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WILEY

**BRIEF REPORT**

# Metformin and β-cell function in insulin-treated patients with type 2 diabetes: A randomized placebo-controlled 4.3-year trial

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In this trial, 390 insulin-treated patients with type 2 diabetes were randomized to either placebo or metformin. Fasting levels of glucose, insulin and C peptide were determined at baseline, after 4 months and yearly thereafter for 4 years to assess fasting estimates of beta cell function. The primary endpoint was the fasting C peptide-to-glucose ratio (FCPGR) and secondary measures were the disposition index (DI) and the fasting C peptide (FCP). We analysed the results with a general linear mixed model. Baseline FCPGR was 5.27 (95% CI, 4.83 – 5.71). Compared to placebo, FCPGR increased in the metformin group with 1.48 (95% CI, 1.09 – 1.87, $P < 0.001$). The DI showed comparable results with a treatment effect of 1.50 (95% CI, 1.17 – 1.83; $P < 0.001$). FCP also increased in the metformin group but did not reach statistical significance vs placebo (0.034 nmol, 95% CI, −0.005 – 0.072; $P = 0.085$). Treatment with metformin vs placebo, added to insulin in patients with type 2 diabetes, improves long-term estimates of beta cell function in the fasting state.

**KEYWORDS**

beta cell function, HOME study, metformin, RCT, type 2 diabetes

## 1 | INTRODUCTION

Metformin is a key drug in the treatment of type 2 diabetes. In the Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) study,[1] we showed that metformin improved glycaemic control and decreased insulin requirements compared with placebo in insulin-treated patients with advanced type 2 diabetes. In this respect, metformin is generally regarded as an insulin sensitizer. Whether metformin can also improve β-cell function is not clear. In the present analysis of the HOME study, we studied the effects of metformin vs placebo on estimates of fasting β-cell function. In addition, we quantified the durability of metformin's effect on these estimates over a period of 4.3 years.

## 2 | METHODS

### 2.1 | Study design and patients

In the HOME study, 390 insulin-treated patients with advanced type 2 diabetes were randomly allocated to either metformin 850 mg (up to 3 times daily if tolerated) or matching identical-looking placebo through a computer program. Most patients (n = 345) were already using monotherapy insulin, either twice-daily premixed NPH/regular insulin (Novomix) or NPH insulin in the evening combined with prandial regular insulin. The remaining 45 patients used a combination of metformin and insulin, and discontinued metformin 3 months before randomization.

All participants provided written informed consent and the study was approved by the medical ethics committees of the 3 participating non-academic hospitals. Study visits took place at baseline and at 1 month, and 3-monthly thereafter, with a follow up of 4.3 years.

## 2.2 | Measures

Blood samples for this analysis of the HOME trial were drawn at baseline and after 4, 17, 30, 43 and 52 months, and were stored at $-80°C$ until analysis. C-peptide plasma samples were available for 363 patients at baseline and at ≥1 follow-up visit(s) (93%), and for 259 patients at their final visit (66%), and were taken using a solid-phase, chemiluminescent enzyme immunoassay (Immulite 2000; Siemens, Camberley, UK). Serum insulin was measured by electrochemiluminescence immunoassay (Modular E170; Roche Diagnostics, Basel, Switzerland). Coefficients of variation are provided in Appendix S1. Because patients used human basal insulin (Insulatard; Novo Nordisk, Bagsværd, Denmark) there was full cross-reactivity between endogenous insulin and exogenous insulin in this assay.

The primary estimate of β-cell function was fasting C-peptide (FCP)-to-fasting plasma glucose (FPG) ratio. To normalize our ratio based on SI units, we used an arbitrary constant of 100 for convenience, resulting in the unitless formula FCP:FPG ratio = $100 \times$ FCP/FPG. As secondary measures we used FCP and the disposition index (DI), defined as the FCP:FPG ratio adjusted for insulin sensitivity (IS), resulting in the unitless formula DI = FCP:FPG ratio $\times IS^{0.2}$. IS was calculated from FPG and FPI using the unitless formula IS = 1000/FPG $\times$ FPI. (For further details see Appendix S1.)

## 2.3 | Statistical analysis

We used all measurements to assess the effects of metformin vs placebo during the entire follow-up period. To quantify the overall treatment effect over time, we used a linear mixed model, simultaneously assessing the significance of the main time effect, main metformin treatment effect, and interaction of metformin treatment effect with time (Appendix S1).

