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Relationship between hemoglobin glycation index and myocardial mechano-energetic efficiency in non-diabetic individual

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Abstract

Background and aims The hemoglobin glycation index (HGI) has been linked to cardiovascular disease in diabetic patients. However, it remains unclear whether an elevated HGI similarly affects the cardiovascular system in individuals with normal glucose tolerance or prediabetes. In this cross-sectional study, we aimed to determine whether increased HGI levels are associated with a reduction in myocardial mechano-energetic efficiency (MEE), a key predictor of cardiovascular events and heart failure, in non-diabetic subjects.

Methods Myocardial MEE per gram of left ventricular mass (MEEi) was assessed via echocardiography in a cohort of 1,074 adults with different glucose tolerance statuses, enrolled in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study. HGI was defined as the difference between the measured HbA1c and the predicted HbA1c, the latter calculated from the linear association between HbA1c and fasting plasma glucose levels.

Results Subjects in the highest HGI quartile exhibited significantly elevated myocardial oxygen consumption and a marked reduction in MEEi compared to those in the lowest quartile. A significant inverse correlation was observed between HGI and MEEi ($r = -0.210$, $P < 0.001$). A multivariate linear regression analysis confirmed the strong relationship between higher HGI levels and lower MEEi, even after adjusting for several potential confounders, including sex, age, body mass index, waist circumference, smoking status, triglycerides, HDL cholesterol, 2-hour post-load glucose, glucose tolerance status, fasting insulin, HOMA-IR, hs-CRP, antihypertensive therapy, and lipid-lowering therapy.

Conclusions These findings support the hypothesis that higher HGI values may affect myocardial mechano-energetic efficiency in non-diabetic individuals.

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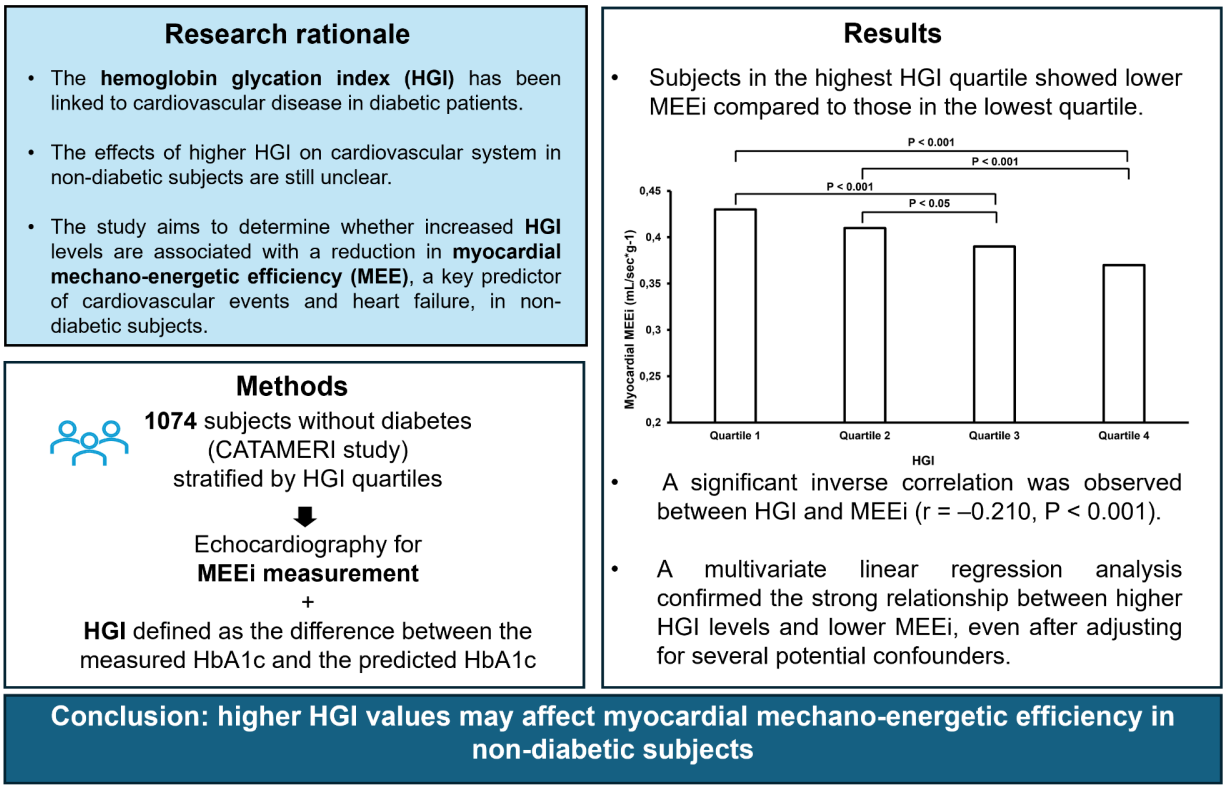
Graphical abstract



