TSH-LOWERING EFFECT OF METFORMIN IN TYPE 2 DIABETIC PATIENTS: DIFFERENCES BETWEEN EUTHYROID, UNTREATED HYPOTHYROID AND EUTHYROID ON L-T4 THERAPY PATIENTS

Running title: TSH-lowering effect of metformin

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Objective - To assess the interplay between metformin treatment and thyroid function in type 2 diabetes.

Research design and methods - Acute and long-term effects of metformin on thyroid axis hormones were assessed in diabetic patients with primary hypothyroidism, either treated or untreated with levothyroxine (L-T4), as well as in diabetic people with normal thyroid function.

Results - No acute changes were found in 11 patients with treated hypothyroidism. After one year of metformin administration, a significant TSH decrease (p<0.001) was observed in diabetic subjects with hypothyroidism, either treated (n=29; from 2.37±1.17 to 1.41±1.21 mIU/L) or untreated (n=18; 4.5±0.37 vs 2.93±1.48) with L-T4, but not in 54 euthyroid subjects. No significant change of FT4 was observed in any group.

Conclusions - Metformin administration influences TSH without change of FT4 in patients with type 2 diabetes and concomitant hypothyroidism. In these patients, a re-evaluation of thyroid function within 6-12 months after starting metformin is indicated.
Metformin is a widely used drug for the treatment of type 2 diabetes (1,2); it is commonly regarded as a safe drug in that no clinically relevant pharmacologic interactions have been described when it is prescribed together with the most commonly used drugs, with the exceptions of folate and B12 vitamin (3-5).

Recently it has been reported that metformin is able to interfere with thyroid hormone profile, as shown by a decrease of the serum levels of TSH to subnormal levels in hypothyroid patients in stable L-T4 treatment (6,7). However, no data are available in untreated hypothyroid patients or in euthyroid diabetic subjects.

Considering that both metformin treatment and hypothyroidism are frequent occurrences in diabetic patients (8), we aimed to further characterize the interplay between metformin consumption and circulating thyroid function parameters, by evaluating thyroid hormone axis in different categories of subjects who were started on metformin because of a first diagnosis of diabetes mellitus.

RESEARCH DESIGN AND METHODS
A pilot study was conducted in 11 diabetic hypothyroid patients who were on stable L-T4 substitution (average dose 89.8±11.5 µg/day), to examine short to mid-term (up to 24 weeks) effects of metformin administration. Serum TSH, free T4 (FT4), free T3 (FT3), total T4 (TT4) and total T3 (TT3) were measured at baseline and 6, 24 and 72 hours after starting metformin treatment, as well as after 3 and 6 months of therapy.

A second study was performed in a larger cohort of diabetic patients, including 29 patients who were euthyroid on L-T4 substitution (Group I), 18 patients in subclinical hypothyroidism who did not receive L-T4 treatment (Group II) and 54 patients in whom thyroid disorders had been excluded by a complete thyroid work-up, based on clinical history, physical examination, measurement of serum FT4, FT3, TSH, Tg-Ab, TPO-Ab, and thyroid ultrasonography (Group III). Type 2 diabetes mellitus was diagnosed in accordance with ADA criteria (9).

All subjects gave their informed consent to the study, which was performed in accordance with the guidelines proposed in the Declaration of Helsinki.

Statistical analysis: Between and within group comparisons were performed by an ANOVA general linear model including repeated measures analysis (SPSS version 13, SPSS Inc., Evanston, IL). A p-value <0.05 was considered statistically significant.

RESULTS
Pilot Study: No changes of FT4, FT3, TT4 and TT3 were observed throughout the study. Overall, a modest reduction of baseline TSH values (from 2.11±0.55 to 1.5±0.36 mIU/L,NS) was observed after 6 months of metformin treatment; however, one patient showed TSH reduction from 0.5 to 0.09 mIU/L and stable values of FT4 (from 13.3 to 12.9 pg/mL), FT3 (from 3.12 to 2.92 pg/mL), TT4 (from 10.7 to 10.2 ug/dL) and TT3 (from 1.07 to 1.04 ng/mL). Withdrawal of metformin in this patient lead to an increase of TSH level, which returned to baseline (pre-metformin) level within three months.

