Rapid Changes in Serum Testosterone in Men With Newly Diagnosed Type 2 Diabetes With Intensive Insulin and Metformin

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OBJECTIVE

To investigate the effect of metformin on testosterone levels in men with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

Seventy men with newly diagnosed drug-naive T2DM and HbA_{1c} >9.0% (75 mmol/mol) were treated with intensive insulin pump therapy for 5 days to achieve glucose normalization. They were randomized to control (continued on intensive insulin only) and metformin (plus metformin) groups (1:1) for 1 month. Testosterone was measured at baseline, randomization, and after 1-month treatment.

RESULTS

Total, free, and bioavailable testosterone increased significantly within 5 days (all $P < 0.001$). After 1 month, compared with the control group, the metformin group had lower total (12.7 vs. 15.3 nmol/L), free (0.20 vs. 0.24 nmol/L), and bioavailable (4.56 vs. 5.31 nmol/L) testosterone (all $P < 0.05$).

CONCLUSIONS

In men with T2DM, 1-month oral metformin may decrease serum testosterone levels independent of blood glucose control. The effects of long-term metformin on testosterone in men need further study.

Metformin is the most commonly prescribed oral medication in type 2 diabetes mellitus (T2DM). It is inexpensive and effective and may have additional benefits in cancer (1), cardiovascular disease, and other conditions (2).

Low testosterone levels are common in men with T2DM (3). They have been attributed to greater insulin resistance (4) and are associated with higher mortality rates (5). The mechanism remains unclear (6). We previously reported that testosterone levels were significantly lower in men with T2DM using metformin than in men not using metformin in a cross-sectional study (7).

In the current study, we performed a randomized controlled trial in men with newly diagnosed T2DM. While following recommended guidelines in China, treatment was initiated with intensive insulin pump therapy (8). We then compared the effect of the addition of metformin on serum testosterone during 1 month of further intensive insulin therapy. This short duration allowed the assessment of the effect of metformin before significant changes in weight and other factors that might affect blood testosterone.

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RESEARCH DESIGN AND METHODS

We recruited men with newly diagnosed drug-naive T2DM aged 18–60 years with an HbA_{1c} >9.0% (75 mmol/mol) (8). We excluded patients on treatment with lipid-lowering or antihypertensive medications or with any condition affecting testosterone levels.

All patients received insulin pump treatment as inpatients until the blood glucose normalized (premeal 3.9–7.0 mmol/L, postprandial 3.9–10.0 mmol/L, >80% of values within the range), usually within 3–5 days. The patients were then randomized into control (insulin only) and metformin (insulin + metformin) groups and continued on intensive insulin therapy for 1 month (Supplementary Fig. 1). The original protocol was designed with three groups: control, metformin, and dapagliflozin. Because of funding reasons, the dapagliflozin arm was stopped very soon after recruitment began. Metformin (Merck Serono) was started at 1,500 mg daily. Patients were discharged and seen as outpatients every 3 days to adjust the insulin dose according to the preceding day's 6-point self-monitoring of blood glucose values to maintain near-normal blood glucose. If gastrointestinal symptoms were present, metformin dosage was reduced to 1,000 mg/day and further reduced if symptoms persisted. Patients with a final dose of metformin <500 mg daily or who did not meet the criteria for three consecutive normal range self-monitoring of blood glucose records were withdrawn.

Weight, HbA_{1c}, blood lipids, fasting blood glucose, C-peptide, total testosterone (TT), and sex hormone binding globulin were measured at baseline, randomization, and 30 ± 2 days after randomization (study end). The International Index of Erectile Function (IIEF-5) questionnaire was assessed at baseline and study end. Free testosterone (FT) and bioavailable testosterone (Bio-T) (9) were calculated.

Differences between the groups were examined using the Student unpaired *t* test or the Mann-Whitney *U* test. The data before and after treatment were analyzed by Student paired *t* test or Wilcoxon test. Categorical data were examined with χ^2 test.

RESULTS

Seventy patients completed the study, with 35 in the control group and 35 in the metformin group. Baseline characteristics were similar between the groups (Supplementary Table 1). Serum testosterone increased significantly after 5 days of intensive insulin therapy in all the patients (baseline vs. randomization: TT 12.07 ± 4.68 vs. 15.35 ± 5.97 nmol/L, FT 0.19 ± 0.08 vs. 0.24 ± 0.10 nmol/L, Bio-T 4.51 ± 1.34 vs. 5.39 ± 1.68 nmol/L, all $P <$ 0.001) and each group (Fig. 1 and Supplementary Table 2).

TT, FT, and Bio-T levels significantly decreased after 1 month only in the metformin group compared with the control group ($P < 0.05$) (Fig. 1*A–C*), and metformin caused superior reductions in TT, FT, and Bio-T versus the control condition (estimated treatment differences: −2.29 [95% CI −4.10, −0.48], −0.04 [−0.08, −0.01], and −0.73 [−1.31, −0.15] nmol/L, $P =$ 0.014, 0.012, and 0.014, respectively) (Supplementary Table 3). TT values calculated for individual patients as a percentage change from baseline also decreased in the metformin group compared with the control group (−27.4% [95% CI −47.2, −7.6], $P = 0.007$) (Fig. 1*D*).

