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Original Article

Impaired insulin sensitivity measured by estimated glucose disposal rate is associated with decreased myocardial mechano-energetic efficiency in non-diabetic individuals

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ABSTRACT

Background and aims: Impaired myocardial mechano-energetic efficiency (MEE) has been associated with cardiac insulin resistance measured by dynamic positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) combined with euglycemic–hyperinsulinemic clamp. Estimate glucose disposal rate (eGDR) index has a good correlation with whole-body insulin sensitivity. It remains unsettled whether eGDR index is a suitable proxy of cardiac insulin sensitivity as well as its association with myocardial MEE. The aims of this study were: 1) to compare eGDR index with HOMA-IR, QUICKI and FIRI indexes for association with myocardial glucose metabolic rate (MrGlu); and 2) to determine the association of eGDR index with myocardial MEE.

Methods: We evaluated MrGlu using PET with 18F-FDG combined with euglycemic–hyperinsulinemic clamp in 50 individuals without history of coronary heart disease. Myocardial MEE per gram of left ventricular mass (MEEi) was measured in 1181 subjects by echocardiography. eGDR (mg kg^{-1}/min) was calculated as: 21.158 - (0.09 × waist circumference in cm) - (3.407 × hypertension, 1 = yes 0 = no) - (0.551 × HbA1c%).

Results: eGDR index was more strongly associated with myocardial MrGlu than HOMA-IR, QUICKI, and FIRI indexes (r = -0.662, r = -0.492, r = 0.570, and r = -0.492, respectively). Individuals in the lower tertiles of eGDR exhibited a significant reduction of MEEi as compared to those in the highest tertile ($P < 0.001$). In a stepwise multivariate linear regression analysis eGDR index was the major determinant of MEEi independently of well-established cardio-metabolic risk factors.

Conclusions: These data suggest that the eGDR index may be a useful marker to identifying individuals at high cardiovascular risk.

1. Introduction

Atherosclerotic cardiovascular diseases encompassing coronary artery disease, and stroke, remain major causes of death worldwide regardless the substantial advances in the prevention and treatment of cardiovascular diseases [1]. Proven risk factors for cardiovascular diseases include non-modifiable factors such as the male sex, age, and family history of cardiovascular diseases, and modifiable factors including overweight/obesity, hypertension, dyslipidemia, and dysglycemia/diabetes mellitus [2].

An impaired myocardial mechano-energetic efficiency (MEE) has been associated with increased risk of adverse cardiovascular outcomes [3-6]. MEE is defined as the ratio of external work performed by left ventricle (LV) (i.e. stroke work) to the total cardiac energy consumption corresponding to myocardial oxygen consumption (MVO_2). Stroke work and MVO_2 can be precisely assessed by invasive procedures such as coronary sinus catheterization or expensive methods such as magnetic resonance, and positron emission tomography, which are not feasible and affordable for both clinical practice and epidemiological studies [7, 8]. Recently, it has been proposed and validated a simple, non-invasive, ultrasound-based method to estimate myocardial MEE by calculating the ratio between LV stroke work (computed as systolic blood pressure x echocardiographic stroke volume) and MVO_2, estimated by the so called "double product" (i.e. heart rate x systolic blood pressure) [9].

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Myocardial MEE has been associated with several metabolic disorders including obesity, metabolic syndrome, dysglycemia, and type 2 diabetes [10-14], all condition characterized by insulin resistance. Prior studies have shown that cardiac insulin sensitivity measured by dynamic positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) combined with euglycemic–hyperinsulinemic clamp is associated with myocardial mechano-energetic efficiency [15]. Although dynamic positron emission tomography with ^{18}F-FDG combined with euglycemic–hyperinsulinemic clamp is considered the gold standard to precisely measure cardiac insulin sensitivity, it is a complex, expensive, and time-consuming technique with limited applicability to clinical settings or large-scale epidemiological studies. Surrogate indexes of insulin sensitivity have been developed using less costly biochemical measurements which are part of a standard diagnostic workup. A simple method based on readily available clinical parameters comprising waist circumference, hypertension, and glycosylated hemoglobin (HbA1c), has been proposed to estimate glucose disposal rate (eGDR) in individuals with different conditions of glucose tolerance including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), type 1 and type 2 diabetes [16-18]. It has been shown that eGDR index has a good correlation with insulin-stimulated whole body glucose disposal assessed by euglycaemic hyperinsulinaemic clamp procedure in both type 2 diabetes and pre-diabetes conditions [19,20]. Moreover, a higher eGDR index has been associated to reduced cardiovascular events [21]. However, whether eGDR index is a suitable surrogate measure of cardiac insulin sensitivity has not been established as well as it remains to be determined whether eGDR index is associated with myocardial MEE.

Therefore, the aims of this study were: 1) to compare eGDR index with the homeostasis model assessment of insulin resistance (HOMA-IR) index, the most widely used surrogate index of insulin resistance, for association with myocardial glucose metabolic rate measured under hyperinsulinemic condition (MrGlu) using dynamic myocardial positron emission tomography (PET) with ^{18}F-FDG combined with euglycemic-hyperinsulinemic clamp; and 2) to determine the association of eGDR index with MEE in non-diabetic individuals with different degree of insulin resistance participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study [22].

