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Improved indices of insulin resistance and insulin secretion for use in genetic and population studies of type2 diabetes mellitus

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Homeostasis model assessment (HOMA) provides indices of insulin secretion (β) and insulin resistance (R) derived from fasting plasma glucose (FPG) and fasting plasma insulin (FPI) levels. However, these indices could not account for a significant heritability of fasting plasma glucose (FPG) ($h^2 = 0.75$, $P < 0.01$) in a group of 214 female twins. This result is consistent with a misclassification between effects due to insulin secretion and resistance in the HOMA indices. We report here evidence of such misclassification in the HOMA indices and describe a minor modification to the model which corrects it. Direct measures of insulin resistance (euglycaemic clamp) and secretion (i.v. glucose bolus) were obtained in 43 non-diabetic subjects. Heritability was estimated by statistical modelling of genetic and environmental influences in data from 214 non-diabetic female subjects. Modified HOMA (HOMA') indices were obtained from β' = (Ln(FPI)−c)/FPG and R' = (Ln(FPI)−c)*FPG where c is a constant derived from regression analysis of Ln(FPI) vs FPG. Indices from both models correlated with the direct measures similarly (r = 0.63 (R), 0.49 (R'), 0.45 (β), 0.39 (β'), all $P < 0.01$). Directly measured insulin resistance and secretion were not significantly correlated (r = 0.13, P = 0.21). However, unmodified HOMA-β and R were strongly related (r = 0.78, $P < 0.0001$ vs 0.13) demonstrating substantial misclassification. The relationship between β' and R' (r = 0.13) was not different from that between the two direct measures and significant heritability of β' ($h^2 = 0.68$, $P < 0.01$) and R' ($h^2 = 0.59$, $P < 0.05$) was evident in the twin data. The proposed modification to HOMA significantly reduces misclassification and reveals separate components of insulin resistance and insulin secretion in the heritability of FPG. Twin Research (2000) 3, 148–151.

Keywords: insulin resistance, insulin secretion, diabetes mellitus, non-insulin-dependent, mathematical model

Introduction

The insulin resistance syndrome (IRS) describes a common cluster of phenotypes including hyperinsulinaemia, dyslipidaemias, glucose intolerance, and cardiovascular disorders associated with insulin resistance.[1,2] Type2 diabetes mellitus is characterised by insulin resistance, often in association with the other features of IRS, and a partial failure of insulin secretion triggered or exacerbated by the insulin resistance.[3,4] Twin studies have pointed to a strong genetic component to the pathophysiology of type2 diabetes.[5,6] More recently in populations with increased risk of developing type2 diabetes, genetic influences have been demonstrated on phenotypic traits related to type2 diabetes,[7–13] in particular, both insulin secretion and insulin resistance.[8,9] With the considerable interest in identifying genes contributing to variations in insulin resistance and secretion in large populations, the use of direct measures of insulin resistance and secretion is invasive and expensive and therefore impractial and indirect measures are necessary for such studies. The homeostasis model assessment (HOMA) approach provides indices of insulin secretion (HOMA-β) and insulin resistance (HOMA-R) from fasting glucose and insulin levels[14] and has been recommended for use in large scale clinical and epidemiological studies where direct measures are not practical. Recently it has been shown to have some prognostic value in a prospective study of the development of type2 diabetes.[15] We have attempted to use the HOMA indices to partition a strong heritability of fasting plasma glucose (FPG) levels in a group of twins, in the absence of significant heritability of fasting plasma insulin (FPI),[16] into components due to

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insulin secretion and resistance. As described below no significant heritability of either index was detected. This result is not consistent with the underlying assumption of the HOMA approach, ie that variations in fasting plasma insulin and glucose between subjects can be accounted for by variations in insulin secretion and insulin sensitivity. The result is, however, consistent with the presence of a misclassification between effects due to insulin secretion and resistance in the HOMA indices so that at least one index is contaminated with variability belonging to the other. We report here direct evidence of substantial misclassification of insulin resistance and secretion in the HOMA indices and describe minor modifications to the HOMA approach which result in no significant misclassification in the modified indices.