After adjustment for age, blood lipids, body weight, HOMA2 of insulin resistance, daily metformin, and insulin dose at the end point, only the daily metformin dose had a statistically significant correlation with Δ TT in the stepwise linear regression ($\beta = 0.300$, $P =$ 0.029). The numbers of patients with testosterone "insufficiency" (TT < 12 nmol/L [346 ng/dL]) (10) decreased after blood glucose normalization compared with baseline in both groups (both $P <$ 0.05) (Supplementary Table 2) and were higher in the metformin group than in the control group (57.14 vs. 28.57%, $P =$ 0.029) at the end point. The change of IIEF-5 scores did not differ between the two groups ($Z = -0.366$, $P = 0.715$), despite the changes in testosterone.

CONCLUSIONS

We have demonstrated that 5 days of intensive insulin therapy and normalization of blood glucose increases testosterone significantly in men with newly diagnosed T2DM. We have also shown for the first time in a randomized controlled study that a further 1 month of metformin treatment decreases testosterone significantly in men with T2DM.

This effect of metformin should not be totally unexpected because metformin treatment is associated with lower testosterone concentrations in women with polycystic ovary syndrome (11), despite their lower baseline levels. Studies in men were surprisingly uncommon. We found only one previous study that showed higher semen volume, higher sperm counts, and higher (but not statistically significant) serum testosterone in men with type 1 diabetes on insulin only compared with men with T2DM treated with metformin (12). Other

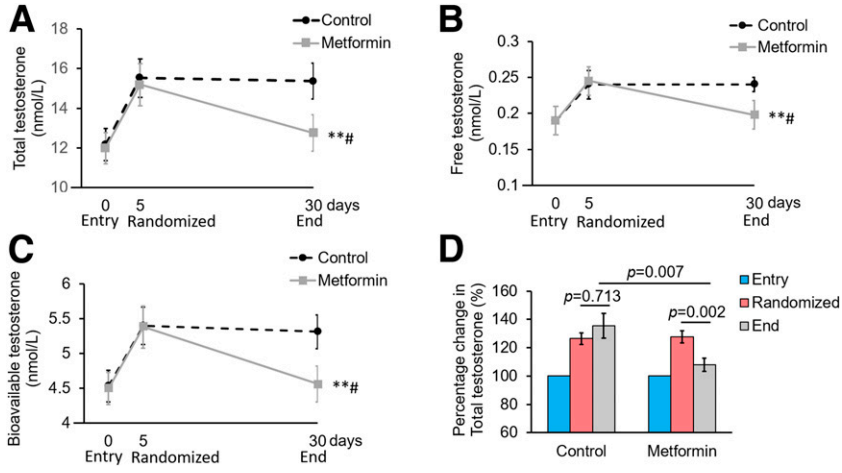

Figure 1—*A–C*: TT, FT, and Bio-T levels at baseline (preinsulin therapy), randomization when blood glucose normalized after 5 days of intensive insulin, and the end point after 1-month therapy with intensive insulin with or without metformin. *D*: Baseline testosterone concentrations calculated individually and expressed as 100%, with the percentage change of TT at randomization and after 1 month of treatment with or without metformin. Data are mean ± SE. $**P <$ 0.001, randomization vs. end point; $\#P <$ 0.05, metformin group vs. control group.

previous studies that we are aware of on the effect of metformin on testosterone in men were confounded by changes in blood glucose and body weight (13,14). These studies concluded that metformin increased serum testosterone and attributed this to the improvement in blood glucose control and weight loss.

Poor diabetes control can lead to low testosterone levels and male sexual dysfunction (10). Our results demonstrate for the first time that the blood glucose normalization with intensive insulin treatment was able to increase blood testosterone even within a short period of 5 days. Our study demonstrates that the effect of metformin on testosterone may be independent of blood glucose and weight change because both groups did not differ in blood glucose control and body weight before and after therapy (Supplementary Table 1).

Our 1-month study has some limitations. The longer-term effect of metformin on testosterone and sexual function remains uncertain. In most parts of the world, intensive insulin is not recommended or used as initial treatment for newly diagnosed diabetes, and thus the rapid initial improvement and its subsequent decrease in testosterone with metformin may not be easily discernable or distinguishable from other effects of metformin on weight and insulin resistance. We did not measure luteinizing hormone/follicle-stimulating hormone to determine whether any subjects had secondary hypogonadism, and we lacked a placebo control; these may influence subjective IIEF-5 scores, although none of the investigators were aware of the testosterone values.

Our preliminary results suggest that the long-term effect of metformin should be investigated, with a placebo control, to determine whether measurement of testosterone concentrations may be useful in men on metformin. We are reminded of the reports on lower vitamin B12 levels in patients on long-term metformin, which are now accepted and therefore monitored (15).

In conclusion, intensive insulin therapy can increase testosterone levels rapidly. With 1-month near normalization of blood glucose, metformin may reduce circulating testosterone levels significantly. The long-term effect of metformin treatment on testosterone needs further study.

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