2. Methods

2.1. Study population

2.1.1. Sample 1

Sample 1 encompasses 50 adult individuals participating in the (CATAMERI), an observational study involving individuals with one or more cardio-metabolic risk factors recruited at a referral hospital of the University “Magna Graecia” of Catanzaro, as previously described in detail [22]. Subjects with type 2 diabetes were treated with a stable dose of metformin (Glucophage) monotherapy (daily dose of ≥1.500 mg). All participants underwent anthropometrical evaluation including assessments of body mass index (BMI) waist circumference and blood pressure. Blood pressure was measured in the sitting position after five minutes of quiet rest. A minimum of three blood pressure readings were taken on three separate occasions, at least two weeks apart, for screening those participants without prior history of hypertension. Baseline blood pressure values were the average of last two of the three consecutive measurements obtained at intervals of three minutes. According to ESC/ESH guidelines, hypertension is defined as office SBP values >140 mmHg and/or diastolic BP (DBP) values >90 mmHg [23]. After an overnight fasting, a 75-g oral glucose tolerance test (OGTT) was performed in subjects with fasting plasma glucose lower than 126 mg/ dl (7.0 mmol/L), HbA1c < 6.5 % (48 mmol/mol), and no history of type 2 diabetes. On the second day, after 12-h fasting, all participants underwent first echocardiography, and then, ^{18}F-FDG PET scan combined with euglycemic hyperinsulinemic clamp to measure global myocardial MRGlu under high plasma insulin condition as previously described in detail [15,22,24].

2.1.2. Sample 2

Sample 2 comprises a distinct group of 1181 non-diabetic subjects participating in the CATAMERI study [11,14]. After an over-night fasting, all individuals underwent a complete medical history and anthropometric measurements including BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. After an overnight fasting, all subjects underwent first to echocardiography and then to a 75-g oral glucose tolerance test (OGTT) to assess glucose tolerance.

A venous blood sample was drawn for metabolic and biochemical determinations. Fasting blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by enzymatic methods (Roche, Switzerland, Basel); plasma insulin concentration was assessed with chemiluminescence-based assay (Immulite®, Siemens, Italy). HbA1c was measured with high performance liquid chromatography using a National Glycohemoglobin Standardization Program (NGSP) certified automated analyzer (Adams HA-8160 HbA1C analyzer, Menarini, Italy).

The study protocol was approved by the hospital ethical committee (Comitato Etico Azienda Ospedaliera “Mater Domini”). Prior any procedures all participants provided written informed consent in accordance with the principles of Helsinki Declaration.

2.2. Echocardiographic measurements

Echocardiographic examinations were performed for each participant by a single skilled examiner using a VIVID-7 Pro ultrasound machine (GE Technologies, Milwaukee, WI) with an annular phased array 2.5-MHz transducer. Measurement of interventricular septum thickness (IVS) was performed at end-diastole. Left ventricular end-diastolic (LVEDV), LV end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were assessed according to Simpson method [25]. LV mass was calculated using the Devereux formula [26] and normalized by body surface area (BSA) [LVMI]) [27].

Stroke volume was calculated as the difference between left ventricular end-diastolic and LV end-systolic volumes. Stroke volume was allometrically normalized by height to obtain stroke index. LV myocardial MEE was determined using the method validated by DeSimone et al. as the ratio between external myocardial work and myocardial oxygen consumption [4,5,9,13,28]. External myocardial work was estimated as stroke work (SW), with SW being computed as systolic blood pressure (SBP) x echocardiographic stroke volume (SV). SV was calculated as the difference between LVEDV and LVESV by the z-derived method [4,13]. Myocardial oxygen consumption (MVO2), reflecting the total amount of energy produced by the myocardium, was estimated using the “double product” of heart rate (HR) and SBP. LV myocardial MEE was calculated as SV x SBP/ SBP x HR = SV/ HR. Because of the close dependence of MEE on LV mass, MEE was normalized by LVM to obtain an estimate of MEE per gram of LVM [i.e., indexed MEE (MEEi)] [4,5,13].

2.3. Calculations

Estimated glucose disposal rate (eGDR) (mg kg^{-1}/min) was calculated as previously described according to the following formula: eGDR = 21.158 − (0.09 x WC) − (3.407 x HT) − (0.551 x HbA1c), where WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0), and HbA1c = HbA1c (%). [29]. Hypertension was defined as systolic blood-pressure >140 mmHg, or diastolic blood-pressure >90 mmHg, respectively, or treatment with anti-hypertensive medication.

Glucose tolerance state was defined according to the ADA criteria, on the basis of OGTT using both fasting and 2-h post-challenge glucose levels [30]. Participants were classified as having normal glucose tolerance (NGT) when fasting plasma glucose was <100 mg/dL (5.5

mmol/l) and 2-hour post-load glucose was <140 mg/dL (7.8 mmol/l), isolated IFG when fasting plasma glucose was 100–125 mg/dL (5.6–6.9 mmol/l), and 2-hour post-load glucose was <140 mg/dL (7.8 mmol/l), isolated IGT when fasting plasma glucose was <100 mg/dL (5.5 mmol/l) and 2-hour post-load glucose was 140–199 mg/dL (7.8–11.0 mmol/l), combined IFG/IGT when fasting plasma glucose was 100–125 mg/dL (5.6–6.9 mmol/l) and 2-hour post-load glucose was 140–199 mg/dL (7.8–11.0 mmol/l), andtype 2 diabetes when fasting plasma glucose was ≥126 mg/dl (>7 mmol/l), 2-h post-load glucose was ≥ 200 mg/dl (>11.1 mmol/l), HbA1c ≥6.5 % or in treatment with antidiabetic drugs.