Methods

Subjects

Insulin resistance and secretion were measured directly in 43 non-diabetic subjects (M/F 8/35, age 39 ± 11 (SD) years, BMI 25.6 ± 4.2 kg/m^2) who participated in published[17] and similar unpublished studies. Modified HOMA (HOMA') model parameters were derived from fasting plasma glucose (FPG) and insulin (FPI) measured in 214 non-diabetic female subjects (107 twin pairs, age 52 ± 14, BMI 25.2 ± 4.2).[16]

Clinical methods

Insulin resistance was determined during the last 30 min of a 2.5 h euglycaemic hyperinsulinaemic (700 pmol/l) clamps; results were expressed as U moles of glucose infused per min per kg body weight (M). Insulin secretory status was determined in the same subjects on another day using an intravenous glucose bolus with blood sampling at 0, 1, 2, 3, 4, 5, 6, 8 and 10 min; results were expressed as the ratio of the areas under the insulin and glucose responses. HOMA indices were derived from FPG and FPI measured before the euglycemic clamp.

Model development

The basic structure and assumptions of the HOMA approach as described by Matthews et al[14] were preserved but modifications to the details were made.

i) The model was reformulated in terms of relationships between Ln(FPI) and FPG, and between Ln(FPI) and insulin sensitivity. As well as being more physiologically plausible than the original relationships with FPI, this normalises both the distribution and the measurement errors in the insulin data, allowing the application of linear regression procedures for identifying model parameters.

ii) The insulin resistance and secretion indices were derived from regression analysis of FPG with Ln(FPI) in the twin data. Since both the glucose and insulin values have associated measurement and sampling errors, simple least squares regression (which assumes lack of error in independent variables) gives biased parameter estimates and therefore diagonally weighted least squares regression was used.[18]

The original HOMA indices of insulin secretion (HOMA-β) and resistance (HOMA-R) are obtained from:[14]

HOMA-β = FPI/(FPG – 3.5) and HOMA-R = FPI* FPG/22.5

The modified indices (HOMA-β' and HOMA-R') are obtained from:

HOMA-β' = (Ln(FPI) – c)/FPG and HOMA-R' = (Ln(FPI) – c)* FPG where c is the intercept on the Ln(FPI) axis in its regression relationship with FPG.

Statistical methods

The distribution of each variable was assessed and deviations from normality were corrected by Ln-transformation in further analyses. Relationships between variables were assessed by simple correlation. The HOMA' model parameters were obtained using diagonally weighted least squares (DWLS) regression.[18] This procedure requires an estimate of the ratio between the error variances in X and Y variables, which we approximated as the ratio of measurement error variances determined from the assay duplicates. DWLS regression was applied to the full data set and the two subsets composed of one representative from each twin pair. Heritability estimates (h^2) and their confidence intervals were obtained from statistical modelling of genetic and shared and specific environmental influences on variables measured in monozygotic (n = 59) and dizygotic (n = 48) twin pairs using univariate model fitting.[19] Differences between correlation coefficients were assessed using Fisher's Z-transformation.

Results

Ln-transformed FPI significantly correlated with FPG in the twin data (r = 0.36, n = 214, P < 0.0001,

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Figure 1). Measurement error variances in FPG and Ln(FPI) calculated from assay duplicates were 0.0121 and 0.0026, respectively (equivalent to CVs of 2.2% at FPG = 5 mmol/l and 2.6% at Ln(FPI) = 2). DWLS regression identified a steeper relationship between Ln(FPI) and FPG than did simple LS regression (Figure 1), illustrating the marked bias that errors in an independent variable can produce in LS estimates of regression coefficients. The y-intercept (c) of –4.66 obtained from the DWLS procedure was used in calculations of the HOMA' indices. When the data were split into two subsets according to twin number, consistent estimates of c were obtained (–3.50, –5.39). The value obtained from the full data set was taken as the best estimate of c; the qualitative nature of the results reported below was not affected if either of the other estimates was used.

The HOMA' indices were not significantly different from those of HOMA as predictors of measured insulin secretion and resistance ($P > 0.14$, Table 1a). However, the original HOMA indices significantly confound insulin resistance and secretion; whereas the measured insulin resistance and secretion were weakly correlated ($r = 0.13$, $P = 0.21$) the original HOMA indices were strongly correlated ($r = 0.78$, $P < 0.0001$, and $P < 0.0001$ vs 0.13, Table 1b). This implies that at least one index is contaminated by variability belonging to the other. In contrast, the relationship between the two HOMA' indices was not significantly different from that between the two direct measures.