Keywords Hemoglobin glycation index, Myocardial mechano-energetic efficiency (MEE), Glucose tolerance, Cardiovascular diseases, Echocardiography

Background

Glycated hemoglobin (HbA1c) is widely regarded as the gold standard for monitoring glycemic control over 2–3 months in patients with diabetes and serves as a well-established prognostic indicator for both microvascular and macrovascular complications [1–3]. However, discrepancies between HbA1c values and plasma glucose concentrations have been reported, with some individuals exhibiting unexpectedly low or high HbA1c levels despite similar glycemia [4–8]. To address these interindividual differences in HbA1c, which may reflect variations in the intracellular glycation process, a statistical measure known as the hemoglobin glycation index (HGI) has been developed [9–10]. HGI is determined as the difference between the observed HbA1c and the HbA1c predicted by inserting the subject's fasting blood glucose (FBG) into a regression equation that describes the linear relationship between HbA1c and FBG [11]. In diabetic patients, higher HGI values have been proposed a proxy of increased non-enzymatic protein glycation which may play a pathophysiological role in vascular complications of diabetes [11–14]. While in non-diabetic subjects, HGI is thought to offer a more refined measure of metabolic health, particularly for identifying individuals at risk of developing diabetes and cardiovascular diseases [15–16]. Elevated HGI in this population may reflect chronic low-level hyperglycemia and increased oxidative stress, all of which could contribute to endothelial dysfunction, vascular stiffness, and the development of atherosclerotic changes over time [17, 18]. However, whether raised HGI values adversely influence the cardiovascular system in subjects with normal glucose tolerance or prediabetes, who generally exhibit lower glucose levels than typical diabetic patients, remains to be established.

The human heart converts chemical energy into mechanical work via a complex interplay of biochemical and biophysical processes involving the coordinated activation and deactivation of enzymes, ion channels, and various proteins, ranging from contractile to structural and membrane-associated types [19, 20]. Myocardial mechano-energetic efficiency (MEE) quantifies the left ventricle's ability to transform the chemical energy

produced by oxidative metabolism into mechanical energy [3]. Typically, MEE is expressed as the ratio of external systolic work (e.g., stroke work) to myocardial oxygen consumption (MVO_2) during contraction [21, 22]. A decline in MEE has been associated with unfavorable cardiovascular outcomes [21, 22]. Although accurate assessment of cardiac energy consumption often relies on invasive methods, such as coronary sinus catheterization [23], or on non-invasive but expensive and time-consuming techniques like positron emission tomography (PET) [24], these approaches are impractical for large-scale observational studies. Recently, a surrogate ultrasound-based method has been introduced to estimate myocardial MEE per gram of left ventricular mass (MEEi) [21, 22, 25, 26]. According to this technique, myocardial MEE is defined as the ratio between the external work performed by the left ventricle (quantifiable as stroke work, i.e., the product of systolic blood pressure and stroke volume) and myocardial oxygen consumption, which is approximated using the "double product" (systolic blood pressure multiplied by heart rate) [21, 22]. Moreover, several studies have shown that decreased MEE is linked to an increased risk of heart failure and adverse cardiovascular outcomes [21, 22], making it a valuable prognostic tool for early detection of myocardial impairment.

