Limitations of the HOMA-B Score for Assessment of β-Cell Functionality in Interventional Trials—Results from the PIOglim study

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Abstract

Background: Drugs with unspecific stimulating effects on β-cell secretion increase the homeostasis model assessment (HOMA)-B score, indicating improved β-cell “function.” We investigated whether the β-cell protection provided by adding pioglitazone (PIO) to glimepiride (GLIM) in comparison to up-titrating the GLIM dose alone is reflected by appropriate changes in several measures of β-cell function, including HOMA-B score.

Methods: This double-blind, parallel prospective 6-month study was performed with 82 patients (47 men, 35 women; age, 61 ± 9 years; duration of disease, 5.3 ± 4.4 years; body mass index, 32.6 ± 6.0 kg/m2; hemoglobin A1c [HbA1c], 7.3 ± 0.7%) with GLIM monotherapy (1–3 mg). They were randomized to receive a GLIM + PIO combination with up-titration (2 mg + 30 mg/4 mg + 30 mg/4 mg + 4 mg) or to remain on GLIM (up-titration 4/5/6 mg). Observation parameters determined at baseline and end point included HOMA-B, HOMA-IR, HbA1c, glucose, insulin, and intact proinsulin.

Results: There was a slight increase in the HOMA-B score in the GLIM group but not in the GLIM + PIO arm (baseline/end point: for GLIM, 71 ± 48/88 ± 64; for PIO + GLIM, 74 ± 56/69 ± 52). Improvements in the other observation parameters were predominantly detected in the PIO + GLIM group (HbA1c, 7.20 ± 0.61%/6.36 ± 0.90%; HOMA-IR, 7.0 ± 4.5/4.1 ± 2.1; intact proinsulin, 12.4 ± 10.3/7.6 ± 4.8 pmol/L [all P < 0.05 vs. baseline]) compared with the GLIM group (HbA1c, 7.45 ± 0.69%/7.15 ± 0.97% [P < 0.05]; HOMA-IR, 7.4 ± 4.5/7.5 ± 4.3 [not significant]; intact proinsulin, 17.3 ± 21.6/16.3 ± 15.5 pmol/L [not significant]).

Conclusions: The PIO + GLIM combination led to overall improvement of laboratory biomarkers for β-cell function, except for HOMA-B. Glimepiride up-titration had no such effects but increased the HOMA-B score. HOMA-B seems to provide misleading results when used as a diagnostic tool in patients treated with sulfonylurea drugs. A corrective term for consideration of proinsulin in the HOMA-B equation may address this limitation.

Introduction

Development of β-cell dysfunction is one of the key deteriorations in the pathophysiology of type 2 diabetes mellitus. In concert with insulin resistance and obesity, it is a driver of the progressive nature of the disease. Assessment of β-cell dysfunction provides a means to understand the clinical stage of the disease and may be helpful in selecting the most appropriate therapy. Methods for determination of β-cell function are usually based on measurement of insulin secretion dynamics in the context of oral or intravenous glucose challenge experiments and require substantial human and time resources. Homeostasis model assessment (HOMA) is one of the static approaches to assess β-cell function by means of fasting laboratory values—glucose, insulin, and/or C-peptide concentrations. The model yields a pair of values for insulin resistance (IR) and β-cell function (%B). The original formula for the determination of β-cell function is:

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HOMA-B (\%) = 20 \times \frac{\text{fasting insulin (in } \mu\text{U/mL})}{(\text{fasting glucose (in mmol/L}) - 3.5)

An updated model, HOMA2, was proposed in 1998 by Levy et al.\textsuperscript{2} This nonlinear computer model contains several improvements. Inter alia, it takes into account the advances in insulin assays. The HOMA2 calculator is available (free of charge) via the internet.\textsuperscript{2} For a detailed discussion, see Wallace et al.\textsuperscript{4} The HOMA-B method can be applied when an increasing demand for insulin is indeed leading to further insulin secretion. HOMA-B has been successfully applied in populations with prediabetes, but exact use ensuring comparability of the published results also requires standardization of the methods: the suitability of the method depends on the accuracy and reproducibility of the laboratory assays used for insulin and glucose determination and may substantially influence the value of the HOMA calculations.