Long-Term Study: Clinical characteristics and most relevant data in the three groups of patients are summarized in Table 1. A significant decrease of TSH levels after one year of metformin treatment was observed in Group I and Group II subjects, but not in Group III. In detail, mean level of TSH was significantly reduced after one year on metformin in Group I, from 2.37±1.17 mIU/L at baseline to 1.41±1.21 mIU/L (p<0.001). Furthermore, 6 patients in this group (20.7%) showed a lower than normal serum TSH level one year after starting metformin.
Mean basal level of TSH in patients of Group II was 4.5±0.37 mIU/L and significantly decreased to 2.93±1.48 mIU/L after one year of metformin, (p<0.001); TSH reduction never reached subnormal levels in individual patients of this Group. Serum FT4 levels did not significantly change while on metformin treatment in any group (Table 1).

CONCLUSIONS
The results of this study showed that: i) the initiation of treatment with metformin was associated with a significant reduction in the serum levels of TSH, in diabetic patients with primary hypothyroidism, both under L-T4 replacement therapy and untreated; ii) TSH reduction was not associated with reciprocal changes in any other thyroid function parameter; iii) the TSH-lowering effect of metformin developed slowly and was detectable after a few months of treatment; iv) metformin had no effect on circulating thyroid function parameters in euthyroid diabetic patients.

These data indicate that the thyroidal repercussion of metformin administration in diabetic patients may be dual: while no effect is detectable in patients with a normal pituitary-thyroid-axis, significant changes do occur in patients with an underlying thyroid deficiency, both under L-T4 therapy or untreated. This is a clinically relevant observation, especially when considering that hypothyroidism occurs in 10-15% of type 2 diabetic patients (8) and many of them are presumably also treated with metformin.

The mechanism(s) by which metformin lowers TSH level is still unclear and the design of the present study does not allow drawing causal inferences. However, the present data would exclude biological interferences of metformin with the TSH assay, increased L-T4 absorption from the gastrointestinal tract or any influence of changes in body weight associated to metformin treatment. We hypothesize that metformin may enhance the inhibitory modulation of thyroid hormones on central TSH secretion; such an effect would not modify circulating FT3 or TSH levels when the closed-loop control system is normally functioning, but may well explain the reduction of circulating TSH levels observed in subjects with altered thyroid-hypophyseal feedback. Another explanatory hypothesis could be that metformin ameliorate the thyroid function reserve in those patients with hypothyroidism both treated and untreated. Future studies will be needed to fully elucidate the mechanisms of the here described TSH-lowering effect of metformin.

In conclusion, the results of this study show that metformin administration in diabetic patients with hypothyroidism, both under L-T4 therapy and untreated, is associated with a significant reduction in the serum levels of TSH, with no change of FT4. No effect is detectable in patients with an intact pituitary-thyroid axis. A major clinically relevant consequence of our findings is that a re-evaluation of thyroid function within 6-12 months after starting metformin seems necessary in diabetic patients with concomitant hypothyroidism.

Disclosure: The Authors have no relevant conflict of interest to disclose.
REFERENCES:

Table 1: Demographic, drug treatment and thyroid function data in the three groups of diabetic subjects

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI baseline</strong></td>
<td>32.8 ( 5.6)</td>
<td>31.2 ( 4.9)</td>
<td>33.0 ( 4.9)</td>
</tr>
<tr>
<td><strong>BMI after 12 months on metformin</strong></td>
<td>32.1( 5.7)</td>
<td>30.7( 4.9)</td>
<td>32.7( 4.9)</td>
</tr>
<tr>
<td><strong>TSH baseline (mIU/L)</strong></td>
<td>2.37 ± 1.17</td>
<td>4.52 ± 0.37**</td>
<td>2.74 ± 0.82</td>
</tr>
<tr>
<td><strong>TSH after 12 months on metformin (mIU/L)</strong></td>
<td>1.41 ± 1.21***</td>
<td>2.93±0.48***</td>
<td>2.56 ± 1.16</td>
</tr>
<tr>
<td><strong>FT4 baseline (pg/ml)</strong></td>
<td>12.49 ± 2.09</td>
<td>12.51 ± 2.05</td>
<td>12.82 ± 1.90</td>
</tr>
<tr>
<td><strong>FT4 after 12 months on metformin (pg/ml)</strong></td>
<td>12.63 ± 2.72</td>
<td>12.25 ± 1.82</td>
<td>13.09 ± 2.23</td>
</tr>
</tbody>
</table>

Non categorical values are given as mean±SD. Between-group differences: *p<0.05 vs.Group II and Group III; **p<0.001 vs.Group I and Group III. Within-group differences: ***p<0.001 on-treatment vs baseline.