To determine whether an elevated HGI, which implies a greater net glycation rate, can identify a distinct non-diabetic subgroup with myocardial damage, we investigated the association between HGI and MEEi in participants of the CATAnzaro MEtabolic RIsk factors (CATAMERI) study.

Methods

Study participants

In 2006, we established the CATAMERI hospital-based cohort, recruiting adult individuals attending the outpatient clinic at the University Hospital of the University "Magna Graecia" of Catanzaro. Participants were selected based on the presence of one or more cardiometabolic risk factors, including dysglycemia, hypertension, dyslipidemia, and overweight/obesity. We excluded individuals with a previous diagnosis of type 1 or type 2 diabetes, established cardiovascular disease, valvular heart disease, a history of malignant or autoimmune diseases, anemia, hemoglobinopathies (including beta-thalassemia trait), erythrocyte disorders, accumulation diseases such as amyloidosis and hemochromatosis, acute or chronic infections, end-stage renal disease, a history of major blood loss or transfusions, chronic pancreatitis, liver cirrhosis, positivity for antibodies to hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg), a history of alcohol consumption exceeding 20 g/day in women or 30 g/day in men, treatment with medications known to affect glucose metabolism (such as corticosteroids and estro-progestins used for hormonal contraception or replacement therapy), and the use of antiplatelet or anticoagulant medications. Only patients with the required variables were included in the analyses. A flowchart outlining the participants' enrollment process is provided in the Supplementary Materials [27, 28]. Comprehensive anthropometric assessments were performed for all participants, including body mass index (BMI) and waist circumference measurements. Participants were classified according to the American Diabetes Association (ADA) criteria [29] as having normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), or combined IFG/IGT based on glucose values during oral glucose tolerance test. The study received approval from the Ethical Committee of the Azienda Ospedaliera "Mater Domini," and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Echocardiographic measurements

A single experienced operator, blinded to other study data, performed echocardiographic examinations using a VIVID-7 Pro ultrasound system (GE Technologies, Milwaukee, WI) equipped with an annular phased array 2.5-MHz transducer [30, 31]. Two-dimensional imaging was utilized to record the tracings, and M-mode measurements were taken at or near the tip of the mitral valve. Measurements of the interventricular septum thickness (IVS) and posterior wall thickness (PWT) were recorded at end-diastole. Left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV) were determined according to Simpson's method and indexed to body surface area (BSA) [32]. The left ventricular mass (LVM) was calculated using the Devereux formula [33]. Myocardial mechano-energetic efficiency (MEE) is defined as the ratio of the external myocardial work performed (i.e., stroke work) to the total myocardial energy consumption, and it was estimated as described in previous studies [34, 35]. External myocardial work was approximated by stroke work (SW), which was calculated using the equation SBP × SV, where SBP represents systolic blood pressure (mmHg), and SV denotes the echocardiographically measured stroke volume (mL). Myocardial oxygen consumption (MVO_2) was estimated using the "double product" (SBP × HR, with HR in beats per minute) [36]. Consequently, MEE is calculated as (SBP × SV) / (SBP × HR) = SV / HR, with HR converted to seconds (HR/60). Given the strong relationship between MEE and left ventricular mass, MEE was normalized to LV mass to yield an energy expenditure index per myocardial mass unit (MEEi, expressed in mL/s/g) [21, 22, 34, 35].

Laboratory determinations

Plasma glucose, triglycerides, total cholesterol, and HDL cholesterol were measured using enzymatic methods (Roche Diagnostics, Mannheim, Germany). HbA1c was quantified via high-performance liquid chromatography on an NGSP-certified automated analyzer (Adams HA-8160 HbA1c analyzer, Menarini, Italy). Plasma insulin levels were determined using a chemiluminescence-based assay (Immulite, Siemens, Italy), and high-sensitivity C-reactive protein (hsCRP) levels were measured with an automated instrument (CardioPhase® hsCRP, Milan, Italy). The homeostasis model assessment index of insulin resistance (HOMA-IR) was defined as fasting insulin x fasting glucose/22.5 [36].

