Measures of Insulin Resistance as a Screening Tool for Dysglycemia in Patients With Coronary Artery Disease: A Report From the EUROASPIRE V Population

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OBJECTIVE

The optimal screening strategy for dysglycemia (including type 2 diabetes and impaired glucose tolerance) in patients with coronary artery disease (CAD) is debated. We tested the hypothesis that measures of insulin resistance by HOMA indexes may constitute good screening methods.

RESEARCH DESIGN AND METHODS

Insulin, C-peptide, glycated hemoglobin A_{1c}, and an oral glucose tolerance test (OGTT) were centrally assessed in 3,534 patients with CAD without known dysglycemia from the fifth European Survey of Cardiovascular Disease Prevention and Diabetes (EUROASPIRE V). Three different HOMA indexes were calculated: HOMA of insulin resistance (HOMA-IR), HOMA2 based on insulin (HOMA2-ins), and HOMA2 based on C-peptide (HOMA2-Cpep). Dysglycemia was diagnosed based on the 2-h postload glucose value obtained from the OGTT. Information on study participants was obtained by standardized interviews. The optimal thresholds of the three HOMA indexes for dysglycemia diagnosis were obtained by the maximum value of Youden's J statistic on receiver operator characteristic curves. Their correlation with clinical parameters was assessed by Spearman coefficients.

RESULTS

Of 3,534 patients with CAD (mean age 63 years; 25% women), 41% had dysglycemia. Mean insulin, C-peptide, and HOMA indexes were significantly higher in patients with versus without newly detected dysglycemia (all $P < 0.0001$). Sensitivity and specificity of the three HOMA indexes for the diagnosis of dysglycemia were low, but their correlation with BMI and waist circumference was strong.

CONCLUSIONS

Screening for dysglycemia in patients with CAD by HOMA-IR, HOMA2-ins, and HOMA2-Cpep had insufficient diagnostic performance to detect dysglycemia with reference to the yield of an OGTT, which should still be prioritized despite its practical drawbacks.

Dysglycemia, defined as either impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM), increases the risk of cardiovascular (CV) events (1,2). According to

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recent estimates by the International Diabetes Federation, about half of people with T2DM are unaware of their condition (3), and previously unrecognized dysglycemia among people with atherosclerotic CV disease (CVD) is common (4–6). Therefore, accurate and clinically feasible screening tests for dysglycemia are important to enable the institution of measures to prevent subsequent complications. A recent risk model based on the European Survey of Cardiovascular Disease Prevention and Diabetes (EUROASPIRE) experiences indicated that uncontrolled diabetes is an independent risk factor for future cardiovascular events (7). Moreover, the origin of novel cardioprotective glucose-lowering agents, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors, offers excellent possibilities to lower this risk (8).

There is an ongoing debate on the optimal screening strategy in terms of precision, prognostic information, cost-effectiveness, and feasibility (9,10). The most commonly used tests are glycated hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT) that includes both FPG and a 2-h postload glucose (2hPG) (11). Although more time-consuming, the OGTT is more informative not only because it is the only diagnostic test for IGT (12), but also because it discloses more people with T2DM than FPG and HbA_{1c} and provides superior prognostic information beyond that of FPG or HbA_{1c} (2,13–15). Still, the European Society of Cardiology (ESC)/European Association for the Study of Diabetes European guidelines on diabetes, prediabetes, and CVD recommend the use of FPG and HbA_{1c} as the first diagnostic tests in people at increased CV risk, restricting the role of OGTT to uncertain cases (16).

The Insulin Resistance Intervention after Stroke (IRIS) trial showed that pioglitazone, a potent insulin-sensitizing drug, decreased the risk of stroke or myocardial infarction in people without established T2DM but with insulin resistance and a recent stroke or transitory ischemic attack (17,18). The possibility to use insulin resistance to detect patients with significant glucometabolic derangement is appealing (19). In epidemiological studies, insulin resistance is usually expressed through HOMA, which can be calculated by fasting blood values of insulin, glucose, and C-peptide (20–22).