According to our own data, the HOMA model cannot be used accurately any more when the \(\beta\)-cells are stressed to such an extent that intact proinsulin is secreted together with or instead of insulin in the fasting state (stage III of \(\beta\)-cell dysfunction\textsuperscript{5,6}). Proinsulin is also able to lower glucose values but is not considered in the HOMA equations. Measurement of fasting intact proinsulin has been shown to be a very specific indicator of late stage \(\beta\)-cell dysfunction and clinically significant IR.\textsuperscript{5} In addition, proinsulin is an independent cardiovascular risk factor,\textsuperscript{6} and recent publications have demonstrated that treatment with sulfonylurea drugs is associated with an increase in fasting plasma proinsulin, which in turn is associated with an increased prevalence of macrovascular complications.\textsuperscript{7,8}

The purpose of this trial was to investigate the effect of an addition of pioglitazone (PIO) to low-dose glimepiride (GLIM) in comparison to GLIM up-titration on HOMA-B and other biomarkers of \(\beta\)-cell dysfunction and IR in patients with type 2 diabetes.

Patients and Methods

This study was performed in accordance with current applicable ethical and regulatory standards, as set forth by the Declaration of Helsinki, the guidelines for Good Clinical Practice, and local German clinical trial regulations. The study was approved by the responsible ethics committee, and patients signed informed consent prior to any study procedure. Patients could be included if they presented with the following criteria: type 2 diabetes patients of either sex 30–75 years old with at least 3 months of pretreatment with GLIM monotherapy (1–3 mg/day) and hemoglobin A1c (HbA1c) between 6.5% and 8.5%. Other than the usual clinical trial criteria (pregnancy, fatal disease, etc.), the most important exclusion reasons were type 1 diabetes mellitus, hypersensitivity to the study drugs or to drugs with similar chemical structures, history of severe or multiple allergies, history of significant cardiovascular (greater than New York Heart Association stage II–IV), respiratory, gastrointestinal, hepatic (alanine aminotransferase >2.5 times the normal reference range), renal (creatinine >1.8 mg/dL), neurological, psychiatric, and/or hematological disease, and pretreatment with antidiabetes therapy other than GLIM (1–3 mg) within the last 3 months. The study was designed as a prospective, comparative, randomized, double-blind, parallel, two-arm multicenter trial. Patients were randomized to receive either an up-titration of their GLIM monotherapy (4, 5, and 6 mg/day) or an up-titration of a combination of GLIM and PIO (2 mg/30 mg, 4 mg/30 mg, and 4 mg/45 mg). The up-titration occurred within 4 weeks, and the entire treatment and observation period was 6 months.

The primary objective of the study was to investigate the effect of both treatments on HOMA-B, which was calculated by means of the formula provided in the Introduction. Secondary observation parameters were HbA1c (measured by high-performance liquid chromatography [Adams, Nichols Diagnostic, San Clemente, CA]), oral glucose tolerance test, insulin (chemiluminescence assay [Invitron, Cardiff, UK]), intact proinsulin (MetaScreen enzyme-linked immunosorbent assay [TECOmedical, Sissach, Switzerland]), C-peptide (Liaison chemiluminescence assay [Byk-SangTec, Neusenburg, Germany]), lipids (dry chemistry [Olympus, Hamburg, Germany]), HOMA-IR score (fasting insulin [\(\mu\text{U/mL}\) \times fasting glucose [in mmol/L]) \div 22.5),\textsuperscript{1} and the HOMA-B/intact proinsulin ratio.

Statistical analysis

Patients for whom efficacy data of at least 3 months of study participation were available were included into the intent-to-treat analysis. Missing data were accounted for by means of the last-observation-carried-forward approach. Demographic and baseline characteristics were summarized descriptively, and the changes in the observation parameters from baseline to endpoint were analyzed in a conﬁrmatory manner using Student’s \(t\) tests. Values of \(P < 0.05\) were considered to be statistically significant. In addition, two-sided 95% confidence intervals for between-group treatment differences were calculated using appropriate methods for continuous or categorical variables. All inferential analyses for the secondary efficacy parameters were interpreted in the exploratory sense. The statistical analyses were performed by means of SAS version 9.1 software (SAS Institute Inc., Cary, NC).

Results

Of 122 initially screened patients, 91 could finally be randomized (reasons for exclusion: 23 not meeting inclusion/exclusion criteria, seven withdrawn consents, one lost to follow-up). The patient characteristics at baseline are provided in Table 1. From nine patients (three in the PIO + GLIM group, five in the GLIM group), no post-baseline assessments under treatment for fasting glucose and fasting insulin between week 12 and week 24 were available. Therefore, the intent-to-treat population comprised 82 patients.