Calculation of the hemoglobin glycation index (HGI)

The hemoglobin glycation index (HGI) was calculated following previously published protocols [37, 38]. The linear relationship between fasting plasma glucose and HbA1c levels was established through linear regression analysis using data from 2,055 non-diabetic adults participating in the CATAMERI study, as detailed elsewhere [39]. The predicted HbA1c for each subject was derived by inputting the fasting plasma glucose into the linear regression equation (HbA1c = 0.0158 × fasting glucose (mg/dl) + 4.0311). HGI was then computed as the difference between the observed HbA1c and the predicted value [11–18, 37, 38]. Participants were stratified into quartiles based on their HGI values.

Statistical analyses

The normality of continuous variables was assessed by Shapiro-Wilk test, kurtosis and skewness measures, and normal probability Q–Q plots. Homoscedasticity was assessed by visually inspecting a plot of the standardized regression residuals versus the independent variable (i.e., myocardial MEEi) (Supplementary Fig. 1). A LOWESS smoothing regression curve has been included in the scatterplot, showing a smooth, nearly straight line without significant curvature, closely following the overall trend of the data points (Supplementary Fig. 2). Due to their skewed distributions, triglycerides, hs-CRP, fasting insulin, and the HOMA-IR index were log-transformed using the natural logarithm for statistical analyses. Continuous variables are presented as means ± standard deviation (SD), while categorical variables were compared using the χ^2 test. Differences in anthropometric and metabolic characteristics among HGI quartiles were assessed using a general linear model adjusted for age and sex, with post hoc pairwise comparisons conducted via Fisher's least significant difference method. Subgroup analyses were performed by stratifying participants by age categories (< 50, 50–65, > 65 years), BMI categories (BMI < 25, 25–29.9, > 30 kg/m^2), and glucose tolerance categories (NGT and prediabetes)Confounders are selected based on univariate analysis, as they may be associated with both the independent variable (HGI) and the dependent variable (MEEi). This approach controls for confounding effects, ensuring the relationship between the variables is not distorted. Variables significantly associated with MEEi are considered potential confounders and further evaluated using multivariate models, minimizing the risk of overfitting and ensuring a more parsimonious model. A multivariate linear regression analysis was then performed to assess the independent contribution of HGI, both as a categorial variable (quartiles) and as continuous variable, to MEEi, excluding variables that are part of the calculation of MEEi and HGI (i.e., fasting plasma glucose and HbA1c) to avoid collinearity issues. A variance inflation factor (VIF) value < 2 was considered acceptable to avoid multicollinearity among variables. For all tests, a P value < 0.05 was considered statistically significant. All analyses were conducted using SPSS software (version 27 for Windows; IBM Corp, Armonk, NY, USA).

Results

The clinical characteristics of the study cohort are summarized in Table 1. The mean age of the participants was 48 ± 14 years, with women comprising 57% (n = 612) of the cohort, and the average BMI was 29.8 ± 6.7 kg/m^2. Among the 1,074 individuals examined, 62.2% (n = 668) exhibited NGT, 13.9% (n = 149) had isolated IFG, 12.8% (n = 138) had isolated IGT, and 11.1% (n = 119) had combined IFG/IGT. As detailed in Table 1, a comparison of the anthropometric and metabolic features of the study subjects stratified by HGI quartiles revealed that subjects in higher HGI quartiles were generally older than those in the lower quartile. After adjustment for age and sex, subjects in the higher HGI quartiles (third and fourth) demonstrated progressively higher levels of BMI, waist circumference, triglycerides, fasting insulin, HOMA-IR, and hs-CRP, along with lower HDL cholesterol concentrations compared to those in the lowest HGI quartile (Table 1). Additionally, an inverse pattern was observed for metabolic parameters: while fasting glucose values decreased HbA1c and 2-hour post-load glucose levels increased across HGI quartiles. Consequently, a higher proportion of individuals with impaired glucose tolerance was noted in the two highest HGI quartiles compared with the lowest (Table 1). Furthermore, a greater prevalence of current and former smokers was observed, as well as increased usage of ACE inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and lipid-lowering medications in the upper HGI quartiles relative to the lowest.