The homeostasis model assessment index of insulin resistance (HOMA-IR) was defined as fasting insulin x fasting glucose/22.5 [31]. Quantitative insulin sensitivity check index (QUICKI) was calculated from fasting plasma glucose and fasting plasma insulin levels according to the formula: QUICKI = 1/[log (fasting plasma insulin in μU/ml) + log (fasting plasma glucose in mg/dl)] [32]. Fasting insulin resistance index (FIRI) was computed according to the formula: FIRI = (fasting glucose × fasting insulin)/25 [33].

2.4. Statistical analysis

Variables with a skewed distribution, including triglycerides and plasma insulin concentration were natural log transformed for statistical analyses. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were compared by $\chi 2$ test. Variables with values of skewness test less to 1 have been considered as normally distributed. A general linear model with post hoc Fisher's least significant difference correction was employed to test pairwise differences in anthropometric and cardio-metabolic parameters among the three study groups after adjusting for confounders using a general linear model. Relationships between MEEi and clinical parameters were determined by Pearson's correlation coefficient or Spearman's correlation coefficient for categorical variables. A stepwise multivariate linear regression analysis was performed to determine the independent predictors of MEEi. Variables that are incorporated into the formula of the MEEi were not computed in the regression model to avoid potential collinearity. Multicollinearity among variables included in the multivariate linear regression model was excluded by the fact that the variance inflection factor was <2. A P-value ≤0.05 was considered statistically significant. All statistical analyses were performed by SPSS software program version 27 for Windows (IBM CORP, Armonk, NY, USA).

3. Results

3.1. Cross-sectional analysis in sample 1

Of the 50 recruited subjects, 8 (16 %) had NGT, 10 (20 %) had IFG, 9 (18 %) had IGT, and 23 (46 %) had type 2 diabetes. Clinical characteristics of the study subjects are shown in Table 1. As shown in Fig. 1, after adjustment for sex and age, the Person correlation coefficient between insulin-stimulated myocardial MrGlu and eGDR was $r = 0.622$ (Fig. 1A) while those of HOMA-IR, QUICKI and FIRI indexes of insulin sensitivity were $r = –0.492$, $r = 0.570$, and $r = –0.492$, respectively (Fig. 1B-D) (differences between correlation coefficients $P < 0.001$). In an analysis carried out in the sub-group of individuals with type 2 diabetes ($n = 23$), the Person correlation coefficient between insulin-stimulated myocardial MrGlu and eGDR was $r = 0.669$ while those of HOMA-IR, QUICKI and FIRI indexes of insulin sensitivity were $r = –0.379$ $r = 0.422$, and $r = –0.379$, respectively, after adjustment for sex and age. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the accuracy of eGDR index to identify individuals with higher cardiac insulin sensitivity defined as the upper tertile of myocardial MrGlu. To this aim, the subjects were stratified into tertiles of myocardial MrGlu, and those in the highest tertile were defined as being insulin sensitive. The AUROC was 0.858 (95 %CI 0.730–0.940), indicative of a very good accuracy for detection of high cardiac insulin sensitivity (Fig. 2). The optimal eGDR cut-off for establishing myocardial insulin sensitive was >7.085 having a sensitivity and specificity of 73.5 % and 93.7 %, respectively.

Table 1
Anthropometric and biochemical characteristics of sample 1 participants ($n = 50$).

Variables	Parameters
Sex (men/women)	26/24
Age *(yrs)*	51 ± 9
BMI *(kg/m^2)*	29.7 ± 4.8
Waist circumference (*cm*) (men/women)	102 ± 11 (105 ± 10 / 99 ± 13)
Smoking status (never smokers/current smokers/ex-smokers) (*number*)	24/23/3
Systolic blood pressure *(mmHg)*	122 ± 15
Diastolic blood pressure *(mmHg)*	76 ± 10
Hypertension (*yes/no*)	23/27
Fasting glucose *(mg/dl)*	113 ± 32
2-h glucose *(mg/dl)*	127 ± 21
HbA1c (%) [*mmol/mol*]	6.49 ± 1.24 [47.4]
Fasting plasma insulin *(μUI/ml)*	12 ± 8
HOMA-IR index	3.5 ± 2.2
QUICKI	0.13±0.1
Fasting insulin resistance index (FIRI)	3.6 ± 2.3
eGDR *(mg kg^{-1}/min)*	6.8 ± 2.5
Glucose tolerance status (NGT/IFG/IGT/T2DM) (*number*)	8/10/9/23
Myocardial MRGlu *(μmol*/min/100 g)	20.7 ± 11.0

Data are means ± SD. BMI= body mass index; eGDR = estimated glucose disposal rate, HOMA-IR= homeostasis model assessment for insulin resistance; NGT= normal glucose tolerance, IFG = impaired fasting glucose; IGT = impaired glucose tolerance, T2DM = type 2 diabetes.

3.2. Cross-sectional analysis in sample 2

The study population includes 1181 individuals with mean age 48 ± 14 years, and 43 % women participating in CATAMERI study. Clinical and anthropometric characteristics of study cohort stratified according to tertiles of eGDR are shown in Tables 2. As shown in Fig. 1S-A eGDR index was normally distributed in the whole study population and among the tertiles with the exception of tertile I, which showed a slightly higher value of skewness (1.25 ± 0.12) (Fig.S1 B-D). Subjects in the lower tertiles of eGDR were more often woman, older, and heavier as compared to patients in the highest eGDR tertile. Moreover, individuals in the two lower tertiles of eGDR showed higher fasting glycemia, HOMA-IR index, blood pressure, total cholesterol and triglycerides and lower HDL cholesterol and as compared with individuals in the highest tertile. Subjects in the lowest tertile of eGDR exhibited significantly higher fasting insulin levels as compared to those in the highest tertile. Further a greater proportion of individuals in the lower tertiles of eGDR have impaired glucose metabolism as compared to those in the highest tertile.

