To the editor,

We read with interest the article published in this journal by Antuna-Puente et al. [1]. The authors are to be complimented on their efforts to study the reproducibility of the formulae of two key indices of insulin resistance – namely, homoeostasis model assessment (HOMA) and the quantitative insulin-sensitivity check index (QUICKI). Their conclusion that coefficients of variation (CVs) should be applied to assess the reproducibility of techniques to measure glucose and insulin rather than of mathematical formulae is an important one, and we agree with their conclusion that insulin variation is likely to be the main determinant of variations in these simple indices of insulin resistance. Whilst the authors have reported absolute CV values for non-diabetic subjects, we have taken this a step further by investigating the trend of these CVs in subjects with different degrees of glucose tolerance. Our findings may have a potential impact on future studies of simple indices of insulin resistance and their clinical application.

We used insulin and glucose data obtained from a previous study of biological variations of insulin-like growth factor-binding protein-1 (IGFBP-1) [2]. The CVs for the HOMA of β-cell function (HOMA-β; 20 × fasting insulin (mU/L)/[fasting glucose (mmol/L) − 3.5]) and of insulin resistance (HOMA-IR; fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5), and for QUICKI (1/[log insulin (μU/mL) + log glucose (mg/dL)]) [3,4], were investigated in subjects from all glycaemic categories. The CVs were obtained over two consecutive visits.

Subjects were between 20 and 65 years of age, with a body mass index (BMI) >20 and <35 kg/m². Each subject attended the clinic on two occasions, separated by an average interval of 10 days. For both visits, subjects fasted for 10 h prior to blood sampling. The glycaemic status of each individual was determined by a standard 75-g oral glucose tolerance test (OGTT) on the first visit, with subjects classified according to WHO criteria [5]. A further fasting sample was collected during the second visit while investigating frequently sampled intravenous glucose tolerance (FSIVGTT) for another study [6]. All patients with type 2 diabetes (DM) were being treated by dietary means alone and had not previously received either oral antidiabetic medications or insulin, and none was being treated with steroids or thyroxine. Participants were instructed to avoid modifying their lifestyles, or exercise and eating patterns, from one week prior to the first blood test until completion of the study. The study was approved by the King Abdulaziz Medical City (Jeddah, Kingdom of Saudi Arabia) and the South West Surrey Local Research Ethics Committee (LREC) at the Royal Surrey County Hospital, Guildford, UK. Informed written consent was obtained from all subjects prior to participation. Within-individual CVs were calculated using the modified method for paired samples between the two visits [7].

Categorization of the subjects was as follows: normal glucose tolerance (NGT = 15); impaired fasting glucose (IFG = 9); impaired glucose tolerance (IGT = 9); and DM = 9. The means and CVs of HOMA-β, HOMA-IR and QUICKI are presented in Table 1. As shown in Fig. 1, the %CV for the HOMA-β model was 17.4% in the NGT subjects and increased with deteriorating glucose tolerance, reaching 68.7% in DM patients. The %CV for HOMA-IR in the NGT group was 25.7%, which reached 52.1% in the DM group. QUICKI showed the great-

Table 1

<table>
<thead>
<tr>
<th>Index</th>
<th>Combined mean</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-β</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>117 (101–134)</td>
<td>17.4</td>
</tr>
<tr>
<td>IFG</td>
<td>119 (94–144)</td>
<td>29.2</td>
</tr>
<tr>
<td>IGT</td>
<td>133 (95–171)</td>
<td>30.9</td>
</tr>
<tr>
<td>DM</td>
<td>106 (69–144)</td>
<td>68.7</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>2.0 (1.7–2.3)</td>
<td>25.7</td>
</tr>
<tr>
<td>IFG</td>
<td>3.6 (2.8–4.3)</td>
<td>30.1</td>
</tr>
<tr>
<td>IGT</td>
<td>4.1 (3.3–4.8)</td>
<td>33.4</td>
</tr>
<tr>
<td>DM</td>
<td>5.5 (3.8–7.3)</td>
<td>52.1</td>
</tr>
<tr>
<td>QUICKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>0.353 (0.343–0.364)</td>
<td>3.8</td>
</tr>
<tr>
<td>IFG</td>
<td>0.324 (0.312–0.336)***</td>
<td>4.1</td>
</tr>
<tr>
<td>IGT</td>
<td>0.320 (0.308–0.331)***</td>
<td>5.0</td>
</tr>
<tr>
<td>DM</td>
<td>0.309 (0.296–0.321)***</td>
<td>5.8</td>
</tr>
</tbody>
</table>

NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: type 2 diabetes. Data are expressed as means (95% confidence intervals). The combined mean of both visits (10-day interval) in the NGT group was compared with the combined mean in every other glycaemic category; ***: P < 0.001.
Fig. 1. Trends of reproducibility for HOMA-β, HOMA-IR and QUICKI in subjects with various degrees of glucose tolerance. NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

Our outcomes for HOMA-IR and QUICKI were comparable to those of Antuna-Puente et al., [1], which involved non-diabetic subjects, although the CVs for the same indices were lower in NGT subjects compared with the other glycaemia categories. However, this was most probably due to the variable activity of β-cell function in DM compared with NGT individuals (Table 1).

In those with DM, Emoto et al. [8] and Sarafidis et al. [9] both reported lower CVs for HOMA-IR (11.7% and 23.5%, respectively) compared with Jayagopal et al. [10] and the CVs obtained in our study (79.3% and 52.1%, respectively). This might be explained by the presence of insulin-resistance-modifying medications, resulting in an improved reproducibility of the measured index. In contrast, in both Jayagopal et al. and our present study, patients with DM were not discontinued or receiving any insulin-resistance-modifying medications that might have caused the reproducibility of indices to deteriorate progressively with increasing severity of glucose intolerance.

In conclusion, it is important for those carrying out epidemiological studies to be aware of the observation that trends of biological variations of simple indices of insulin resistance, addition to those of insulin levels, are greatly influenced by the degree of glucose tolerance and by insulin-resistance-modifying medications. These factors would also be expected to affect the reproducibility not only of HOMA-IR and QUICKI, but of all other indices of insulin resistance as well.

Conflicts of interest

The authors do not have any conflicts of interest to declare.

Acknowledgements

The authors gratefully acknowledge the financial support of the Kingdom of Saudi Arabia government, as represented by the Saudi National Guard Health Affairs.

References

Further research should address these aspects and investigate whether or not intra- and inter-individual variations can be further reduced and/or whether or not the numerous requisite precautions to appropriately estimate insulin sensitivity can be simplified with no significant impact on findings.

Conflicts of interest

The authors do not have any conflicts of interest to declare.

References


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27 January 2010  
Available online 31 March 2010

doi:10.1016/j.diabet.2010.01.005