The echocardiographic parameters of participants, stratified by HGI quartiles, are presented in Table 2. Individuals in the highest two HGI quartiles exhibited

Table 1 Echocardiographic parameters of study participants stratified according to according to quartiles of hemoglobin glycation index

Variables	Whole study group	Quartile 1 (– 1.385; -0.211)	Quartile 2 (– 0.206; – 0.006)	Quartile 3 (– 0.001; 0.205)	Quartile 4 (0.206; 1.136)	*P*
Sex (Men/Women)	462/612	108/161	120/149	113/154	121/148	0.64
Age (yrs)	48 ± 14	44 ± 14	46 ± 14	50 ± 15 [a, b]	54 ± 13 [a, c,e]	< 0.001*
BMI (kg/m2)	29.8 ± 6.7	28.3 ± 5.9	29.5 ± 6.5 [b]	29.8 ± 6.5 [b, d]	31.6 ± 7.2 [a, c,e]	< 0.001
Waist circumference (cm)	101 ± 15	97 ± 14	100 ± 14	102 ± 15 [b]	107 ± 16 [a, c,e]	< 0.001
Smoking status (never smokers/current smokers/ex-smokers) (number)	597/233/244	173/50/46	152/62/54	144/51/72 [b]	127/70/72 [a]	0.002
Systolic blood pressure (mmHg)	125 ± 16	122 ± 16	124 ± 17	126 ± 17	129 ± 15	0.43
Diastolic blood pressure (mmHg)	78 ± 11	76 ± 10	77 ± 10	78 ± 11	79 ± 10	0.44
Total cholesterol (*mg/dl*)	197 ± 40	190 ± 37	195 ± 40	200 ± 39	200 ± 41	0.20
HDL (mg/dl)	52 ± 14	53 ± 13	52 ± 14	51 ± 14 [b]	50 ± 14 [a, c]	< 0.001
Triglycerides (mg/dl)	119 ± 67	104 ± 55	117 ± 69	122 ± 71 [b]	133 ± 71 [a, d]	< 0.001
hsCRP (mg/l)	3.0 ± 2.7	2.6 ± 2.7	2.8 ± 2.5	3.0 ± 2.7 [b]	3.7 ± 3.0 [a, c,f]	< 0.001
Fasting insulin (μU/ml)	13 ± 9	12 ± 7	13 ± 10 [b]	13 ± 8 [b]	15 ± 9 [a, d,f]	< 0.001
HOMA-IR index	3.1 ± 2.1	2.8 ± 1.8	3.1 ± 2.3	3.1 ± 2.1	3.5 ± 2.3 [a, d,f]	0.002
Fasting glucose (mg/dl)	92 ± 11	94 ± 11	92 ± 10 [b]	92 ± 10 [b]	91 ± 12 [a]	0.005
2-h post-load glucose (mg/dl)	122 ± 30	113 ± 28	119 ± 31	122 ± 29 [b]	133 ± 30 [a, c,f]	< 0.001
HbA1c (%)	5.5 ± 0.4 (36.6 mmol/mol)	5.1 ± 0.2 (32.2 mmol/mol)	5.4 ± 0.2 [a] (35.5 mmol/mol)	5.6 ± 0.2 [a, c] (37.7 mmol/mol)	5.9 ± 0.3 [a, c,e] (41.0 mmol/mol)	< 0.001
Glucose tolerance status (NGT/IFG/IGT/combo IFG + IGT) (number)	668/149/138/119	185/48/14/22	173/32/36/28 [b]	174/32/36/25 [b]	136/37/52/44 [a, d,f]	< 0.001
ACE inhibitor or Angiotensin receptor blocker therapy, No (%)	376 (35%)	64 (23.8%)	82 (30.5%)	108 (40.4%) [a, d]	122 (45.3%) [a, b]	< 0.001
Beta blocker therapy, No (%)	171 (15.9%)	35 (13.0%)	32 (11.9%)	52 (19.5%) [d]	52 (19.3%) [d]	0.02
Diuretic therapy, No (%)	186 (17.3%)	23 (8.6%)	37 (13.8%)	57 (21.3%) [a, d]	69 (25.7%) [a, c]	< 0.001
Calcium channel blocker therapy, No (%)	133 (12.4%)	34 (12.6%)	29 (10.8%)	36 (13.5%)	34 (12.6%)	0.80
Lipid-lowering therapy, No (%)	127 (11.8%)	21 (7.8%)	27 (10.0%)	30 (11.2%)	49 (18.2%) [a, d,f]	0.001