Table 3 shows echocardiographic parameters of the participants stratified by tertiles of eGDR. Individuals in the lower tertiles of eGDR displayed significantly higher levels of left ventricular (LV) end-systolic volume, LV end-diastolic volume, and left ventricular mass index in comparison to subjects in the highest tertile after adjusting for age and sex. Conversely, no differences were detected among tertiles in interventricular septal thickness (IVS), and posterior wall thickness (PWT). In addition, individuals in the lower tertiles of eGDR exhibited higher values of stroke work, and myocardial oxygen consumption (Table 3), and significant reduction of myocardial MEEi as compared to those in the highest tertile (Fig. 3, Table 3).

Next, in an attempt to identify clinical variables associated with myocardial MEEi, we performed a univariate analysis including several cardiovascular risk factors. As shown in Table 4, MEEi was inversely related to male sex, age, BMI, waist circumference, total cholesterol,

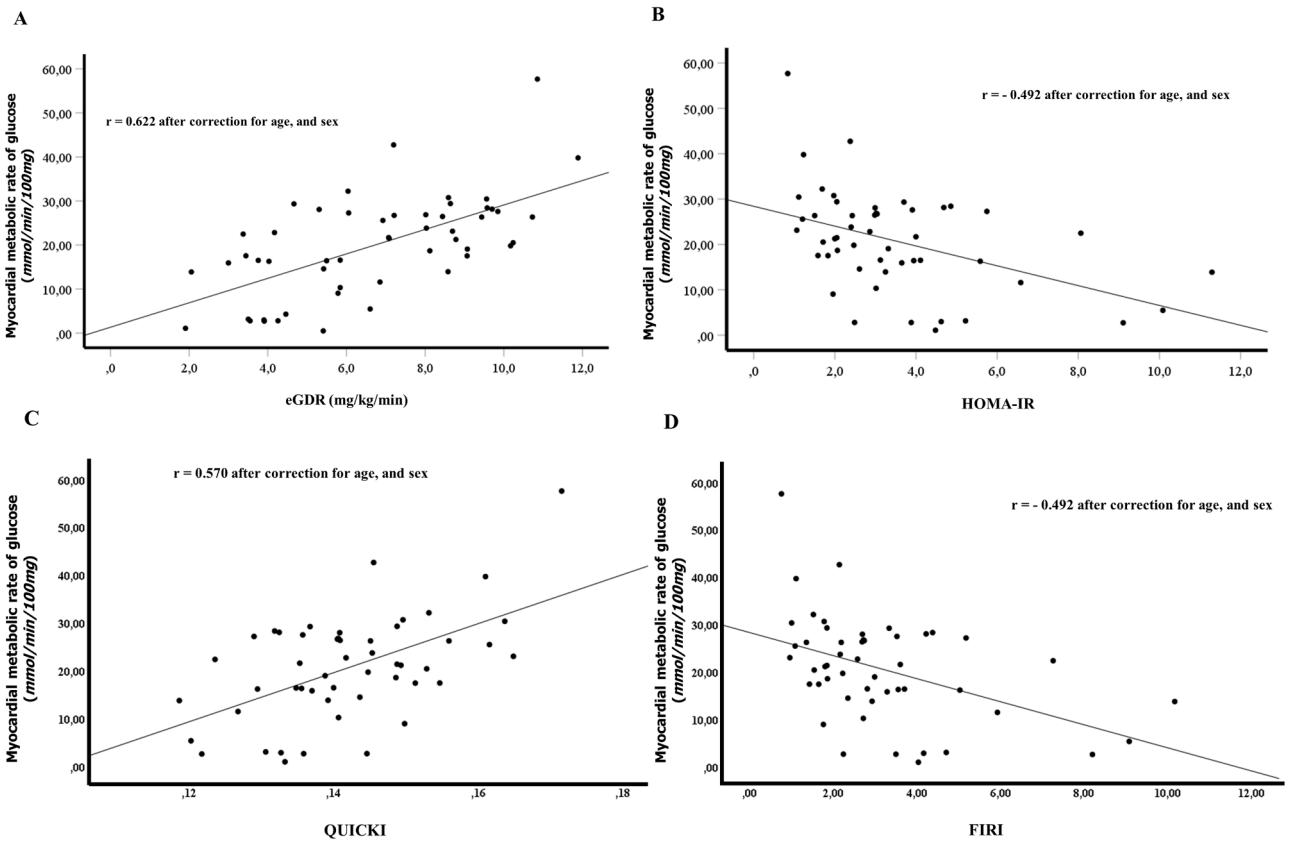

Fig. 1. Association between insulin-stimulated myocardial glucose metabolic rate (MrGlu) and eGDR (panel A), HOMA-IR index (panel B), QUIKI (panel C), or FIRI (panel D).