When the two models were applied to the twin data, the results were consistent with the above analysis. The significant heritability of plasma glucose ($h^2 = 0.75$, $P < 0.01$) was not accounted for by any heritability of the HOMA indices (Ln(HOMA-β); $h^2 = 0.28$, $P > 0.3$; Ln(HOMA-R): $h^2 = 0.08$, $P > 0.5$), whereas both HOMA' measures were significantly heritable (HOMA-β': $h^2 = 0.68$, $P < 0.01$; Ln(HOMA-R'): $h^2 = 0.59$, $P < 0.05$). Detailed results of the genetic modelling are published in Samaras et al.[16]

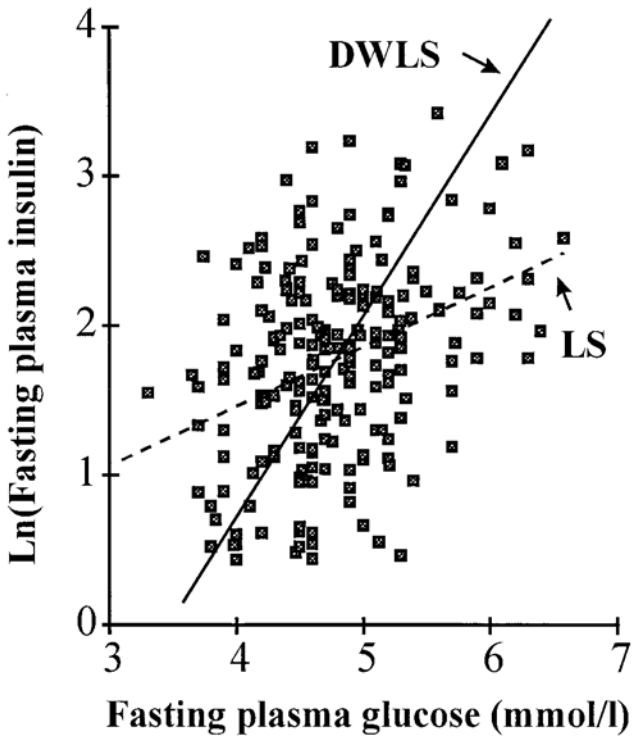

Figure 1 Relationship between fasting plasma glucose and insulin in 214 non-diabetic females (107 twin pairs). Regression lines obtained from diagonally weighted (DWLS) and simple (LS) least squares regression procedures are shown as solid and dashed lines, respectively

Discussion

This analysis demonstrates that there is significant misclassification of effects due to insulin resistance and insulin secretion in the HOMA indices and describes a simple modification to the HOMA model which corrects the misclassification in the test data set. The modified indices (HOMA') reveal separate components of insulin resistance and insulin secretion in the heritability of FPG in the twin sample which were not apparent when using the original HOMA indices. While conventional HOMA indices insulin resistance and insulin secretion were strongly correlated with one another, neither the direct measures nor the modified estimates showed any such correlation.

Clearly a close relationship between the indirect indices and the direct measures is highly desirable, but in these data the correlations derived from either model, though significant, were not high in a measurement context ($r = 0.4 – 0.6$ accounting for around 15–35% of the variance). In the case of HOMA-R and R', the correlations with directly measured insulin sensitivity were in or near the

Table 1 Simple correlations (r) between indirect and direct measures of insulin secretion and insulin resistance in 43 non-diabetic subjects

a: Correlations between direct and indirect measures

Direct measures	HOMA	HOMA′
Insulin resistance: Ln (1/M)	0.63*	0.49*
Insulin secretion: Ln (insulin/glucose areas)	0.45*	0.39*

b: Correlations of measures of insulin resistance with measures of insulin secretion

Direct measures	HOMA	HOMA′
0.13	0.78*†	0.13

*$r > 0$, $P < 0.01$; †significantly different to the correlation between the direct measures (0.13) $P < 0.0001$.

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range reported in previous validation studies with non-diabetic subjects (r = 0.57 – 0.73).[20,21] In the case of HOMA-β and -β', some of the imprecision may be due to problems with the direct measure of insulin secretion, which itself suffers from poor reproducibility.[4] This may account for the absence of published validations of the HOMA-β index and for the fact that HOMA estimates of β-cell function are often not present in studies reporting the HOMA-R index. Imprecision can be overcome by using large sample sizes. However, any inaccuracy caused by misclassification cannot be overcome by large samples, and may lead to erroneous conclusions concerning the relative roles of insulin resistance and insulin secretion in disease processes.

We conclude that these modifications to the HOMA method improve its reliability, and will be particularly beneficial in large scale genetic studies where biased indices may have profound effects on the partitioning of variances among covariates and latent factors or loci.

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