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Prediction of insulin resistance in type 2 diabetes mellitus using routinely available clinical parameters

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ABSTRACT

Aims: To determine if insulin resistance (IR), an important predictor of cardiovascular risk in the general population and in type 2 diabetes mellitus, can be assessed using simple parameters which are readily available in clinical practice.

Methods: This cross-sectional study included 194 patients with type 2 diabetes. Body mass index, waist index (WI), triglyceride levels, 1/HDL, triglyceride/HDL, uric acid and urine albumin:creatinine ratio were investigated as possible predictors of IR.

Results: WI correlated more strongly than any other parameter with log insulin levels, log fasting glucose to insulin ratio (FGIR), log fasting glucose to insulin product (FGIP), homeostatic model assessment (HOMA-IR) and quantitative insulin check index (QUICKI). WI also emerged as the strongest independent predictor of IR indices studied in regression as well as in ROC analyses. At a cut-off of 1.115, WI had a 78% sensitivity and 65% specificity for predicting IR when HOMA-IR was used as indicator of IR, and 74% sensitivity and specificity when QUICKI was used as indicator of IR. Combining WI with other variables did not improve performance significantly.

Conclusions: In our cohort of patients with type 2 diabetes, WI was the parameter with the strongest association with, and the best predictor of, IR.

Introduction

Insulin resistance (IR) is a pathological condition characterized by inadequate peripheral tissue metabolic response to circulating insulin, and plays an important pathophysiological role in type 2 diabetes mellitus (T2DM). Furthermore, IR is associated with atherosclerosis [1,2] and results in a number of metabolic and haemodynamic disturbances that are collectively referred to as the metabolic syndrome. IR is also an important predictor of cardiovascular morbidity and mortality both in the general population [3,4] and in patients with T2DM [5,6]. It is also associated with increased cancer mortality independent of diabetes [6].

The gold standard method for measurement of IR is the euglycaemic hyperinsulinaemic clamp [7], whereby the rate of whole-body glucose disposal during steady-state hyperinsulinaemia is assessed. However, this technique is costly, time-consuming and metabolically invasive, making it impractical to use in large cross-sectional or longitudinal studies or in clinical practice. Simple indices have thus been developed and validated for quantification of IR, based on measurement of fasting plasma insulin and glucose levels and calculated with different mathematical formulas. These include the homeostatic model assessment (HOMA-IR) [8], the quantitative insulin sensitivity check index (QUICKI) [9], fasting glucose to insulin ratio (FGIR) and fasting insulin glucose product (FIGP). These are better suited for use in clinical studies. Nonetheless, since insulin levels are not routinely measured in clinical practice, they are still of limited value. Hence, in spite of the important clinical implications of IR, it cannot be readily detected.

The goal of the present study is to assess how variables which are more readily available in routine clinical practice are associated with IR in a cohort of adults with T2DM and whether they can be used to predict IR.

Subjects, materials and methods

Study population

This cross-sectional study was conducted in 194 Europid patients with T2DM. All participants gave written informed

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consent. The study was approved by the University of Malta Research Ethics Committee.

All patients were assessed for a medical and medications history. Height and weight were measured using a calibrated balance and a stadiometer with the subject wearing light indoor clothing without shoes. Waist circumference was measured to the nearest 0.5 cm in the horizontal plane at the midpoint between the lowest rib and the iliac crest [10]. Waist index (WI) was calculated as waist circumference (cm) divided by 94 for men and 80 for women [11].

Blood samples were taken in the overnight fasting state. No medication was taken on the morning of the examination. Patients who were treated with insulin discontinued injections after 22:00 on the day preceding the examination. Urinary albumin:creatinine ratio (ACR), erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) were also determined for each patient. Serum insulin was assayed using an immunoenzymometric assay (IMMULITE 2000 insulin); various surrogate markers of IR were thus assessed, including fasting plasma insulin, FGIR, FIGP, HOMA-IR and QUICKI. In addition, all participants performed 24-h heart rate (HR) and blood pressure monitoring and ankle-brachial index was measured.

Statistical analysis

Correlation analysis between each of the above-mentioned markers of IR with body mass index (BMI), WI, triglyceride levels, 1/high-density lipoprotein (HDL), triglyceride/HDL, uric acid and ACR were performed. Logarithmic transformation was performed when variables were not normally distributed. Forward stepwise multivariate linear regression analysis was consequently performed to identify independent predictors of the various indices of insulin resistance.

Univariate followed by multivariate logistic regression analyses were also performed to identify independent predictors of IR using a cut-off point of $\geq$2.5 for HOMA-IR and of $<$0.357 for QUICKI to define IR as validated by other authors [12–15]. Based on logistic regression models, an IR risk score was calculated: $IR = X_1 \times \beta_1 + X_2 \times \beta$,.... + $X_p \times \beta_p$, where, X_1, X_2,..., X_p are baseline predictors and β_1, β_2,..., β_p are, respectively, the estimated coefficients of baseline predictors 1 to p. Receiver-operator curve (ROC) analysis was consequently performed in order to determine the best cut-off of parameters studied to predict IR (using both HOMA-IR and QUICKI) and to assess their performance.