In addition, we conducted a mediation analysis to assess the indirect (mediating) effect of glycated haemoglobin (HbA1c) in the change of FCP:FPG ratio. For this purpose, we added HbA1c as a covariate in the model, and evaluated the mediating HbA1c effect by the product of the effects (metformin → HbA1c) and (HbA1c → FCP:FPG ratio) and confidence interval (CI), calculated by bootstrapping (details in Appendix S1).

## 3 | RESULTS

Figure 1A–C show the time course of HbA1c, β-cell function and IS during all visits. Table 1 shows the results of the mixed linear model in which, for each variable, the baseline value, time effect, treatment effect and time–treatment interaction are shown. Treatment effect in the model is defined as the constant post-baseline change in the metformin group vs placebo, expressed as an absolute change. In addition, this change is described as a relative change compared with baseline.

Compared with the placebo group, the FCP:FPG ratio increased in the metformin group. Mixed-model results showed a constant treatment effect from the first post-baseline visit until the end of the trial of 1.48 (95% CI, 1.09 to 1.87; $P < .001$), no change in time (0.00/year, 95% CI, −0.001 to +0.001; $P = .92$) and no time–treatment interaction (−0.010/year, 95% CI, −0.021 to 0.001; $P = .058$). Relative to baseline, the treatment effect was 28% (95% CI, 23 to 33).

The DI results were similar to those observed with the FCP:FPG ratio: a small decrease in the placebo group and an increase in the metformin group. Mixed-model results confirmed a significant decrease in time of −0.01/year (95% CI, −0.01 to −0.001; $P = .023$) for the placebo group, a constant treatment effect during the whole post baseline period of 1.50 (95% CI, 1.17 to 1.83; $P < .001$), and no time-treatment interaction (−0.01 [95% CI, −0.02 to 0.00]; $P = .128$). Relative to baseline, the treatment effect was 32% (95% CI, 27 to 36).

The FCP level decreased in the placebo group and increased in the metformin group. Mixed-model results showed a non-significant treatment effect (0.034 nmol [95% CI, −0.005 to 0.072; $P = .085$], no time effect (0.00 nmol/L/year [95% CI, −0.00 to 0.00]; $P = .61$), and no time–treatment interaction (0.00 nmol/L/year, 95% CI, −0.00 to 0.00; $P = .26$). Relative to baseline, the treatment effect was 7% (95% CI, −1 to 14).

The HbA1c level increased in the placebo group and decreased in the metformin group. Mixed-model results confirmed a significant change in time of 0.07%/year in the placebo group (95% CI, 0.04 to 0.10; $P < .001$), a treatment effect of −0.93% (95% CI, −1.06 to −0.80; $P < .001$) from the first post-baseline visit until the end of the trial, and a time–treatment interaction of 0.011%/year (95% CI, 0.008 to 0.015; $P < .001$).

We assessed the indirect (mediating) effect of HbA1c in FCP:FPG ratio improvement by adding HbA1c as a covariate in the model. In comparison with the initial model, the mediating effect of HbA1c (metformin → HbA1c → FCP:FPG ratio) on the overall effect (metformin → FCP:FPG ratio) was small (0.53 [95% CI, 0.45 to 0.73]), accounting for a small proportion of the variance (36.1% [95% CI, 25.4 to 49.5]).

There was an increase in IS in the metformin group and a decrease in the placebo group. Mixed-model results showed a treatment effect of 0.33 (95% CI, 0.03 to 0.63; $P = .031$), no significant change in time for the placebo group (0.00/year, 95% CI, −0.00 to 0.01; $P = .69$), and no time–treatment interaction (−0.00/year [95% CI, −0.01 to 0.01]; $P = .612$). Relative to baseline, the treatment effect was 36% (95% CI, 3 to 69).

## 4 | DISCUSSION

The present study shows that metformin added to insulin improves fasting based estimates of β-cell function durably in comparison with placebo. These effects were for the most part (64%) independent of changes in glycaemic control. Additionally adjusting for IS, by calculating the DI, did not alter the results.

