HOMA or QUICKI: Is it useful to test the reproducibility of formulas?

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Abstract

Aim. – HOMA and QUICKI are the most widely used indices for assessing insulin sensitivity. Both are based on fasting glucose and insulin measures, and mainly differ by the log transformation of these variables in QUICKI. However, HOMA is less reproducible than QUICKI, and log HOMA does not improve its reproducibility. The aim of this study was to investigate the various mathematical transformations of HOMA and to assess its reproducibility.

Method. – We used data from a clamp study involving 123 non-diabetic overweight and obese postmenopausal women. Fasting insulin and glucose were measured in two visits 15 and 30 days apart. This allowed us to calculate HOMA as \( \frac{\text{fasting glucose} \times \text{fasting insulin}}{22.5} \) and QUICKI as \( \frac{1}{\log \text{fasting glucose} + \log \text{fasting insulin}} \) twice for subjects who were weight-stable between visits.

Results. – QUICKI had better reproducibility (CV = 3.9%) than either HOMA (CV = 26.7%) or log HOMA (CV = 22.0%). However, log-transforming HOMA using log (glucose \times insulin)/log (22.5) and log-transforming HOMA without transforming the constant denominator improved its CV to 6.5% and 5.7%, respectively.

Conclusion. – By modifying the mathematical expression of HOMA, we were able to achieve comparable CVs for QUICKI and HOMA. However, the CV should be used to assess the reproducibility of techniques to measure glucose and insulin, not of mathematical formulas. When evaluating indices for the assessment of insulin sensitivity, the key point is how well they correlate with the ‘gold-standard’ glucose clamp.

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1. Introduction

The euglycaemic hyperinsulinaemic (EH) clamp technique is the ‘gold-standard’ method of measuring insulin sensitivity [1]. However, this method is expensive, time-consuming and only used in research. For these reasons, more simple methods for measuring or estimating insulin sensitivity have been developed. The homoeostasis model assessment (HOMA; fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5) [2] and the quantitative insulin sensitivity check index (QUICKI; 1/[log fasting insulin (µU/mL) + log fasting glucose (mg/dL)]) [3] have become the most widely used surrogate indices. Both are based on fasting plasma glucose and insulin values, and correlate well with the EH clamp [2–7]. For this reason, log HOMA is similar to QUICKI, as both are based on the same underlying physiological principles and similar mathematical formulations. The similarity between these two indices was recently discussed by Boyko and Jensen [8]. Thus, log HOMA can be reformulated as 1/QUICKI – 1.35, where 1.35 is the logarithm of 22.5 [8]. However, QUICKI and HOMA have different reproducibility, as the coefficient of variance (CV) of QUICKI between two visits in the same population displayed better reproducibility than HOMA (CV = 7.8% and 23.5%, respectively) [4]. However, if the log transformation of HOMA is the only mathematical difference between these two indices, a smaller CV difference after log transformation would be expected, which is not the case. Many epidemiological studies have relied on these surrogate indices, and it was brought to our attention by reports that took into account the reproducibility of each formula [4,5] as a possible determinant for choosing one index rather than the other. Therefore, our objective was to assess why there are differences between two formulas that take into account the same biological measures.

2. Methods

We used data from a clamp study that involved 123 non-diabetic overweight and obese postmenopausal women (aged 57.7 ± 0.4 years; BMI: 32.3 ± 0.4 kg/m²) who were recruited for a weight-loss study at the Department of Nutrition at the University of Montreal [6,9]. Subjects underwent an EH clamp with an insulin infusion rate of 75 mU/m² min for 180 min, as previously described [6]. Glucose disposal was calculated as the mean rate of glucose infusion during the last 30 min of the clamp, and expressed as mg/min/kg of fat-free mass. Measurements of fasting insulin and glucose were taken at two separate visits 15 and 30 days apart. This allowed us to calculate HOMA1 and HOMA2, as well as QUICKI1 and QUICKI2, for subjects whose weight was stable between visits.

Continuous values were compared using Pearson’s correlation. We calculated the CV for each index, and for fasting glucose and insulin according to the formula: CV = (SD/√2) × 100/x, where SD was the standard deviation of the difference between the two visits, and x was the mean value of the two visits [4].

