. The remaining 26 patients were euthyroid with no detectable thyroid disease. Two patients in this group were excluded from the study during the follow-up: one patient for lack of compliance to metformin treatment and the other one for having missed the scheduled visit plan. Thus, thirty-three patients (seven hypothyroid being treated with L-thyroxine, two untreated with subclinical hypothyroidism and 24 euthyroid) completed the study.

The diagnosis of PCOS was formulated according to the criteria established by the Rotterdam consensus workshop.[14] The mean (±SD) age of patients with PCOS was 25·9 ± 5·9 years, and their mean BMI was 30·7 ± 4·2 Kg/m^2. The mean daily dose of metformin in the whole study group was 1·383 ± 539 mg.

Body mass index (BMI) and serum FT_4, FT_3, TSH were evaluated before and 4 months after starting metformin treatment. Blood samples for assaying FT4, FT3 and TSH were drawn between 08:00 and 09:00 a.m., after an overnight fast. BMI was calculated as the weight (kg) divided by the square of height (m). All subjects gave their informed consent to be included into the study, which was performed in accordance with the guidelines proposed in the Declaration of Helsinki.

Serum assays

Serum concentrations of free triiodothyronine (FT3, normal range 3·7–7·2 pmol/l), free thyroxine (FT4, normal range 9·0–23·2 pmol/l) and thyroid-stimulating hormone (TSH, normal range 0·4–4·0 mIU/l) were measured using immune-chemiluminescent assays by an automated analyser (Immulite 2000; DPC Cirrus, Los Angeles, CA, USA) employing commercially available kits (all from Diagnostic Products Corporation, Los Angeles, CA, USA). In these assays, the intra-assay coefficient of variation ranged from 4·3% to 8·4% for FT3, from 5·2% to 7·5% for FT4 and from 5·1% to 12·5% to for TSH. The interassay coefficient of variation ranged from 5·4% to 10·0% for FT3, from 7·7% to 9·0% for FT4 and from 6·4% to 12·5% 6·4% for TSH. The analytical sensitivities were 1·54 pmol/l for FT3, 3·9 pmol/l for FT4 and 0·004 mIU/l for TSH (Third-generation TSH assay). Samples were assayed in duplicate. Quality control pools at low, normal and high concentrations for all parameters were present in each assay, respectively.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS, Inc., Evanston, IL, USA). All comparisons between groups were performed by Student's *t* test for unpaired data and Mann–Whitney *U* test according to the parametric or nonparametric distribution of data. Owing to the nonparametric distribution of the data, pretreatment and on-treatment results were compared by Wilcoxon test. A *P*-value <0·05 was considered statistically significant.

Results

When patients with PCOS were evaluated as a whole group, no significant change in the serum concentrations of FT4 and TSH was observed by comparing data found before and after the 4-month course of metformin treatment. However, when hormone data from euthyroid and hypothyroid (either treated or untreated with L-thyroxine) patients with PCOS were evaluated separately, a different picture emerged. In the twenty-four euthyroid patients with PCOS, the median serum levels of TSH before starting metformin were 1·4 mIU/l (range = 0·4–3·8 mIU/l) and did not significantly change after a 4-month course of metformin: 1·6 mIU/l (range = 0·4–3·7 mIU/l). Similarly, the median serum levels of FT4 did not significantly change being 15·9 pmol/l (range = 12·6–19·3 pmol/l) before starting metformin and 16 pmol/l (range = 14–19·3 pmol/l) after a 4-month course of the drug. In the nine hypothyroid patients with PCOS, either treated with L-thyroxine or untreated, the median pretreatment serum levels of TSH (3·2 mIU/l, range = 0·4–7·1 mIU/l) significantly decreased after a 4-month course of metformin (1·7 mIU/l, range = 0·5–5·2 mIU/l) ($P < 0·05$). The individual plots of serum TSH concentrations in the nine hypothyroid patients before and after metformin treatment are shown in Fig. 1. In these patients, no significant change in the median serum levels of FT4 before (15·9 pmol/l, range = 11·6–18·0 pmol/l) and after (15·9 pmol/l, range = 11·3–17·9 pmol/l) the 4-month course of metformin treatment was observed. None of our patient with PCOS and hypothyroidism experienced a suppressed TSH during metformin treatment.

