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Metformin Reduces Serum TSH Concentration in Patients with Diabetes

Cappelli C, Rotondi M, Pirola I, Agosti B, Formenti A, Zarra E, Valentini U, Leporati P, Chiovato L, Castellano M. Thyreotropin levels in diabetic patients on metformin treatment. Eur J Endocrinol 2012;167:261-5. Epub May 29, 2012.

SUMMARY

Background

Metformin therapy in patients with diabetes induces a significant lowering in serum TSH concentrations. The objective of this retrospective study was to evaluate changes in TSH concentrations in diabetic patients treated or not treated with metformin and/or L-T_4.

Methods

Three hundred thirty-nine patients with euthyroidism and diabetes were divided into three groups on the basis of metformin and/or L-T_4 treatment. Group (M–/L–): 119 patients never treated with metformin and L-T_4; group (M+/L–): 203 patients who started metformin treatment at recruitment; and group (M+/L+): 71 patients taking L-T_4 who started metformin at recruitment.

Results

The effect of metformin on serum TSH concentrations was analyzed in relation to the basal value of TSH (below 2.5 mIU/L [Group 1] or between 2.51 and 4.5 mIU/L [Group 2]]. In group M+/L+, the mean (±SD) TSH significantly decreased independently from the basal level (Group 1: from 1.45±0.53 to 1.01±1.12 mU/L; P = 0.037; Q2: from 3.60±0.53 to 1.91±0.89 mU/L; P<0.0001). In group M+/L–, the decrease in TSH was significant only in patients with a basal high-normal serum TSH (Group 2: from 3.24±0.51 to 2.27±1.28 mU/L' P = 0.004); in group M–/L–, no significant changes in TSH levels were observed.

In patients of group M+/L–, who showed high-normal basal TSH levels, a significant decrease in TSH was observed independently from the presence or absence of TPOAb (Q2 TPOAb+: from 3.38±0.48 to 1.87±1.08 mU/L; P<0.001; Q2 TPOAb–: from 3.21±0.52 to 2.34±1.31 mU/L; P<0.001).

Conclusions

These data strengthen the known TSH-lowering effect by metformin in patients with diabetes who are undergoing L-T_4 treatment and also show a significant reduction of TSH in euthyroid patients with higher baseline TSH levels independently from the presence of TPOAb.

ANALYSIS AND COMMENTARY

In our daily clinical practice, both hypothyroidism and diabetes mellitus are common diagnoses; metformin therapy is recommended as the first hypoglycemic pharmacologic agent when diabetes type 2 or prediabetes is diagnosed (1). Another indication for metformin is in the treatment of women with polycystic ovary syndrome (PCOS) (2). Type 2 diabetes may develop in patients who are known to have hypothyroidism while undergoing L-T_4therapy, or on the contrary, patients with diabetes mellitus who are undergoing metformin therapy could be diagnosed with hypothyroidism and prescribed L-T_4therapy. In the past few years, several clinical observations have consistently shown a lowering of serum TSH levels in patients with newly diagnosed hypothyroidism or undergoing L-T_4substitution therapy, following the administration of metformin (3,4). In one study, thyroid-function parameters did not change in euthyroid patients with PCOS after starting metformin therapy, but they decreased significantly in patients with hypothyroidism and PCOS after a 4-month course of metformin treatment, from the basal median serum

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levels of TSH (3.2 mIU/L [range, 0.4 to 7.1 mIU/L] to 1.7 mIU/L [range, 0.5 to 5.2 mIU/L]); as in other studies, no significant change in the serum levels of FT_4 was observed (5). In addition, the TSH-lowering effect of metformin was not related to the dose of the drug administered. The study by Cappelli et al. included three groups of patients with diabetes, confirming previous published observations of decreased serum TSH levels in patients with hypothyroidism who were undergoing L-T_4 treatment after metformin therapy; the two new interesting findings were that in patients with metformin-treated diabetes and who were not undergoing L-T_4 therapy, the decrease in TSH levels was significant only in the patients with a high-normal basal serum TSH (between 2.5 and 5 mIU/L)— from 3.24±0.51 to 2.27±1.28 mU/L (P = 0.004). In contrast, TSH significantly decreased independently from the basal level in patients undergoing L-T_4 therapy. The second finding of interest is that the effect of metformin appears to occur independently of the presence or absence of TPOAb.

At the moment, the mechanisms by which metformin would exert its TSH-lowering effect remain not fully elucidated. The two emerging hypothesis to explain the effect of metformin on TSH involves the action of metformin on 5′ adenosine monophosphate–activated protein kinase (AMPK) (6) and the central effect of metformin mediated by a reduction of circulating fatty acids (7).

What is the clinical impact of these observations on the care of our patients with diabetes and/or hypothyroidism? Since a vast majority of our patients with both disorders are at higher risk for other cardiovascular risk factors, a careful assessment of thyroid function to prevent the development of subclinical hyperthyroidism is highly recommended in patients with untreated subclinical hypothyroidism and in those undergoing L-T_4 therapy when metformin is added to their therapeutic regimen.

— Jorge H. Mestman, MD

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