The objective of the current study was to test the hypothesis that a HOMA index may constitute a novel, simplified screening method for glucose perturbations in people at high CV risk by comparing different expressions of HOMA with the outcome of an OGTT in patients with coronary artery disease (CAD) in the fifth EUROASPIRE (EUROASPIRE V [EAV]) cohort.

RESEARCH DESIGN AND METHODS

Study Design

The EAV cross-sectional survey was conducted from 2016 to 2017 in 131 centers across 27 countries under the auspices of the European Society of Cardiology–EURObservational Research Programme (EORP). Patients, <80 years old, with a first or recurrent clinical diagnosis or treatment of: *1*) elective or emergency coronary artery bypass graft; *2*) elective or emergency percutaneous coronary intervention; *3*) acute myocardial infarction (ICD-10 I21); and *4*) acute myocardial ischemia (ICD-10 I20) 6 months to 2 years prior to the date of the present investigation were selected for the study. The median time between the index event and the present investigation was 1.1 years (interquartile range 0.8–1.6).

A comprehensive description of the study protocol and glycemic status assessment has been given elsewhere (23,24). At baseline, 4,440 of the 8,261 patients in the survey did not have a history of diabetes and underwent screening for dysglycemia with an OGTT comprising an FPG and a 2hPG, as well as measurement of HbA_{1c} (24).

Research personnel trained for the study procedures conducted a standardized interview, including personal and demographic details, lifestyle habits, and medical history, and performed a physical examination (23).

Definitions

Dysglycemia

The reference values for dysglycemia were those recommended by the World Health Organization (i.e., a 2hPG value ≥11.1 mmol/L [200 mg/dL] for T2DM and a 2hPG ≥7.8–11.0 mmol/L [140–200 mg/L] for IGT) (25).

Smoking

Smoking was defined as self-reported smoking habits and/or a breath carbon monoxide >10 ppm by means of Smokerlyzer (Model Micro+; Bedfont Scientific Limited) at the time of interview.

Height and Weight

Height and weight were measured in indoor clothes without shoes (SECA scales 701 and measuring stick model 220).

Obesity

Obesity was defined as a BMI ≥30 kg/m^2.

Waist Circumference

Waist circumference was measured in the standing position by a metal tape placed horizontally in the midaxillary line midway between the lowest rim of the rib cage and the superior iliac crest (26).

Central Obesity

Central obesity was defined as a waist circumference ≥102 cm for men or ≥88 cm for women.

The physical activity target was defined by the following question: ''Do you take regular physical activity of at least 30-min duration on average 5 times a week?''

Low educational level was defined as having attended primary school only or less.

Blood pressure was measured twice on the right upper arm with the participant in the sitting position using an automatic digital sphygmomanometer (Omron M6).

HOMA of insulin resistance (HOMA-IR) was calculated according to the formula

$$HOMA\text{-}IR = \frac{\text{glucose (mmol/L)} \times \text{insulin } (\mu\text{U/mL})}{22.5}$$

HOMA2 based on insulin (HOMA2-ins) and HOMA2 based on C-peptide (HOMA2-Cpep) were obtained by the calculator at https://www.dtu.ox.ac.uk/homacalculator/. The HOMA2 model is an updated version of the HOMA model that accounts for variations in hepatic and peripheral glucose resistance and the contribution of circulating proinsulin (27). In both cases, low HOMA values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (i.e., insulin resistance).

Laboratory Measurements

Venous blood specimen was drawn for a lipid assessment and HbA_{1c} carried out at the central laboratory in Helsinki (Biomarkers Team, Finnish Institute for Health and Welfare, Helsinki, Finland, accredited

by the Finnish Accreditation Service and fulfilling requirements of the standard SFS-EN ISO/IEC 17025:2017). The scope of accreditation covers all analyses, except for C-peptide. Specific assays used have been previously reported (23). Plasma glucose obtained from the OGTT in the fasting state and after 2 h was analyzed with the validated point-of-care technique HemoCue (Glucose 201RT; HemoCue, Ängelholm, Sweden) (28,29).