The HOMA-B score increased in the GLIM up-titration group from 71 ± 48 at baseline to 88 ± 64 after 6 months (+16.8%), whereas it decreased from 74 ± 56 to 69 ± 49 in the PIO + GLIM group (-4.8%). The differences between the groups at baseline or end point and for the changes from baseline did not reach the level of statistical significance. As the difference in the mean change of HOMA-B between the PIO + GLIM group and the GLIM group was -21.57%, i.e., ≤0%, the null hypothesis \(H_0\) of non-superiority of the combination therapy could statistically not be rejected, and HOMA-B alone did not indicate an improvement in \(\beta\)-cell function when PIO is added to GLIM in comparison to GLIM.
Table 1. Demographic Characteristics of the Study Participants at Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pioglitazone + glimepiride</th>
<th>Glimepiride up-titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>26/22</td>
<td>26/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 8</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>4.8 ± 4.3</td>
<td>5.9 ± 4.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.5 ± 6.2</td>
<td>31.7 ± 5.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1 ± 0.6</td>
<td>7.4 ± 0.7</td>
</tr>
</tbody>
</table>

There were no significant differences between the groups for any of the reported parameters. ACE, angiotensin converting enzyme; BMI, body mass index; HbA1c, hemoglobin A1c.

Discussion

After onset of type 2 diabetes, patients are usually treated with lifestyle modifications with or without different combinations of oral drugs. One first-line drug class is the sulfonylurea drugs, which are preferably provided to patients who are not obese. The mode of action of sulfonylureas is to increase insulin release from the pancreatic b-cells. This, however, was the case when considering intact proinsulin by calculating the HOMA-B/intact proinsulin ratio, which significantly improved in the combination arm only. Major differences between the groups were also observed for the other secondary observation parameters. There was a decrease in HbA1c in both groups that was significant for the other secondary observation parameters.

Table 2. Baseline and End Point Values of the Observation Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pioglitazone + glimepiride</th>
<th>Glimepiride up-titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.2 ± 0.6</td>
<td>6.4 ± 0.9†</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>8.9 ± 1.4</td>
<td>7.6 ± 1.4†</td>
</tr>
<tr>
<td>OGTT AUCglucose</td>
<td>1,116 ± 383</td>
<td>848 ± 368</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>18.1 ± 12.3</td>
<td>12.5 ± 6.7†</td>
</tr>
<tr>
<td>OGTT AUCinsulin</td>
<td>6,299 ± 5,791</td>
<td>6,094 ± 4,798</td>
</tr>
<tr>
<td>Intact proinsulin (pmol/L)</td>
<td>12.4 ± 10.3</td>
<td>7.6 ± 4.8†</td>
</tr>
<tr>
<td>OGTT AUCintact proinsulin</td>
<td>2,132 ± 1,847</td>
<td>1,975 ± 1,705</td>
</tr>
<tr>
<td>C-peptide (ng/L)</td>
<td>0.80 ± 0.38</td>
<td>0.68 ± 0.40</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>74 ± 56</td>
<td>69 ± 49</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>7.0 ± 4.5</td>
<td>4.2 ± 2.1†</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.1 ± 10.0</td>
<td>5.3 ± 0.9</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.4 ± 0.8</td>
<td>3.5 ± 0.7</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.1 ± 0.3</td>
<td>1.3 ± 0.3†</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.2 ± 1.1</td>
<td>1.8 ± 1.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>94.9 ± 15.5</td>
<td>97.3 ± 15.9</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136 ± 13</td>
<td>132 ± 12‡</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 ± 8</td>
<td>79 ± 6*</td>
</tr>
</tbody>
</table>

Data are mean ± SD values. HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OGTT AUC, oral glucose tolerance test area under the curve.

1*P < 0.05 for changes from baseline; †P < 0.01 for changes between the groups.
increase β-cell secretion, but it could be shown that they lead to deterioration of the β-cell secretion product over time, resulting in increased proinsulin secretion and disease progression. In this study patients were enrolled who were inefficiently treated with a low-dose GLIM monotherapy. Consequently, further treatment of such patients requires either the increase of the sulfonylurea dose or a combination therapy with a second oral antidiabetes drug. Combination therapy of sulfonylurea drugs with glitazones has been shown to counterbalance the effect of deteriorated β-cell secretion and to improve insulin sensitivity and the levels of proinsulin, C-peptide, and other laboratory surrogate markers for cardiovascular risk.