Data are means ± SD. Fasting insulin, triglycerides, HOMA-IR index, and hsCRP were log-transformed for statistical analysis, but the values in the table represent the back-transformation to the original scale. Categorical variables were compared using the χ^2 test. Comparisons among the four groups were performed using a general linear model for multiple comparisons. *P*-values refer to results after analysis of the differences among the four groups, with adjustments for age and sex. **P* values refer to results after analyses with adjustment for sex.

BMI: body mass index; hsCRP: high sensitivity C reactive protein; HDL: high density lipoprotein; ACE: angiotensin-converting-enzyme.

[a] $P < 0.001$ vs. Quartile 1 of HGI.

[b] $P < 0.05$ vs. Quartile 1 of HGI.

[c] $P < 0.001$ vs. Quartile 2 of HGI.

[d] $P < 0.05$ vs. Quartile 2 of HGI.

[e] $P < 0.001$ vs. Quartile 3 of HGI.

[f] $P < 0.05$ vs. Quartile 3 of HGI.

significantly lower MEEi values compared to those in the lowest quartile (see Fig. 1; Table 2). Moreover, individuals in the highest HGI quartile (quartile 4) had significantly higher myocardial oxygen consumption values compared to those in the lowest quartile (Table 2). A univariate analysis incorporating various cardiometabolic risk factors was performed to determine the anthropometric and metabolic determinants associated with MEEi. As detailed in Table 3, MEEi showed a significant negative correlation with factors such as male sex, age, BMI, waist circumference, smoking status, triglycerides, 2-hour post-load glucose, glucose tolerance status, fasting insulin, HOMA-IR, hs-CRP, HGI, and the use of ACE inhibitors/angiotensin receptor blockers, diuretics, calcium channel blockers, and lipid-lowering drugs. Conversely, a positive correlation was observed with HDL cholesterol levels. Sensitivity analyses were performed to examine how different subgroup categories affect the association between HGI and myocardial MEEi. The study cohort was stratified into three age categories: individuals aged < 50 years ($n = 563$), between 50 and 65 years ($n = 387$), and > 65 years ($n = 124$). After adjustment for sex, the association between HGI levels and myocardial MEEi remained statistically significant in participants aged < 50 years ($\beta = -0.139$, $P < 0.001$), aged 50–65 years ($\beta = -0.169$, $P < 0.001$), and aged > 65 years ($\beta = -0.173$, $P < 0.05$). Next, the participants were stratified into three BMI categories: individuals with

Table 2 Univariate analysis of myocardial MEEi and clinical parameters

Variables	Quartile 1 (– 1.385; – 0.211)	Quartile 2 (– 0.206; – 0.006)	Quartile 3 (– 0.001; 0.205)	Quartile 4 (0.206;1.136)	*P*
LV end-systolic volume (mL)	32 ± 12	34 ± 14	35 ± 17	36 ± 17	0.15
LV end-diastolic volume (mL)	117 ± 32	122 ± 36	122 ± 38	123 ± 38	0.46
LVM (g)	176 ± 56	189 ± 59 [b]	197 ± 63 [a]	206 ± 63 [a, d]	< 0.001
Stroke volume (mL)	85 ± 23	88 ± 24	86 ± 25	87 ± 25	0.82
Stroke work (mmHg*ml)	10,677 ± 3728	11,053 ± 3574	11,011 ± 3730	11,258 ± 3410	0.92
Heart rate (bpm)	70 ± 10	70 ± 9	71 ± 11	71 ± 10	0.15
Myocardial oxygen consumption (mmHg x bpm)	8682 ± 1616	8781 ± 1612	9005 ± 1948	9257 ± 1779 [b, d]	0.05
Myocardial MEEi (mL/sec*g^{-1})	0.43 ± 0.12	0.41 ± 0.11	0.39 ± 0.10 [a, d]	0.37 ± 0.09 [a, c]	< 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; MEEi = LVM-normalized mechano-energetic efficiency