Fasting serum insulin and C-peptide were measured on frozen plasma samples, obtained during the OGTT, and stored at the central laboratory in Helsinki at −70°C. Both insulin and C-peptide were measured using chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL) on a clinical immunochemistry analyzer (Architect ci8200; Abbott Laboratories). Sample quality was assessed based on visual evaluation and internal controls. To ensure standardization of measurements, the laboratory took part in External Quality Assessment Schemes organized by Labquality (Helsinki, Finland). The coefficient of variation (mean ± SD) and systematic error (bias) (mean ± SD) were 2.2 ± 0.4% and 1.1 ± 0.2% for insulin and 4.0 ± 0.7% and −10.2 ± 0.5% for C-peptide, respectively.

Statistical Analysis

Descriptive statistics (means, SD, and proportions) were used to present patient characteristics. Patients with and without newly diagnosed dysglycemia were compared according to the Mann-Whitney *U* test. Since there are no established reference values for HOMA indexes, their optimal thresholds (i.e., the values with the best balance between sensitivity and specificity) were obtained by the maximum value of Youden's J statistic on receiver operator characteristic (ROC) curves. The diagnostic performance of such thresholds was tested for both T2DM (2hPG value ≥11 mmol/L) and dysglycemia (2hPG value ≥7.8 mmol/L). The associations between 2hPG and the other screening parameters, as well as between HOMA indexes and clinical features, were characterized by Spearman correlation coefficients. All statistical analyses were undertaken using SAS statistical software release V.9.3 (SAS Institute, Cary, NC).

Ethics

Data from the participating centers were collected via an eCRF developed by the ESC-EORP department (European Heart House, Sophia Antipolis, France). They were checked for completeness, internal consistency, and accuracy and stored under the provisions of the National Data Protection Regulations.

Local ethics committees' approvals were obtained by national coordinators. Each participant provided written informed consent that was stored in the patient file.

Role of the Funding Source

The sponsors and supporters had no role in the design, data collection, data analysis, data interpretation, decision to publish, or writing the manuscript.

Data and Resource Availability

The study protocol, statistical analysis plan, and results can be made available upon reasonable request to the authors who are guarantors of this work (G.F., D.D.B., and L.R.) via e-mail to the corresponding author, with no time limits. Deidentified individual patient data can be made available after approval of a proposal, with a signed agreement, with the European Society of Cardiology administrative headquarters: European Heart House, Les Templiers, 2035 Route des Colles, CS 80179 Biot, 06903 Sophia Antipolis Cedex, France.

RESULTS

A total of 4,440 patients underwent an OGTT, from whom 4,036 samples were received and stored at the central laboratory. The present analysis was performed on samples from 3,534 of the study participants, as those from 502 patients were considered unreliable according to the quality assessments as detailed in Fig. 1.

Baseline characteristics of the study population are reported in Table 1. The mean age of the patients was 63 years, and 25% were women. As regards the CV risk factors, 54% of the patients had central obesity, 18% were current smokers, mean blood pressure was 133/80 mmHg, and mean LDL-cholesterol 2.4 mmol/L. The OGTT revealed that 1,439 (41%) of the 3,534 with available insulin and C-peptide values were dysglycemic (IGT, 24%; T2DM, 16%) (Fig. 1). The complete glycemic profile, including the FPG, 2hPG, HbA_{1c}, fasting serum insulin, and C-peptide and HOMA indexes, is reported in Table 1.

The mean values of all different screening tests were significantly higher in patients

