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

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Introduction

Metformin is a key drug in the treatment of type 2 diabetes. In our 'Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) Study' we showed that metformin vs placebo improved glycemic control and decreased insulin requirements in insulin-treated patients with advanced type 2 diabetes (1).

In this respect, metformin is generally regarded as an insulin sensitizer. Whether metformin also may improve beta-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 beta-cell function. In addition, we quantified the durability of metformin's effect on these estimates over a period of 4.3 years.

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Methods

Design and patients

In the HOME trial, 390 insulin-treated patients with advanced type 2 diabetes were randomly allocated to either metformin 850 mg (up to thrice daily if tolerated) or matching identical looking placebo through a computer program. Most patients (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 stopped metformin three months before randomisation.

All participants provided written informed consent and the study was approved by the medical ethical committees of the three participating non-academic hospitals. Study visits were at baseline, at one month and three months after with a follow up of 4.3 years.

Measures

Blood samples for this analysis of the HOME trial were drawn at baseline and after 4, 17, 30, 43, and 52 months, and stored at -80°C until analysis. C-peptide plasma samples were available for 363 patients at baseline and at one or more follow up visits (93%), and for 259 patients at their final visit (66%) and was performed with a solid-phase, chemiluminescent enzyme immunoassay (Immulite 2000, DPC). Serum insulin was measured by electrochemiluminescence immunoassay (Modular E170, Roche Diagnostics). Coefficients of variation are provided in the appendix. Because patients used human basal insulin (Insulatard, Novo Nordisk) there was full cross-reactivity between endogenous insulin and exogenous insulin in this assay.

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

Statistical analysis

We used all measurements to assess the effects of metformin vs placebo during the total period of follow-up. In order 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 (detail in the statistical appendix).

In addition we did a mediation analysis to assess the indirect (mediating) effect of HbA_{1c} in the change of FCPGR. For this purpose, we added HbA_{1c} as a covariate in the model and evaluated the mediating HbA_{1c} effect by the product of the effects ($\text{metformin} \rightarrow \text{HbA}_{1c}$) and ($\text{HbA}_{1c} \rightarrow \text{FCPGR}$), and confidence interval calculated by bootstrapping (detail in the statistical appendix).

Results

Figure 1 shows the time course of HbA_{1c} , beta cell function and insulin sensitivity 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 versus placebo, expressed as an absolute

change. In addition this change is described as a relative change compared to baseline.

Compared with placebo group, FCPGR 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 - 1.87, $p<0.001$), no change in time (0.00/year, 95%CI -0.001 - +0.0.01; $p=0.92$) and no time-treatment interaction (-0.010/year, 95%CI -0.021-.001; $p=0.058$). Relative to baseline, the treatment effect was 28% (95%CI 23-33).

DI showed results comparable to those with the FCPGR: 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 - -0.001; $p=0.023$) for placebo group, a constant treatment effect during the whole post baseline period of 1.50 (95%CI 1.17 - 1.83; $p<0.001$), and no time-treatment interaction (-0.01, 95%CI -0.02 -0.00; $p=0.128$). Relative to baseline, the treatment effect was 32% (95%CI 27-36).

FCP (nmol/l) 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 - 0.072; $p=0.085$), no time effect (0.00 nmol/l/year, 95% CI, -0.00 - 0.00; $p=0.61$), and no time-treatment interaction (0.00 nmol/l/year, 95%CI, -0.00 - 0.00; $p=0.26$). Relative to baseline, the treatment effect was 7% (95%CI -1;14).

HbA_{1c} (%) 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 placebo (95%CI 0.04 - 0.10; $p<0.001$), a treatment effect of -0.93 % (95%CI -1.06 - -0.80; $p<0.001$) 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 - 0.015; $p<0.001$).

We assessed the indirect (mediating) effect of HbA_{1c} in FCPGR improvement in adding in the model HbA_{1c} as covariate. In comparing with the initial model, the mediating effect of HbA_{1c} (Metformin→ HbA_{1c}→FCPGR) on the overall effect (Metformin→FCPGR) was small (.53, 95%CI .45, .73), accounting for a small proportion of the variance (36.1%; 95% CI,25.4-49.5).

Insulin sensitivity increased in the metformin group and decreased in the placebo group. Mixed model results showed a treatment effect of 0.33 (95%CI 0.03-0.63; $p=0.031$), no significant change in time for placebo (0.00/year, 95%CI -0.00 - 0.01; $p=0.69$), and no time-treatment interaction (-0.00/year, 95%CI -0.01 - 0.01; $p=0.612$). Relative to baseline, the treatment effect was 36% (95%CI 3-69).

Conclusions

The present study shows that metformin vs placebo added to insulin, improves fasting based estimates of beta cell function durably. These effects were for the greatest part (64%) independent of changes in glycemic control. Also adjusting for insulin sensitivity by calculating the disposition index, did not alter the results.

Depending on the estimate used, the increase in beta cell function was 28% (95%CI 23-33) for FCPGR and 32% (95%CI 27-36) for DI. Insulin sensitivity, assessed by a HOMA-derived fasting index, also improved by 36% (95%CI: 3-69).

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 fasting glucose at baseline of 10 mmol/l. To adjust for this hyperglycemic stimulus, we chose the FCPGR as our primary endpoint.

Meier et al. (3), showed a good correlation of FCPGR with human pancreatic beta cell mass in a small group of patients that underwent pancreatic surgery. Okuna(4) showed in a much bigger population of type 2 diabetes patients, that FCPGR strongly correlates with accepted measures as the HOMA-B ($r=0.79$) and hyperglycaemic clamp (iAUCins/gluc90, $r = 0.721$).

Because beta cell function depends on prevailing insulin sensitivity, we adjusted for insulin sensitivity by calculating the disposition index. The use of exogenous insulin in may confound the assessment of insulin sensitivity, unless a steady state has been achieved without fast changes in glucose transport (5). In our 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 beta cell function and insulin sensitivity (6). Because we used C-peptide-based data for our beta cell estimate and insulin-based data for our insulin sensitivity estimate, we avoided intrinsically interdependent estimates. To assess this independency, we did an additional correlation analysis that showed a weak correlation ($R = 0.29$ (95% CI 0.19-0.38) for C-peptide and insulin.

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

There are two major trials (7,8) which evaluated long-term metabolic changes related to beta cell function in metformin users, as compared to other treatment modalities: the UK Prospective Diabetes Study (UKPDS) and the A Diabetes Outcome Progression Trial (ADOPT). Both trials also observed modest improvement of beta cell function in metformin users. However, in the UKPDS long term follow up of beta

cell function is difficult to interpret because of the slowly rising FPG during the study and its influence on the HOMA-B estimate which was used (9).

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

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

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

Our study is limited by studying the effects of metformin on estimates of beta cell function and insulin sensitivity in the fasting state. Effects of metformin through the incretin system may also improve prandial beta cell function, which we did not study in the present study.

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

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Legends

Figure 1

Time course of HbA_{1c} , FCPGR and IS, data are means with SEM

Table 1

Data are estimates [95% CI]; Time effect and time-treatment interaction are expressed as change per year; * $p < 0.05$ (1) Constant treatment effect from the first post-baseline visit until the end of the study.

Table 1. Mixed model fixed effects parameter estimates

	FCPGR	Disposition index	C-peptide (nmol/l)	Insulin sensitivity	HbA _{1c} (%)
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 ⁽¹⁾	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]

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