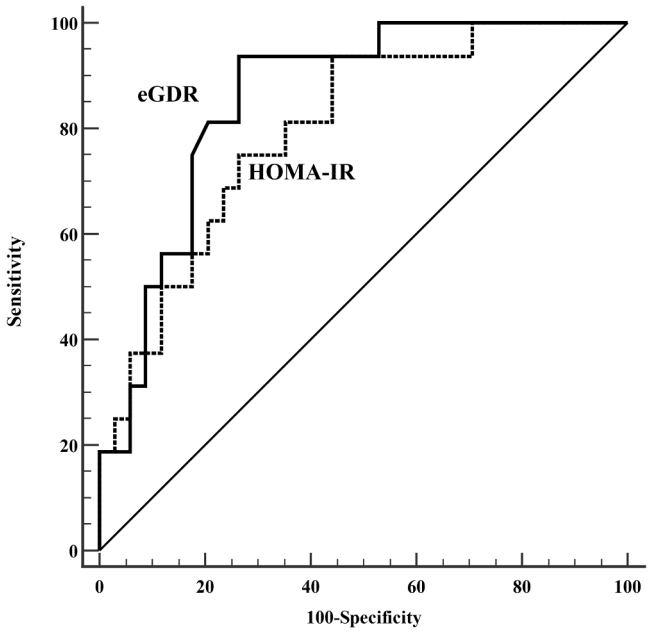

Fig. 2. ROC curves comparing the accuracy of eGDR index and HOMA-IR index in identifying higher cardiac insulin sensitivity.

triglycerides, fasting glucose, fasting insulin, HOMA-IR index, and glucose tolerance status and positively correlated with HDL levels, and eGDR. Variables reaching statistical significance were included in a stepwise multivariate linear regression analysis model to determine the independent contributors to myocardial MEEi (Table 5). We found that eGDR was the major contributor of MEEi explaining 11 % of its variation ($P < 0.0001$) followed by age and HOMA-IR index which accounted for 1.7 %, and 1.6 % of MEEi variation, respectively ($P < 0.0001$). Other independent predictors were HDL cholesterol and waist circumference explaining each an additional 0.6 % of MEEi variation (Table 5).

4. Discussion

The novel finding of the present study is that eGDR index is independently, and more strongly, associated with cardiac insulin sensitivity than HOMA-IR, QUICKI and FIRI indexes of insulin sensitivity. Furthermore, by performing a ROC curve analysis, we observed that the area under the ROC curve of the eGDR index was 0.858, indicating that it has a very good diagnostic accuracy in identifying cardiac insulin sensitivity. Moreover, given that our group have previous demonstrated a strong association between MrGlu and MEEi an emergent marker of cardiovascular risk [3-6], we investigated a possible correlation between eGDR index and MEEi. Therefore, we confirmed that eGDR index was associated with myocardial MEEi in subjects with different glucose tolerance status without history of coronary heart disease. Notably, we observed for the first time, that lower values of eGDR index were associated with a progressive decrease in myocardial MEEi, after adjusting for age and sex. This observation was strengthened by the results of a stepwise multivariate linear regression analysis showing that eGDR index was the major determinant of myocardial MEEi independently of well-established cardio-metabolic risk factors including sex, age, BMI, waist circumference, total and HDL cholesterol, triglycerides, glucose tolerance status, and HOMA-IR index. Notably, impairment in cardiac insulin sensitivity might contribute to alter myocardial MEEi by shifting the use of energy sources from glucose and lactate to fatty acid (FFA). Under normal condition, 60–70 % of myocardial energy is produced by FFA oxidation, while 30–40 % of total energy is produced by

Table 2
Demographics and metabolic risk profile of sample 2 participants stratified according to eGDR tertiles.

Variables	Tertile 1 $n = 388$	Tertile 2 $n = 390$	Tertile 3 $n = 403$				
				P	*P* 1 vs 2	*P* 2 vs 3	*P* 1 vs 3
Sex (Male/Female)	175/213	193/197	308/95	<0.001	0.05	<0.001	<0.001
Age *(years)*	52 ± 13	52 ± 13	40 ± 12	<0.001	0.78	<0.001	<0.001
BMI *(kg/m2)*	34 ± 6.3	28 ± 5.1	27 ± 5.8	<0.001	<0.001	0.07	<0.001
(lean/overweight/obese kg/m^2)	(24 ± 0.9/28 ± 1.2/ 34 ± 6.3)	(24 ± 1.4/27 ± 1.2/ 35 ± 5.5)	(22 ± 1.2/27 ± 1.47/ 35 ± 4.1)				
Waist circumference (*cm*)	114 ± 12	96 ± 10	93 ± 13	<0.001	<0.001	0.02	<0.001
(Male/Female)	(114 ± 12/115 ± 12)	(96 ± 12/97 ± 9)	(91 ± 13/97 ± 9.6)				
Smoking status (never smokers/current smokers/ ex-smokers) (*number*)	200/77/111	208/90/92	254/95/54	<0.001	0.20	0.001	<0.001
Systolic blood pressure *(mmHg)*	132 ± 14.6	132 ± 16.2	112 ± 11.5	<0.001	0.86	<0.001	<0.001
Diastolic blood pressure *(mmHg)*	82 ± 9.7	80 ± 10	71 ± 8.6	<0.001	0.003	<0.001	<0.001
Total cholesterol (*mg/dl*)	196 ± 38.1	203 ± 40.7	190 ± 38.7	<0.001	0.02	<0.001	0.02
HDL (*mg/dl*)	47 ± 12	52 ± 14	56 ± 14	<0.001	<0.001	<0.001	<0.001
Triglycerides (*mg/dl*)	138 ± 67	124 ± 66	95 ± 60	<0.001	0.003	<0.001	<0.001
Fasting Glucose *(mg/dl)*	97 ± 10	93 ± 10	86 ± 9.3	<0.001	<0.001	<0.001	<0.001
Fasting Insulin (*μU/ml*)	18 ± 12	12 ± 7.8	10 ± 8.4	<0.001	<0.001	0.11	<0.001
HOMA-IR index	4.2 ± 2.5	2.8 ± 1.8	2.1 ± 1.5	<0.001	<0.001	0.002	<0.001
HbA1c (%) [mmol/l]	5.6 ± 0.3 [37.7]	5.4 ± 0.3 [35.5]	5.3 ± 0.3 [34.4]	<0.001	<0.001	<0.001	<0.001
eGDR *(mg kg^{-1}/min)*	4.3 ± 1.1	6.3 ± 0.5	9.5 ± 1.2	<0.001	<0.001	<0.001	<0.001
Glucose tolerance (NGT/IFG/IGT/IFG-IGT)	184/69/54/81	229/64/63/34	326/26/36/15	<0.001	<0.001	<0.001	<0.001