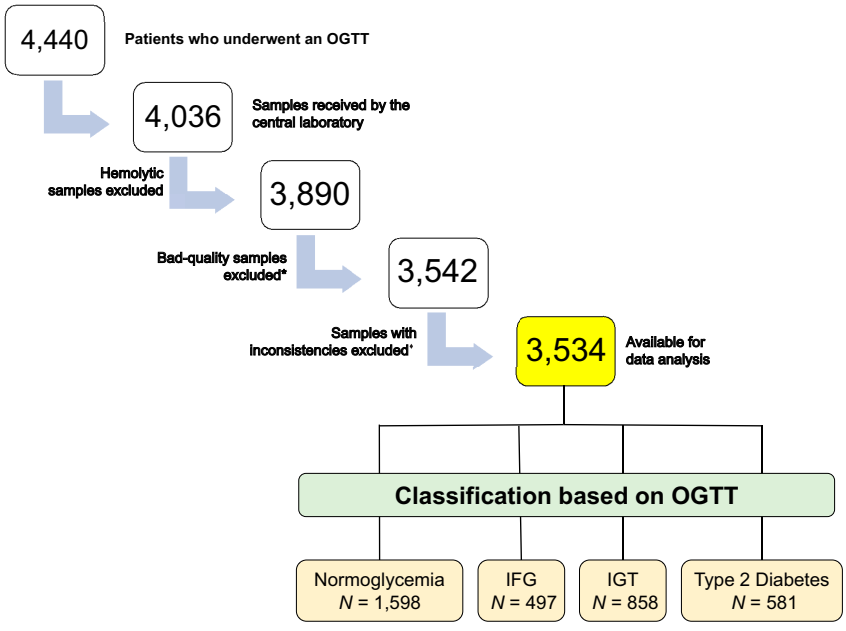

Figure 1—Sample selection. Flowchart describing the sample selection process and reasons for sample exclusion. In total, 3,534 samples were considered for the current analyses. The glycemic status of patients was classified based on the results of the OGTT. IFG, impaired fasting glucose. *Bad quality includes samples with extremely out-of-range insulin and/or C-peptide values and out-of-range calcium values and samples that arrived in poor condition at visual assessment. ◆Inconsistencies includes molar ratio of insulin to C-peptide > 1.

Table 1—Baseline characteristics of the study population

Variable	All (n = 3,534)	Men (N = 2,667)	Women (N = 867)
Age (years)	63.4 (9.6)	62.8 (9.7)	65.4 (9.1)
Low educational level	11.9 (418)	11.2 (297)	14.0 (121)
Current smoking	18.1 (640)	19.1 (510)	15.0 (130)
Low physical activity	61.5 (1,977)	58.8 (1,433)	69.8 (544)
Cardiovascular medical history			
CABG	17.7 (624)	19.8 (528)	11.1 (96)
PCI	83.8 (2,960)	84.1 (2,244)	82.6 (716)
Stroke	3.4 (120)	3.0 (79)	4.7 (41)
Heart failure	4.4 (155)	3.9 (104)	5.9 (51)
Clinical assessment			
BMI (kg/m^2)	28.7 (4.6)	28.7 (4.4)	28.9 (5.4)
Obesity (BMI ≥30 kg/m^2)	34.4 (1,214)	33.2 (885)	38.2 (329)
Waist circumference (cm)	100.2 (12.5)	101.6 (11.9)	95.7 (13.4)
Central obesity	54.3 (1,851)	48.3 (1,249)	72.8 (602)
Systolic blood pressure (mmHg)	133 (18)	134 (18)	132 (19)
Diastolic blood pressure (mmHg)	80 (11)	81 (11)	79 (11)
Heart rate (bpm)	89 (139)	90 (144)	84 (122)
Laboratory assessment (serum)			
Total cholesterol (mmol/L)	4.3 (1.2)	4.2 (1.1)	4.7 (1.3)
LDL-cholesterol (mmol/L)	2.4 (1.0)	2.4 (0.9)	2.7 (1.1)
HDL-cholesterol (mmol/L)	1.2 (0.3)	1.1 (0.3)	1.4 (0.3)
Triglycerides (mmol/L)	1.5 (1.0)	1.5 (1.0)	1.5 (0.9)
Creatinine (mg/dL)	87.9 (27.8)	91.9 (28.9)	75.5 (19.6)
eGFR (mL/min/1.73 m^2)	83.9 (19.3)	79.9 (17.6)	96.3 (18.9)
Glycometabolic status			
FPG (mmol/L)	5.9 (0.9)	6.0 (0.9)	5.9 (0.9)
2hPG (mmol/L)	7.6 (2.5)	7.5 (2.5)	7.8 (2.5)
HbA_{1c} (%) [mmol/mol]	5.6 (0.4) [37]	5.6 (0.4) [37]	5.6 (0.4) [38]
Fasting serum insulin (μU/mL)	11.4 (6.6)	11.4 (6.5)	11.4 (6.9)
Fasting serum C-peptide (nmol/L)	0.74 (0.36)	0.75 (0.36)	0.73 (0.37)
HOMA-IR	3.1 (2.0)	3.1 (1.9)	3.0 (2.0)
HOMA2-ins	1.5 (0.9)	1.5 (0.9)	1.5 (0.9)
HOMA2-Cpep	1.7 (0.9)	1.7 (0.8)	1.7 (0.9)
Cardiovascular medical therapy			
RAAS blockers	74.6 (2,616)	74.6 (1,977)	74.5 (639)
β-Blockers	79.3 (2,785)	79.1 (2,098)	80.0 (687)
Antiaggregant	93.1 (3,270)	93.4 (2,476)	92.2 (794)
Lipid-lowering	84.7 (2,971)	85.4 (2,262)	82.5 (709)