Depending on the estimate used, the increase in β-cell function was 28% (95% CI, 23 to 33) for FCP:FPG ratio and 32% (95% CI, 27 to 36) for DI. IS, assessed by a homeostatic model assessment
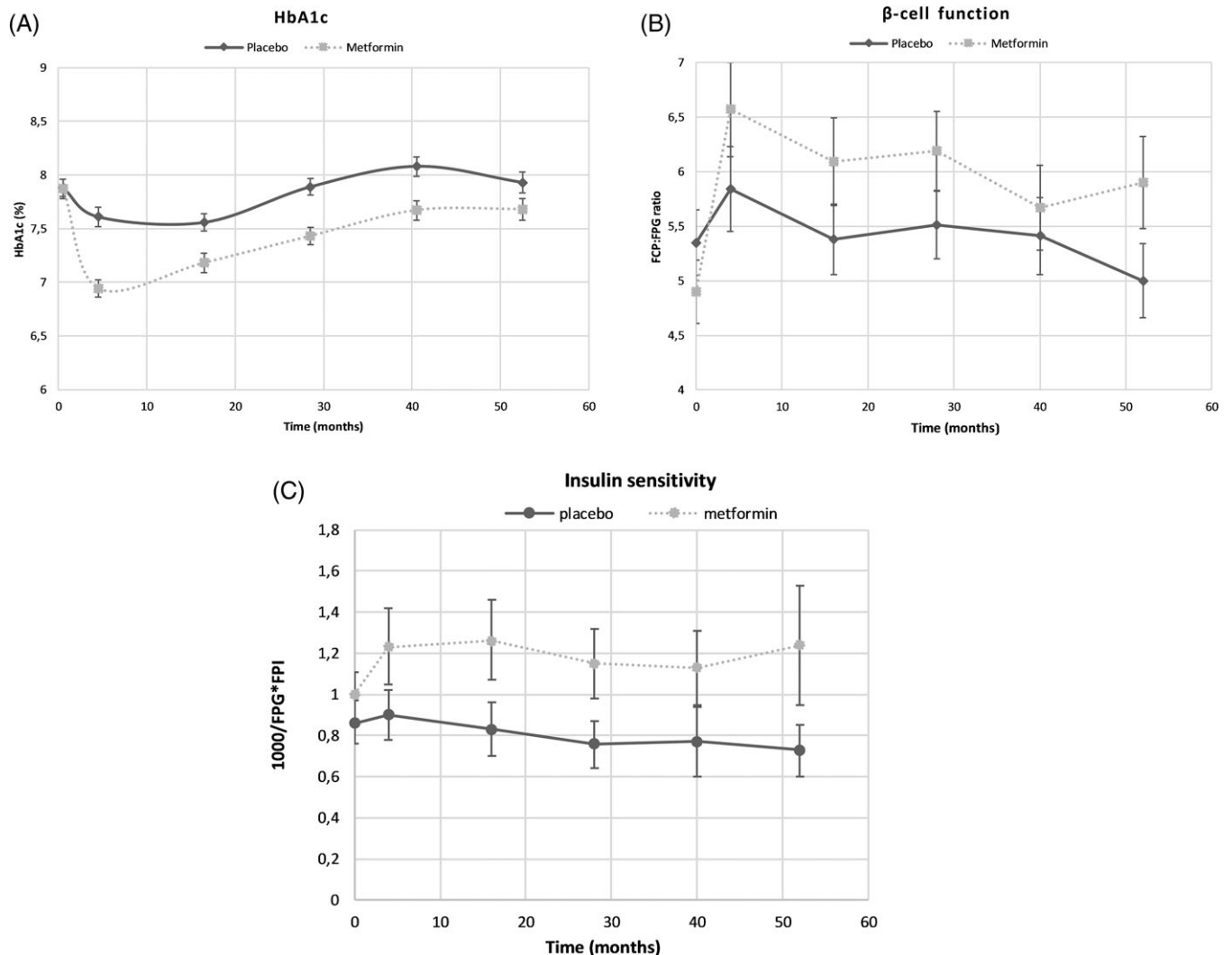
(A) HbA1c

(B) β-cell function

(C) Insulin sensitivity

**FIGURE 1** Time course of A, HbA1c; B, FCP:FPG ratio and C, IS. Data are given as means with standard error of the mean

**TABLE 1** Mixed-model fixed effect estimates

|  | FCP:FPG ratio | DI | C-peptide, nmol/L | IS | HbA1c, % |
|---|---|---|---|---|---|
| Baseline | 5.27 (4.83; 5.71) | 4.73 (4.36; 5.10) | 0.50 (0.46; 0.54) | 0.90 (0.74; 1.07) | 7.79 (7.68; 7.89) |
| Treatment effect[a] | 1.48* (1.09; 1.87) | 1.50* (1.17; 1.83) | 0.03 (0.00; 0.07) | 0.33* (0.03; 0.63) | −0.93* (−1.06; −0.80) |
| Time effect | −0.00 (−0.09; 0.08) | −0.08* (−0.15; −0.01) | 0.00 (−0.01; 0.01) | 0.01 (−0.05; 0.08) | 0.07* (0.04; 0.10) |
| Time–treatment interaction | −0.12 (−0.26; 0.01) | −0.09 (−0.20; 0.02) | 0.01 (−0.01; 0.02) | −0.03 (−0.14; 0.08) | 0.14* (0.09; 0.18) |

Data are estimates (95% CI). Time effect and time–treatment interaction are expressed as change per year.