The present study shows that the addition of PIO to GLIM treatment in patients with type 2 diabetes is a safe, well-tolerated, and highly efficient antidiabetes treatment approach. Fasting and stimulated glucose levels were considerably lowered, and HbA1c values were considerably improved—close to normoglycemic conditions—in patients receiving the combination therapy, whereas the group receiving GLIM monotherapy did not show clinically relevant improvements in glycemic control. HOMA-B, the indicator of insulin sensitivity at the insulin receptor site, considerably improved in agreement with the understanding of the pharmacological action of thiazolidinediones. However, the HOMA-B score, an indicator of pancreatic β-cell function and primary end point variable in the present study, did not follow the hypothetical expectations. HOMA-B instead slightly declined with PIO combination and increased with the glimepiride monotherapy. This difference is physiologically plausible, when anticipating that endocrine pancreatic function was attenuated in the PIO combination group in a glucose-regulated feedback loop to prevent from hypoglycemic decompensation. It was even expected that the reductions in insulin, C-peptide, and proinsulin with PIO would result in the decline in HOMA-B scores in the present study. In contrast to GLIM, which does not follow any glucose-controlled regulation, the observations of excellent metabolic control with PIO and the functional down-regulation of β-cell activity in the present study both highlight the positive value of thiazolidinediones in modern antidiabetes therapy.

These effects were not indicated by the HOMA-B score, a supposed marker of β-cell function. The HOMA-B and the HOMA-IR score are measures of, respectively, β-cell function and IR, which are frequently used in epidemiological clinical studies. They are based on the assumption that under normal conditions a certain serum insulin concentration is required to achieve normoglycemia in the fasting normal state. Any requirement of more insulin to maintain normoglycemia or any hyperglycemia occurring at similar insulin levels is an indicator of deteriorated homeostasis due to IR and/or β-cell dysfunction. This model assumes that all glucose-lowering action is provided by correctly processed insulin derived from the β-cells. A severely deriorated β-cell, however, also secretes intact proinsulin, which substantially contributes to the glucose-lowering effect and is not considered in the model. Wrongly “positive” results can be obtained when calculating the HOMA-B score, especially for patients treated with drugs.
unspecificaly driving β-cell secretion, such as sulfonylureas or glinides. This situation has been observed in outcome studies, like the ADOPT trial, where a head-to-head comparison was performed among metformin, GLIM, and rosiglitazone regarding the duration of a successful monotherapy without requirement of a second oral drug. Rosiglitazone monotherapy was significantly better in maintaining HbA1c target values over 4 years than GLIM and metformin, but β-cell function as indicated by HOMA-B was highest at all time points with GLIM. This drug, however, showed the highest monotherapy failure rate.

In consequence, HOMA-B should not be termed to be a score for β-cell “function” but rather β-cell “activity,” which would more correctly describe the results of this study and other recent clinical findings. A mathematical model to correct for these limitations would be to consider intact proinsulin by introducing an additional factor into the HOMA-B equation. A HOMA-B equation for β-cell “function” considering the fasting morning level of intact proinsulin correction could, for instance, be:

\[
\text{HOMA-B}_{\text{corr}} \text{ (in \%)} = \frac{(20 \times \text{insulin [in } \mu \text{U/mL}] \times \text{RefiPi/iPi})}{\left(\text{glucose [in mmol/L]} - 3.5\right)}
\]

where iPi is the fasting intact proinsulin level and RefiPi is the mean intact fasting intact protein value of a healthy control populations measured with the method used for intact proinsulin determination. Applying this corrective term, the HOMA-Bcorr score shows a much lower β-cell “function” in the case of insufficient insulin processing than the original value, but it now reflects the improvement in β-cell function when combining PIO with GLIM (PIO + GLIM, +19.3%; GLIM up-titration, +31.8% [not significant vs. baseline in both cases] [Fig. 2]). However, this study can only serve as a pilot study for the development of such a term to correct for confounding proinsulin effects. More and larger studies, including an appropriately designed clamp trial, would now be warranted to evaluate the degree of improvement to the HOMA-B score specificity by introducing such a corrective term for intact proinsulin.

In conclusion, addition of PIO to GLIM led to an overall improvement of laboratory biomarkers for β-cell function, except HOMA-B. GLIM up-titration had no such effects, but increased the HOMA-B score. HOMA-B seems to provide misleading results when used as a diagnostic tool in patients treated with sulfonylurea drugs. A corrective term for consideration of fasting intact proinsulin in the HOMA-B equation may address this limitation.

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