Data are percent (n) or mean (SD) unless otherwise indicated. CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system.

with versus without newly diagnosed dysglycemia (all $P < 0.0001$) as reported in Table 2.

The optimal thresholds identified by the ROC analyses for different glycemic parameters are showed in Table 3 as regards their diagnostic performance for T2DM (2hPG value ≥11 mmol/L) and dysglycemia (2hPG value ≥7.8 mmol/L). Table 3 reports the diagnostic performances of HOMA-IR, HOMA2-ins, HOMA2-Cpep, fasting serum insulin, and fasting serum C-peptide for patients with newly detected T2DM, identified by a 2hPG value ≥11.1 mmol/L, and with newly detected dysglycemia (IGT and T2DM), identified by a 2hPG value ≥7.8 mmol/L. The diagnostic performance of HOMA indexes in detecting dysglycemia was slightly worse than FPG or HbA_{1c}, but this difference was not significant (data not shown).

There were no differences in the diagnostic performance of HOMA indexes between men and women or in participants older and younger than 65 years of age.

The associations between 2hPG and the other parameters in the total sample were weak, with Spearman correlation coefficients of 0.15 for fasting insulin, 0.19 for C-peptide, 0.24 for HOMA-IR, 0.18 for HOMA2-ins, and 0.22 for HOMA2-Cpep.

HOMA-IR, HOMA2-ins, and C-peptide were strongly correlated with BMI (Spearman correlation coefficient 0.47 for all three parameters) and waist circumference (Spearman correlation coefficient 0.43, 0.44, and 0.44, respectively). In contrast, FPG, 2hPG, and HbA_{1c} did not have any strong correlation with either BMI (Spearman correlation coefficient 0.14, 0.15, and 0.21, respectively) or waist circumference (Spearman correlation coefficient 0.16, 0.15, and 0.19, respectively).

CONCLUSIONS

To the best of our knowledge, this is the first attempt to use expressions of

Table 2—Glycemic parameters in patients with CAD without vs. with newly diagnosed dysglycemia

	No dysglycemia (N = 2,095)	Newly diagnosed dysglycemia (N = 1,439)
FPG (mmol/L)	5.6 (0.7)	6.4 (1.0)
2hPG (mmol/L)	6.1 (1.1)	9.8 (2.3)
HbA_{1c} (%) [mmol/mol]	5.5 (0.3) [37]	5.7 (0.5) [39]
Fasting serum insulin (μU/mL)	10.7 (6.2)	12.4 (7.0)
Fasting serum C-peptide (nmol/L)	0.7 (0.3)	0.8 (0.37)
HOMA-IR	2.7 (1.6)	3.6 (2.2)
HOMA2-ins	1.4 (0.8)	1.7 (0.9)
HOMA2-Cpep	1.6 (0.8)	1.9 (0.9)

Data are mean (SD) unless otherwise indicated. Dysglycemia is defined as either IGT or T2DM according to the OGTT.

insulin resistance as screening tools for dysglycemia in a high-risk population of patients with CAD. However, the substitution of the OGTT with HOMA-IR, HOMA2-ins, and HOMA2-Cpep did not turn out to be reliable, still leaving OGTT as the best screening tool for dysglycemia. Overall, the sensitivity and specificity of HOMA indexes, fasting insulin, and C-peptide were low and poorly correlated with the result of the OGTT. Internationally recommended thresholds of FPG and HbA_{1c} for the screening of T2DM and IGT had a higher specificity than all of the other tests.