*$P < .05$. [a]Constant treatment effect from the first post-baseline visit until the end of the study.

(HOMA)-derived fasting index, also improved by 36% (95% CI, 3 to 69).

A C-peptide with a concurrent glucose level of >8 mmol/L might be considered a non-fasting value.[2] This did apply to our population with a mean FPG at baseline of 10 mmol/L. To adjust for this hyperglycaemic stimulus, we chose the FCP:FPG ratio as our primary endpoint.

Meier et al.[3] reported a good correlation of FCP:FPG ratio with human pancreatic β-cell mass in a small group of patients who underwent pancreatic surgery. Okuno et al.[4] showed in a much bigger population of patients with type 2 diabetes, that FCP:FPG ratio strongly correlates with accepted measures as the HOMA-β ($r = 0.79$) and hyperglycaemic clamp (increase in Area Under the Curve insulin/glucose 90 minutes, $r = 0.721$).

Because β-cell function depends on prevailing IS, we adjusted for IS by calculating the DI. The use of exogenous insulin may confound the assessment of IS, unless a steady-state has been achieved without rapid changes in glucose transport.[5] In the present study, fasting insulin levels were drawn in the morning, during which a standard condition (a certain steady-state) of intermediate-acting NPH insulin levels had been achieved without fast changes in insulin-driven glucose transport. Further, a valid DI should incorporate independent estimates of β-cell function and IS.[6] Because we used C-peptide-based data for our β-cell estimate and insulin-based data for our IS estimate, we avoided intrinsically interdependent estimates. To assess this independency, we performed an additional correlation analysis that showed a weak correlation ($r = 0.29$ [95% CI 0.19 to 0.38) for C-peptide and insulin.

Although the improvements in β-cell function and IS were maintained during the 4.3-year follow-up period, there was no time–treatment interaction for either β-cell function or IS, indicating that the improvement constitutes an immediate treatment effect without additional change over time relative to placebo.

Two major trials[7,8] have evaluated long-term metabolic changes related to β-cell function in metformin users as compared with other treatments: the UK Prospective Diabetes Study (UKPDS) and A Diabetes Outcome Progression Trial (ADOPT). Both trials also observed modest improvement in β-cell function in metformin users; however, in the UKPDS, long-term follow-up of β-cell function is difficult to interpret because of the slowly rising FPG levels during the study and their influence on the HOMA-β estimate that was used.[9]

In ADOPT, apart from HOMA-β, the oral glucose tolerance test was used as an estimate of β-cell function. It was shown that metformin during 4 years of follow-up improved β-cell function as compared with glyburide, although this was less pronounced than with rosiglitazone and had a much smaller effect size (2.5%) than in the present study (28%).

This discrepancy may be partially explained by differences between the study populations. Patients included in ADOPT were newly diagnosed patients, while in the HOME study, patients with advanced diabetes receiving insulin therapy were included. Advanced type 2 diabetes is characterized by more β-cell failure than new-onset type 2 diabetes, and may have more potential for improvement (provided β-cell damage is partially reversible). Moreover, our placebo-controlled design allows a comparison with placebo instead of the comparator-based design of ADOPT.

Although metformin has no direct short-term insulin secretory effects on the β cells of normal glucose-tolerant individuals,[10,11] multiple mechanisms may explain its β-cell-enhancing effect in patients with type 2 diabetes. Apart from decreased glucotoxicity, improved incretin secretion[12,13] and reduced lipotoxicity[14] may be involved in the action of metformin to improve β-cell function.

The present study is limited by studying the effects of metformin on estimates of β-cell function and IS in the fasting state. Effects of metformin through the incretin system, which were not assessed in the present study, may also improve prandial β-cell function.

In conclusion, the present study shows that metformin results in long-term improvement in fasting estimates of β-cell function in addition to an improvement in IS, contributing to a durably improved glycaemic control in insulin-treated patients, even in advanced type 2 diabetes.

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