3. Results

In accord with previous results [4,6], HOMA1 (r = 0.53; P < 0.0001) and HOMA2 (r = 0.39; P < 0.0001) showed higher correlation coefficients with the EH clamp than did QUICKI1 (r = 0.48; P = 0.0001) and QUICKI2 (r = 0.34; P < 0.0005) for the two visits. We corroborated the results of Sarafidis et al. [4] and noted that QUICKI had better reproducibility (CV = 3.9%) than HOMA (CV = 26.7%). Logarithmic transformation of HOMA did not improve the CV (22.0%). According to the HOMA formula and as log 1 = 0, it was evident that log HOMA could not improve the CV, especially in subjects with a HOMA value of around 1. However, we were able to improve the CV to 5.7 and 6.5%, respectively, by log-transforming HOMA by either leaving the denominator out of the transformation, calculated as (log [glucose × insulin])/22.5, or log-transforming HOMA as follows: (log [glucose × insulin])/log (22.5). In addition, we obtained a CV of 6.5% with log HOMA using its entire original formulation when glucose was expressed in mg/dL instead of mmol/L. Finally, we calculated the CV for fasting plasma glucose (mmol/L) and insulin, obtaining a 7.6% CV for glucose and a 23.3% CV for insulin.

4. Discussion

Both HOMA and QUICKI are based on fasting glucose and insulin values, and mainly differ in their normalization factor—log transformation in QUICKI, and the constant denominator in HOMA. However, HOMA has been reported to be less reproducible than QUICKI [4,7]. This could be due to the normalization by logarithmic transformation of the values. Nevertheless, log HOMA does not improve its reproducibility. To further explore this, we investigated different mathematical expressions of HOMA. As expected, QUICKI had better reproducibility than HOMA, and log HOMA did not improve its CV. Thus, following the example of Boyko and Jensen [8], we decided to investigate the mathematical factors that may account for the difference between the two indices. We found that the CV was improved when we log-transformed HOMA either without transforming the constant denominator, by log-transforming the numerator and denominator independently or when glucose was expressed in mg/dL before the log-transformation of HOMA.
It should be noted that validity and reproducibility are important factors for whichever method is used. However, caution is required in the interpretation of the numbers. For HOMA, the reproducibility reflected by the CV could give an erroneous impression of poor reproducibility. The CV has an important disadvantage when the mean value is close to zero, so that even a test with good precision may have a high CV [5]. Mather et al. [5] have assessed the variability between these two indices according to their CV and discrimination ratio (DR), which takes into account between- and within-subject variations [10]. Interestingly, using the DR, QUICKI reproducibility was comparable to that of HOMA [5]. Thus, the study by Mather et al. [5] and the present study both show, by either using another way to assess reproducibility or modifying the mathematical expression of HOMA, comparable reproducibility for the two indices.

Furthermore, we found a similar CV for insulin and HOMA, suggesting that HOMA could be more sensitive to variations in insulin values. This could be due to the lower capacity of normalization by the constant denominator used in HOMA compared with the log transformation used in QUICKI or the separate log transformation of the numerator and denominator components of HOMA. In addition, the underlying biological variability of insulin levels remains the major source of variation. This was recently illustrated in a population of postmenopausal women, with and without type 2 diabetes, where the intraindividual variance of HOMA was higher in the diabetic patients than in the controls, which may have been due to the greater variation of fasting insulin levels in diabetes [7].

Finally, the CV should only be used to assess the reproducibility of different measurement techniques, not mathematical formulas. We believe that these mathematical formulas are similar to a biological phenomenon (such as insulin resistance), and their reproducibility depends solely on the quality of the glucose and insulin values used in their calculation. What is important when evaluating indices for the assessment of insulin sensitivity is their validity—which is to say, how well they correlate with the gold-standard EH clamp and the reproducibility of each biological measurement necessary for the calculation of the index. Currently, both HOMA and QUICKI have largely been validated, and the next step should be to improve insulin measurement and, in particular, its standardization [11].

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