To detect T2DM, international guidelines put different emphasis on different tests: ESC/European Association for the Study of Diabetes European guidelines on diabetes, prediabetes, and CVD recommend to start with FPG or HbA_{1c} and to proceed to OGTT if the results are uncertain (16); the American Diabetes Association guidelines equally recommend the use of HbA_{1c}, FPG, and 2hPG (30); the World Health Organization points out the discrepancies among the three tests, specifying that HbA_{1c} ≥48 mmol/mol may be superior for the prediction of retinopathy (31) and that its assessment is unreliable in common conditions, such as pregnancy, recent blood loss, transfusion, erythropoietin therapy, hemoglobinopathies, anemia, glucose-6-phosphate dehydrogenase deficiency, HIV, and hemodialysis. Since these conditions are more prevalent in countries where the cost of HbA_{1c} is a major issue, the World Health Organization advises policy-makers to ensure that accurate blood glucose measurement should be generally available before introducing HbA_{1c} measurement (31).

Several reasons led us to consider 2hPG as the "gold standard" in the present work. IGT can only be diagnosed by a 2hPG during the OGTT, and accumulating evidence has established its association with adverse CV outcomes and death (2,14,15,32,33). Second, 2hPG reflects the pathophysiology behind glucose perturbations better than FPG and HbA_{1c}, since it mirrors the postprandial condition, when preserved β-cell function is essential for keeping glucose levels normal (34). Another reason is that the 2hPG by means of the OGTT is more sensitive (i.e., discloses more people with T2DM than FPG and HbA_{1c}). Compared with FPG ≥7 mmol/L or 2hPG ≥11 mmol/L, HbA_{1c} ≥6.5% (48 mmol/mol) has the lowest sensitivity for the diagnosis of T2DM according to the Noncommunicable disease Risk Factor Collaboration (NCD-RisC) (35). The prevalence of diabetes based on FPG alone was 2–6% lower than that based on 2hPG, and HbA_{1c} seems to underdiagnose T2DM particularly in overweight and obese people (12). Results from the Diabetes Prevention Program highlight the lack of overlap between traditional screening methods among participants with newly diagnosed T2DM, in which only 26% of those diagnosed by FPG or 2hPG also had an HbA_{1c} ≥6.5% (48 mmol/mol), and 55% of those with an HbA_{1c} ≥6.5% (48 mmol/mol) had a current or previous diagnosis of T2DM by FPG or 2hPG (36). These results are confirmed by our previous investigation on EAV, in which only 3.4% of the 4,440 patients undergoing the OGTT had dysglycemia according to all three traditional screening methods (24). Finally, 2hPG is a stronger predictor

Table 3—Diagnostic performance for type 2 diabetes (according to 2hPG value ≥11.1 mmol/L) and dysglycemia (according to 2hPG value ≥7.8 mmol/L) of the optimal thresholds of different glycemic parameters obtained by Youden's J statistic on ROC curves

	Threshold	Sensitivity (%)	Specificity (%)	AUC
Patients with newly detected type 2 diabetes (N = 581)				
HOMA-IR	2.73	68.0	57.2	0.66
HOMA2-ins	1.32	65.0	51.8	0.61
HOMA2-Cpep	1.69	65.6	59.3	0.64
Fasting serum insulin (μU/mL)	7.9	79.2	35.2	0.59
Fasting serum C-peptide (nmol/L)	0.74	61.7	60.4	0.62
Patients with newly detected dysglycemia (N = 1,439)				
HOMA-IR	2.81	54.9	64.1	0.62
HOMA2-ins	1.32	58.2	55.3	0.59
HOMA2-Cpep	1.44	67.6	49.7	0.61
Fasting serum insulin (μU/mL)	7.9	50.3	61.7	0.57
Fasting serum C-peptide (nmol/L)	0.63	65.6	49.8	0.59

AUC, area under the curve.

of future CVD than FPG and HbA_{1c} in patients with CVD (2,15,33,37).