Data are expressed as mean ± SD. Comparisons between the three groups were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons.
BMI= body mass index, eGDR = estimated glucose disposal rate, HDL: high density lipoprotein, HOMA-IR= homeostasis model assessment for insulin resistance, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, NGT: normal glucose tolerance.

Table 3
Echocardiographic parameters of study cohort stratified according to eGDR tertiles.

Variables	Tertile 1 $n = 388$	Tertile 2 $n = 390$	Tertile 3 $n = 403$				
				P	*P* 1 vs 2	*P* 2 vs 3	*P* 1 vs 3
LV end-systolic volume (mL)	40.2 ± 20.7	34.2 ± 19.6	31.1 ± 13.4	<0.001	<0.001	0.01	<0.001
LV end-diastolic volume (mL)	133 ± 39.1	119 ± 40.1	111 ± 32.4	<0.001	<0.001	0.002	<0.001
Interventricular septal thickness (IVS) (cm)	1.39 ± 0.19	1.44 ± 0.28	1.24 ± 0.17	0.06	–	–	–
Posterior wall thickness (PWT) (cm)	1.50 ± 0.22	1.50 ± 0.25	1.37 ± 0.19	0.21	–	–	–
LVM (g)	226 ± 64.7	194 ± 57.2	156 ± 47.4	<0.001	<0.001	<0.001	<0.001
LVM index (g/m$^{2.7}$)	111 ± 31.1	106 ± 29.4	86.1 ± 21.7	<0.001	0.007	<0.001	<0.001
Stroke volume (mL)	93.7 ± 25.9	85.4 ± 26.4	80.3 ± 22.6	<0.001	<0.001	<0.001	<0.001
Stroke work (mmHg*ml)	12,425 ± 3711	11,321 ± 3615	9077.3 ± 2777	<0.001	<0.001	0.005	<0.001
Heart rate (bpm)	71 ± 10	71 ± 10	70 ± 10	0.59	–	–	–
Myocardial oxygen consumption (mmHg x bpm)	9482 ± 1873	9475 ± 1845	7976 ± 1463	<0.001	0.96	<0.001	<0.001
Myocardial MEEi (mL/*secg^{-1})**	0.36 ± 0.10	0.38 ± 0.11	0.45 ± 0.12	<0.001	0.02	<0.001	<0.001

Data are means ± SD. Comparisons between the three groups were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons. P values refer to results after analyses with adjustment for sex and age.
LV = Left Ventricular; LVM = Left ventricular mass; LVMI = left ventricular mass index; MEEi = LVM-normalized mechano-energetic efficiency.

glucose-pyruvate oxidation [13]. FFA oxidation is associated with impaired energetic efficiency due to a lower yield of ATP per mole of oxygen consumed (phosphate-to-oxygen ratio = 2.28) as compared to glucose-pyruvate oxidation (phosphate-to-oxygen ratio = 2.58). Under conditions of insulin resistance, impaired myocardium glucose metabolism leads to a substrate shift toward FFA oxidation resulting in lower efficiency of cardiac energy utilization, and loss of myocardial metabolic flexibility. Accordingly, we found that the graded reduction of eGDR index is associated with a progressive increase in MEEi, which was highly significant and independent of demographical data, and major cardio-metabolic risk factors. Therefore, eGDR index could be considered as a powerful independent correlate of MEEi, and its use could be suitable to recognize cardiac insulin resistance among subjects with various conditions of glucose tolerance. The availability of simple and inexpensive tests such as the eGDR index may help to better identifying individuals at high cardiovascular risk, expanding the benefits of screening.

Although dynamic myocardial PET with 18F-FDG combined with euglycemic-hyperinsulinemic clamp is the gold standard method to measure cardiac insulin sensitivity, it is time consuming and costly and not suitable for large-scale epidemiological studies or clinical settings. The HOMA-IR is the most widely used surrogate index of insulin resistance and has been associated with reduced MEE in non-diabetic individuals [10,13]. However, HOMA-IR index has some limitation of accuracy in individuals with lower BMI, lower pancreatic beta cell function, higher fasting glucose levels, and in patients receiving insulin treatment [34]. Moreover, plasma insulin levels are not routinely measured, which also limits the use of HOMA-IR index. By contrast, the eGDR index offers some practical? benefits over assessment of the HOMA-IR index since it does not require fasting plasma glucose and insulin values, uses routine clinical parameters, and is valid, regardless of insulin treatment.