Furthermore, the sensitivity and specificity of the metabolic syndrome, as defined by both the International Diabetes Federation (IDF) [16] and the 2002 National Cholesterol Education Program (NCEP) criteria [17] in predicting IR were calculated for comparison.

All data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) and all analyses were performed using SPSS version 21.0. Comparisons of continuous variables between groups were made using independent-samples *t*-test and Mann–Whitney *U* test for normally and non-normally distributed data respectively. Categorical variables were compared using the Chi-squared test. Variables with a *p* value less than 0.1 in univariate analysis were included in the multivariate model to identify predictors for the occurrence of IR. Predictors were removed from the model if their *p*-value exceeded 0.05. All tests were two-sided, and a value of $p < 0.05$ was considered to be statistically significant.

Results

The baseline characteristics of the study population are outlined in Table 1. The mean ± SD age was 64.8 ± 9.8 years, diabetes duration was 18.4 ± 9.4 years, BMI was 31.7 ± 5.4 and WI was 1.19 ± 0.17. Sixty per cent (n = 117) had a HOMA-IR of $\geq$2.5 and 73% (n = 142) had a QUICKI of $<$0.357.

Table 1
Characteristics of patients included in the study.

Patient characteristics (n = 194)	Values
Male: female (n)	112:82
Age (years)[a]	64.75 ± 9.77
Diabetes duration (years)[a]	18.42 ± 9.39
Body mass index (kg/m^2)[b]	30.98 (27.97–34.13)
Waist index[a]	1.19 ± 0.17
Microalbuminuria (n (%))	65 (33.5%)
Macroalbuminuria (n (%))	45 (23.2%)
Retinopathy (n (%))	194 (100%)
Neuropathy (n (%))	96 (44.3%)
Peripheral arterial disease (n (%))	51 (26.3%)
Ischaemic heart disease (n (%))	56 (28.9%)
Cerebrovascular disease (n (%))	19 (9.8%)
Hypertension (n (%))	134 (69.6%)
Dyslipidaemia (n (%))	160 (82.5%)
Smoking status (Ex: Non: Current)	103:73:18
Metformin (n (%))	135 (69.6%)
Sulphonylurea (n (%))	100 (51.5%)
Insulin/insulin analogues (n (%))	90 (46.4%)
HbA1c (%)[b]	8.4 (7.1–9.6)
Fasting plasma glucose (mmol/L)[a]	10.01 ± 3.59
Total cholesterol (mmol/L)[a]	5.09 ± 1.08
LDL-cholesterol (mmol/L)[a]	3.20 ± 1.02
HDL-cholesterol (mmol/L)[a]	1.13 ± 0.33
Triglyceride (mmol/L)[a]	1.71 ± 0.95
HOMA-IR[b]	3.39 (1.41–7.20)
QUICKI[b]	0.32 (0.29–0.36)

Values are expressed as mean ± SD[a] or median (IQR)[b] or number (% of patients).

Significant factors derived from Pearson's correlation and multivariate analysis with the surrogate markers of IR are outlined in Table 2. In the study population, WI correlated more strongly with log insulin levels (r = 0.435, $p < 0.001$), log FGIR (r = −0.381, $p < 0.001$), log FIGP (r = 0.449, $p < 0.001$), HOMA-IR (r = 0.449, $p < 0.001$) and QUICKI (r = −0.457, $p < 0.001$) than did any other parameter (Table 2).

In linear regression analysis, WI also emerged as the strongest independent predictor of all the indices of IR studied. Thus, significant predictors of log insulin were WI and log 1/HDL, significant predictors of log FGIR were WI, log 1/HDL and log uric acid and those of log FIGP were WI and log triglyceride/HDL. Similarly WI and log triglyceride/HDL were found to be independent predictors of log HOMA-IR and log QUICKI.

The occurrence of IR was also analysed as a categorical variable using the cut-off point of $\geq$2.5 for HOMA-IR and of $<$0.357 for QUICKI. The following variables were significant ($p < 0.05$) in univariate analysis when HOMA-IR was used to assess for IR: female gender, use of aspirin, metformin, sulphonylurea, insulin, angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), β-blocker, calcium channel blocker (CCB), diuretic, fibrate, statin, smoking history, mean heart rate, BMI, WI, white cell count (WCC), platelet count, ESR, hsCRP, alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), glycated haemoglobin (HbA1c), triglyceride levels and HDL/triglyceride ratio. Logistic regression analysis was consequently performed to identify independent predictors of IR in our T2DM population. All significant variables in univariate analysis (above-mentioned) were included in the first model; in the second model use of sulphonylurea, insulin, ACE-I, ARB, CCB, WCC, platelet count, ALT and GGT were not included. In both models, WI emerged as a very strong predictor of IR (Table 3).

Similarly, univariate followed by multivariate analysis was performed with QUICKI used as cut-off for IR. The following variables were significant ($p < 0.05$) in univariate analysis: use of metformin, sulphonylurea, insulin, ARB, statin, smoking history,