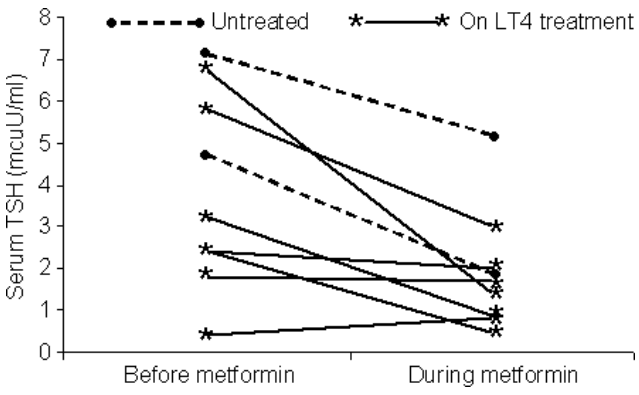

Fig. 1 Individual plots of serum TSH concentrations before and 4 months after starting metformin treatment in hypothyroid patients with polycystic ovary syndrome.

Clinical and anthropometric findings did not significantly differ when comparing the 24 euthyroid PCOS patients with the nine hypothyroid ones. In particular, no significant difference emerged regarding median age and in BMI. More interestingly, no significant difference as to the mean administered dose of metformin was found between the 24 euthyroid and the nine hypothyroid patients with PCOS (1322 ± 402 mg *vs* 1406 ± 589, respectively). During metformin treatment, no significant change in the mean BMI score was observed, both in the 24 euthyroid patients (pretreatment = 31·0 ± 4·2 Kg/m^2; posttreatment = 30·1 ± 3·7 Kg/m^2) and in the nine hypothyroid (pretreatment = 29·9 ± 4·6 Kg/m^2, posttreatment = 29·5 ± 4·4 Kg/m^2) patients with PCOS.

Discussion

Treatment with metformin in euthyroid patients with PCOS is not associated with significant changes in the serum levels of TSH and FT4. On the other hand, metformin treatment results in a significant reduction in serum TSH concentrations in hypothyroid patients with PCOS, independently from the concomitant substitution therapy with L-thyroxine.

Previous studies reported a significant fall in serum TSH concentrations and a slight, even if not significant, increase in serum FT4 values following initiation of metformin therapy in patients with diabetes and hypothyroidism either treated with L-thyroxine or untreated.[11–13] The mechanisms by which metformin would lead to a lowering of serum TSH levels are still debated. Several mechanisms have hypothesized for explaining this phenomenon: i) a change in the affinity or in the number of TSH receptors; ii) an increase in the central dopaminergic tone; or iii) a direct effect of metformin on TSH regulation. The design of the current study does not allow conclusions to be drawn in this regard, nevertheless the observation that metformin has a TSH-lowering effect also in patients with PCOS and hypothyroidism seems relevant. In particular, the observation that this TSH-lowering effect of metformin also occurs in untreated hypothyroid patients excludes that the effect is because of increased absorption of L-T4 in the gastrointestinal tract. Neither can the TSH-lowering effect be ascribed to the dose of metformin, which was similar in euthyroid as compared with hypothyroid patients with PCOS. Moreover, our findings in euthyroid patients with diabetes[13] and PCOS, and those reported by Oleandri *et al.*,[15] showing no change of serum thyroid hormones and TSH levels in euthyroid patients with abdominal obesity after 3 months of metformin therapy, would not be in line with the previously hypothesized direct effect of metformin on TSH regulation. Taken together, our results have not disclosed the precise mechanism by which metformin exerts its ''thyroid effect'', but provide further insights for future investigations.

The amelioration of thyroid function in PCOS patients with subclinical hypothyroidism following initiation of metformin treatment might also be viewed as an adjunctive mechanism by which metformin has beneficial effects in this condition. It is known that hypothyroidism may worsen PCOS by further decreasing the levels of sex hormone–binding globulin and by increasing the conversion of androstenedione to testosterone and its aromatization to oestradiol.[16,17] Thus, correction of hypothyroidism might be helpful for the management of PCOS. If future studies enrolling larger series of patients with PCOS will confirm our observation, a further step in our understanding of the beneficial effect of metformin in these patients might be performed.

In conclusion, the results of this study show that treatment with metformin in hypothyroid patients with PCOS leads to a significant decrease in the serum levels of TSH. No such effect is observed in euthyroid patients with PCOS. This observation seems of clinical relevance. Indeed, as stated by Haugen in his recent review, metformin may affect thyroid function tests and TSH levels in hypothyroid patients.[18] Thus, monitoring serum TSH and free T4 levels is recommended in patients taking both metformin and L-thyroxine. Our results extend the observations of the TSH-lowering effect of metformin, previously described only in hypothyroid patients with diabetes, also to hypothyroid patients with PCOS.

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