The present study has some strengths that merit consideration. A major strength o is that, to the best of our knowledge, this is the first study demonstrating a relationship between the eGDR index and myocardial glucose metabolism under hyperinsulinemic condition in subjects with various states of glucose tolerance using cardiac dynamic PET in combination with the euglycemic-hyperinsulinemic clamp

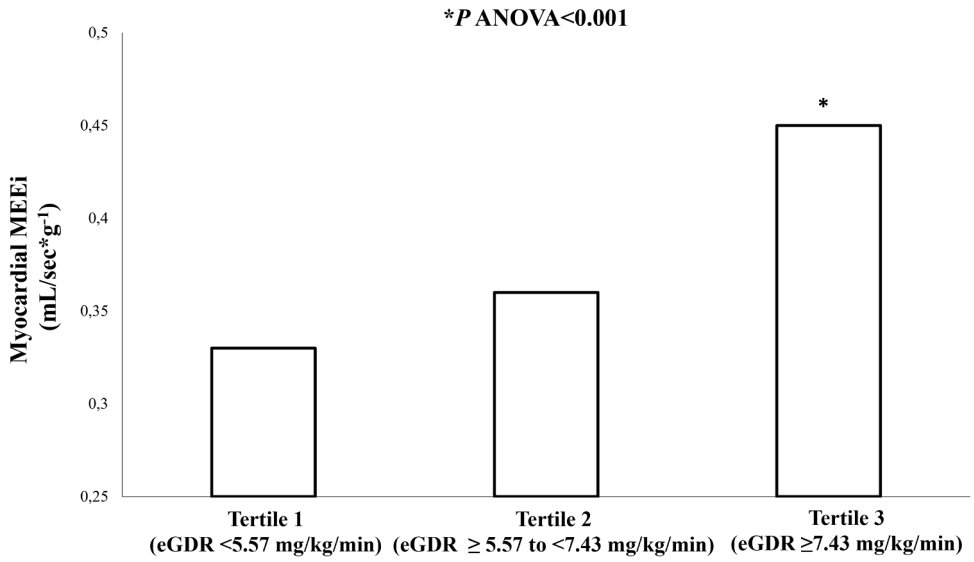

Fig. 3. Myocardial MEEi values of study population stratified according to eGDR tertiles.

Table 4
Univariate analysis between myocardial MEEi and clinical parameters.

Variables	Myocardial MEEi R	P
Sex[a]	−0.15	<0.001
Age ***(years)***	−0.24	<0.001
BMI (kg/m^2)	−0.13	<0.001
Smoking status (never smokers/current smokers/ex-smokers)[a]	−0.06	0.02
Waist circumference (cm)	−0.18	<0.001
Total cholesterol (mg/dL)	−0.06	0.01
HDL-C (mg/dL)	0.17	<0.001
Triglycerides (mg/dL)	−0.17	<0.001
Glucose tolerance status[a]	−0.22	<0.001
HOMA-IR	−0.21	<0.001
eGDR *(mg kg^{-1}/min)*	0.33	<0.001

[a] Spearman coefficient

BMI= body mass index, eGDR = estimated glucose disposal rate, eGFR=estimated glomerular filtration rate, HDL: high density lipoprotein, HOMA-IR= homeostasis model assessment for insulin resistance, MEEi: LVM-normalized mechano-energetic efficiency.

Table 5
Stepwise multiple regression analysis with MEEi as dependent variable.

	Myocardial MEEi		
Variables	Total R2 (%)	Partial R^2 (%)	P
eGDR *(mg kg^{-1}/min)*	11.2	11.2	< 0.0001
Age *(years)*	12.9	1.7	< 0.0001
HOMA-IR	14.5	1.6	<0.0001
HDL *(mg/dl)*	15.1	0.6	0.003
Waist circumference *(cm)*	15.7	0.6	0.016

Independent variables associated to MEEi after stepwise regression analysis in a model including sex, age, BMI, waist circumference, total and HDL cholesterol, triglycerides, glucose tolerance status, HOMA-IR and eGDR.
eGDR = estimated glucose disposal rate, HDL: high density lipoprotein, MEEi: LVM-normalized mechano-energetic efficiency.

technique, the gold standard technique for valuation of cardiac insulin sensitivity. Another strength of the study is that the association of eGDR index with MEE was studied in a relatively large sample of adults including both men and woman, without prior diagnosis of diabetes or cardiovascular disease, who were carefully characterized according to a standardized protocol with the exclusion of subjects treated with corticosteroids, antiplatelet and anticoagulant drugs or affected by disorders potentially affecting hemoglobin concentration. Moreover, assessments of biochemical and hematological parameters were performed in fresh, rather than stored, blood samples thus preventing possible problems of degradation and cell lysis. Additional strengths of the present study are the centralized determinations of biochemical parameters comprising a rigorously standardized HbA1c assay, and the measurements of echocardiographic parameters performed by a single trained examiner who was blinded to the clinical data of the participants.

Nevertheless, the present study has some limitations that deserve comment. First, although myocardial MEEi was evaluated by indirect measures rather than by coronary sinus catheterization, this latter measurement is invasive, and time-consuming thus making this procedure not suitable in large epidemiological studies. A second limitation of the present study is its cross-sectional design, and, therefore, a causal relationship between increased cardiac insulin resistance and compromised myocardial mechano-energetic state cannot be established. Additionally, the study population consisted of White adult men and women recruited at a single institution, thus, the generalizability of the results to other ethnic groups remains to be established. Finally, this study is not a randomized trial, but rather an observational study, and thus, the results may be subject to residual unknown confounding factors.

5. Conclusion

The current study suggests that eGDR index is a better surrogate measure of cardiac insulin sensitivity than HOMA-IR, QUICKI, and FIRI indexes. eGDR index is associated with reduced myocardial MEEi in a large cohort of nondiabetic individuals independently of other cardiometabolic risk factors. These findings support the notion that a decrease in cardiac insulin resistance may be one of the key mechanisms leading to impaired myocardial energetics, measured by myocardial MEEi. Thus, the eGDR index may reflect cardiac insulin resistance and may be a useful marker to identify individuals at higher cardiovascular risk.

