

# TSH-Lowering Effect of Metformin in Type 2 Diabetic Patients

Differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients

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## RESEARCH DESIGN AND

**METHODS** — A pilot study was conducted with 11 diabetic hypothyroid patients who were on stable L-T4 substitution (average dose  $89.8 \pm 11.5 \mu\text{g/day}$ ) to examine the 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 h 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 euthyroid patients on L-T4 substitution (group I), 18 subclinical hypothyroid patients who did not receive L-T4 treatment (group II), and 54 euthyroid patients in whom thyroid disorders had been excluded by a complete thyroid workup based on clinical history, physical examination, measurement of serum FT4, FT3, TSH, Tg-Ab, and TPO-Ab, as well as thyroid ultrasonography (group III). Type 2 diabetes was diagnosed in accordance with American Diabetes Association criteria (9).

All subjects gave their informed consent to the study, which was performed in accordance with 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, Evanston, IL). A  $P$  value  $<0.05$  was considered statistically significant.

## RESULTS

### Pilot study

There were no changes of FT4, FT3, TT4, and TT3 observed throughout the study. Overall, a modest reduction of baseline TSH values (from  $2.11 \pm 0.55$  to  $1.5 \pm 0.36$  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

**OBJECTIVE** — To assess the interplay between metformin treatment and thyroid function in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — The acute and long-term effects of metformin on thyroid axis hormones were assessed in diabetic patients with primary hypothyroidism who were either untreated or treated with levothyroxine (L-T4), as well as in diabetic patients with normal thyroid function.

**RESULTS** — No acute changes were found in 11 patients with treated hypothyroidism. After 1 year of metformin administration, a significant thyrotropin (TSH) decrease ( $P < 0.001$ ) was observed in diabetic subjects with hypothyroidism who were either treated ( $n = 29$ ; from  $2.37 \pm 1.17$  to  $1.41 \pm 1.21$  mIU/l) or untreated ( $n = 18$ ;  $4.5 \pm 0.37$  vs.  $2.93 \pm 1.48$ ) with L-T4, but not in 54 euthyroid subjects. No significant change in free T4 (FT4) was observed in any group.

**CONCLUSIONS** — Metformin administration influences TSH without change of FT4 in patients with type 2 diabetes and concomitant hypothyroidism. The need for reevaluation of thyroid function in these patients within 6–12 months after starting metformin is indicated.

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**M**etformin 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 in the serum levels of thyrotropin (TSH) to subnormal levels in hypothyroid patients in sta-

ble levothyroxine (L-T4) treatment (6,7). However, no data are available for untreated hypothyroid patients or for euthyroid diabetic patients.

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

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

	Group I	Group II	Group III
BMI (kg/m <sup>2</sup> )			
Baseline	32.8 ± 5.6	31.2 ± 4.9	33.0 ± 4.9
After 12 months on metformin	32.1 ± 5.7	30.7 ± 4.9	32.7 ± 4.7
TSH (mIU/l)			
Baseline	2.37 ± 1.17	4.52 ± 0.37*	2.74 ± 0.82
After 12 months on metformin	1.41 ± 1.21†	2.93 ± 0.48†	2.56 ± 1.16
FT4 (pg/ml)			
Baseline	12.49 ± 2.09	12.51 ± 2.05	12.82 ± 1.90
After 12 months on metformin	12.63 ± 2.72	12.25 ± 1.82	13.09 ± 2.23

Noncategorical data are means ± SD. Between-group differences: \* $P < 0.001$  for group I vs. group III. Within-group differences: † $P < 0.001$  for on treatment vs. baseline.

10.7 to 10.2  $\mu\text{g/dl}$ ), and TT3 (from 1.07 to 1.04 ng/ml). Withdrawal of metformin in this patient led to an increase of TSH level, which returned to the baseline (pre-metformin) level within 3 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 1 year of metformin treatment was observed in group I and group II subjects but not in group III subjects. In detail, mean TSH level was significantly reduced after 1 year on metformin in group I, from  $2.37 \pm 1.17$  mIU/l at baseline to  $1.41 \pm 1.21$  ( $P < 0.001$ ). Furthermore, six patients in this group (20.7%) showed a serum TSH level lower than normal 1 year after starting metformin.

Mean basal TSH level in patients of group II was  $4.5 \pm 0.37$  mIU/l and significantly decreased to  $2.93 \pm 1.48$  after 1 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 during metformin treatments in any group (Table 1).

**CONCLUSIONS**— The results of this study showed that 1) 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 with L-T4 replacement therapy and untreated; 2) TSH reduction was not associated with reciprocal changes in any other thyroid function parameter; 3) the TSH-lowering effect of metformin developed slowly and was detectable after a few months of treatment; and 4) metformin had no effect on circulating thyroid func-

tion parameters in euthyroid diabetic patients.

These data indicate that the thyroidal repercussion of metformin administration in diabetic patients may be dual: Although no effect is detectable in patients with a normal pituitary-thyroidaxis, significant changes do occur in patients with an underlying thyroid deficiency, both with L-T4 therapy and 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 with 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 ameliorates 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 di-

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

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