Unfortunately, an OGTT requires people to fast, it takes time, and it is more expensive than HbA_{1c} (9). Several of these drawbacks could be resolved by having a different test. The idea behind HOMA assessments is that they may be able to identify early glucometabolic disturbances, complying with the necessity of a screening test to be capable of detecting a high proportion of disease in its preclinical state (38). Moreover, insulin resistance measured by HOMA can be targeted by insulin-sensitizing interventions. This was the pathophysiological basis of the IRIS trial, which eventually proved the benefit of pioglitazone on major CV outcomes in a population without diabetes but insulin resistance and established CVD (18). In the IRIS trial, a cutoff value of 3 for HOMA-IR was chosen based on a single previous study in which it marked the highest quartile of insulin resistance in a small population sample without known diabetes (39). It must be kept in mind that, to date, no cutoff to define insulin resistance has been established, since data from large, high-risk populations are missing and no medications are specifically approved to treat insulin resistance. Thus, we calculated the optimal thresholds of HOMA-IR, HOMA2-ins, and HOMA2-Cpep by ROC curve analysis. Despite finding values quite close to 3 for HOMA-IR, none of these indexes performed well enough in terms of sensitivity and specificity for diagnosing dysglycemia based on the OGTT results. Indeed, the frequency of false positives was too high to consider HOMA indexes as good screening tests for dysglycemia. One possible explanation is that HOMA indexes mirror metabolic derangements beyond the glycemic status: accordingly, we found a strong correlation with BMI and waist circumference (i.e., markers of visceral fat). This positive correlation between visceral adiposity and insulin resistance has been extensively reported in adults with and without T2DM with varying CVD profiles (40,41). Results from the study by D'Agostino et al. (42) and from the ARIC study (43) reported that the classic risk factors for atherosclerotic CVD only explain ~70% of observed CV events, and it has been postulated that insulin resistance might be responsible for the remaining 30% (44). In conclusion, presently, the OGTT should be prioritized to identify dysglycemia despite its practical drawbacks (24). Meanwhile, further studies are warranted to establish whether some measures of insulin resistance could be better markers of metabolic derangement and predictors of CV events in high-risk populations.

Strengths and Limitations

The main strength of our report is that in the EAV registry, all data were obtained from the standardized interviews and examinations, performed by specifically trained personnel, in a large cross-sectional population with CAD from 27 European countries. Serum insulin, C-peptide, and HbA_{1c} were measured at the central laboratory with the same assay, and careful sample selection and quality assessments were performed. Likewise, FPG and 2hPG were assessed by the HemoCue 201+ equipment for glucose determination with the appropriate quality control (28).

A possible limitation of this study is that screening for dysglycemia was only performed once, while current guidelines recommend at least two positive results to confirm the diagnosis of T2DM (25). However, in patients with an acute coronary event, a single OGTT at least 4 to 5 days after symptom onset correctly classified patients with dysglycemia by strongly correlating with subsequent tests at 3 and 12 months (45).

Conclusion

Screening for dysglycemia in patients with CAD by means of serum insulin, C-peptide, HOMA-IR, HOMA2-ins, and HOMA2-Cpep had a low sensitivity and specificity to detect glucometabolic abnormalities compared with the gold-standard 2hPG.

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Author Contributions. G.F., D.D.B., and L.R. are responsible for conceptualization, statistical planning, quality assessment, data analysis, interpretation, literature search, manuscript drafting, critical revision, and administrative handling. D.D.B. is responsible for conceptualization, data analysis, interpretation, manuscript drafting, and critical revision. V.G., K.K., L.M., A.N., O.S., J.T., and D.W. contributed to planning, interpretation, and critical revision of the manuscript. I.E. and T.V. were responsible for sample analysis, quality assessment, data handling, and critical revision of the manuscript. All authors agreed to be accountable for all aspects of work, ensuring integrity and accuracy, and gave final approval of publication. G.F. and L.R. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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