Statements and declarations

Competing interests: The authors have no competing interests to declare that are relevant to the content of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.09.008.

References

[1] Virani SS, et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. Circulation 2020;141(9):e139–596.
[2] Vaduganathan M, et al. The global burden of cardiovascular diseases and risk: a compass for future health. J Am Coll Cardiol 2022;80(25):2361–71.
[3] Juszczyk A, et al. Depressed cardiac mechanical energetic efficiency: a contributor to cardiovascular risk in common metabolic diseases-from mechanisms to clinical applications. J Clin Med 2020;9(9).
[4] de Simone G, et al. Depressed myocardial energetic efficiency is associated with increased cardiovascular risk in hypertensive left ventricular hypertrophy. J Hypertens 2016;34(9):1846–53.
[5] Losi MA, et al. Depressed myocardial energetic efficiency increases risk of incident heart failure: the strong heart study. J Clin Med 2019;8(7).
[6] Manzi MV, et al. Low mechano-energetic efficiency is associated with future left ventricular systolic dysfunction in hypertensives. ESC Heart Fail 2022;9(4): 2291–300.
[7] Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. J Physiol 2004;555(Pt 1):1–13.
[8] Knaapen P, et al. Myocardial energetics and efficiency: current status of the noninvasive approach. Circulation 2007;115(7):918–27.
[9] de Simone G, et al. Myocardial mechano-energetic efficiency in hypertensive adults. J Hypertens 2009;27(3):650–5.
[10] Cefalo CMA, et al. Metabolic syndrome and C reactive protein are associated with a reduced myocardial mechano-energetic efficiency. J Clin Endocrinol Metab 2023 Oct 18;108(11):e1264–71.
[11] Vanessa Fiorentino T, et al. Depressed myocardial mechano-energetic efficiency in subjects with dysglycemia. Diabetes Res Clin Pract 2021;177:108883.
[12] Mancusi C, et al. Effect of diabetes and metabolic syndrome on myocardial mechano-energetic efficiency in hypertensive patients. the campania salute network. J Hum Hypertens 2017;31(6):395–9.
[13] Mancusi C, et al. Myocardial mechano-energetic efficiency and insulin resistance in non-diabetic members of the strong heart study cohort. Cardiovasc Diabetol 2019; 18(1):56.
[14] Succurro E, et al. Sex-specific differences in left ventricular mass and myocardial energetic efficiency in non-diabetic, pre-diabetic and newly diagnosed type 2 diabetic subjects. Cardiovasc Diabetol 2021;20(1):60.
[15] Succurro E, et al. Impaired insulin-stimulated myocardial glucose metabolic rate is associated with reduced estimated myocardial energetic efficiency in subjects with different degrees of glucose tolerance. Cardiovasc Diabetol 2023;22(1):4.
[16] Karamanakos G, et al. The association of insulin resistance measured through the estimated glucose disposal rate with predictors of micro-and macrovascular complications in patients with type 1 diabetes. Prim Care Diabetes 2022;16(6): 837–43.
[17] Epstein EJ, et al. Use of the estimated glucose disposal rate as a measure of insulin resistance in an urban multiethnic population with type 1 diabetes. Diabetes Care 2013;36(8):2280–5.
[18] Penno G, et al. Insulin resistance, diabetic kidney disease, and all-cause mortality in individuals with type 2 diabetes: a prospective cohort study. BMC Med 2021;19 (1):66.
[19] Zabala A, et al. Estimated glucose disposal rate and risk of stroke and mortality in type 2 diabetes: a nationwide cohort study. Cardiovasc Diabetol 2021;20(1):202.
[20] Cefalo CMA, et al. Frequency of prediabetes in individuals with increased adiposity and metabolically healthy or unhealthy phenotypes. Diabetes Obes Metab 2024.
[21] Sun R, et al. Association of insulin resistance with cardiovascular disease and all-cause mortality in type 1 diabetes: systematic review and meta-analysis. Diabetes Care 2024.
[22] Succurro E, et al. Reduction in Global Myocardial Glucose Metabolism in Subjects With 1-Hour Postload Hyperglycemia and Impaired Glucose Tolerance. Diabetes Care 2020;43(3):669–76.
[23] Williams B, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021–104.
[24] Succurro E, et al. Metabolic syndrome is associated with impaired insulin-stimulated myocardial glucose metabolic rate in individuals with type 2 diabetes: a cardiac dynamic (18)F-FDG-PET study. Front Cardiovasc Med 2022;9:924787.
[25] Lang RM, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28(1):1–39.e14.
[26] Devereux RB, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57(6):450–8.
[27] de Simone G, et al. Normalization for body size and population-attributable risk of left ventricular hypertrophy: the strong heart study. Am J Hypertens 2005;18(2 Pt 1):191–6.
[28] De Marco M, et al. Influence of Left Ventricular Stroke Volume on Incident Heart Failure in a Population With Preserved Ejection Fraction (from the Strong Heart Study). Am J Cardiol 2017;119(7):1047–52.
[29] Williams KV, et al. Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes 2000;49(4):626–32.
[30] ElSayed NA, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S19–40.
[31] Matthews DR, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–9.
[32] Katz A, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85(7):2402–10.
[33] Duncan MH, et al. A simple measure of insulin resistance. Lancet 1995;346(8967): 120–1.
[34] Kang ES, et al. Limitation of the validity of the homeostasis model assessment as an index of insulin resistance in Korea. Metabolism 2005;54(2):206–11.