[a] $P < 0.001$ vs. Quartile 1 of HGI

[b] $P < 0.05$ vs. Quartile 1 of HGI

[c] $P < 0.001$ vs. Quartile 2 of HGI

[d] $P < 0.05$ vs. Quartile 2 of HGI

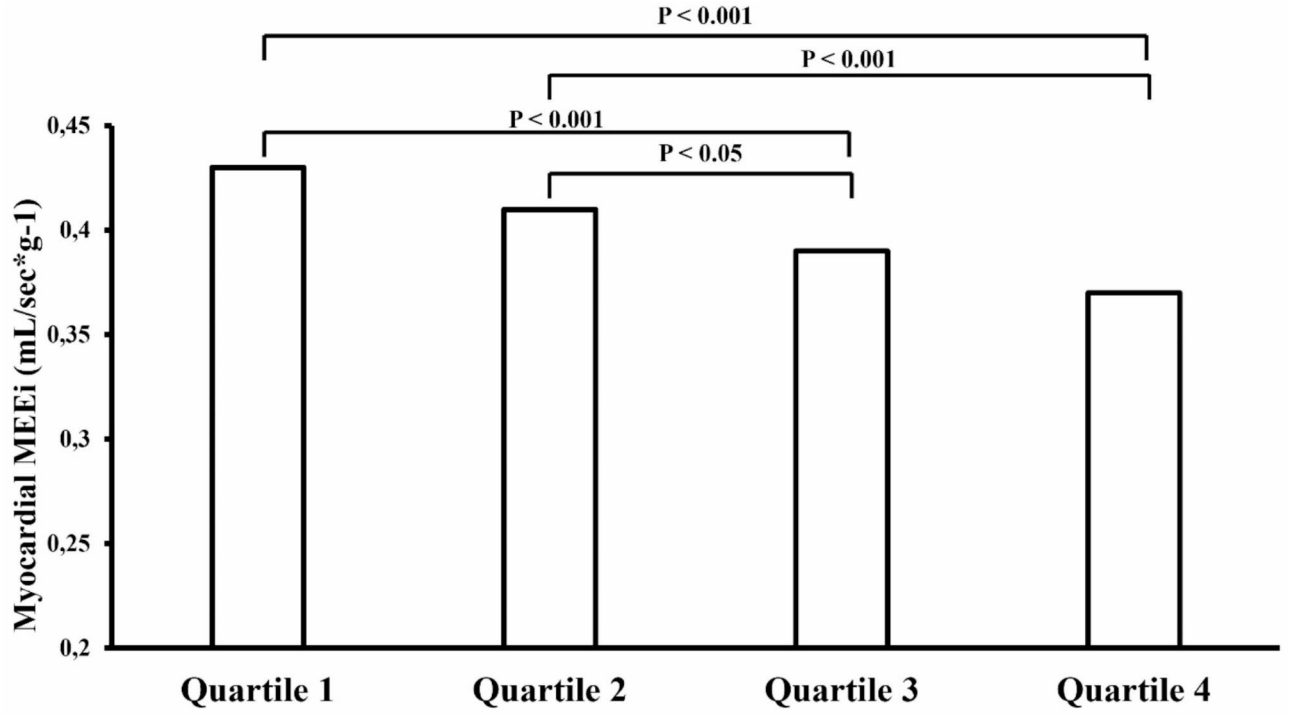


Fig. 1 Association between quartile of HGI and myocardial MEEi values. Quartile 1 ranging from – 1.385 to – 0.211, Quartile 2 ranging from – 0.206 to -0.006; Quartile 3 ranging from – 0.001 to 0.205 and Quartile 4 ranging from 0.206 to 1.136. MEEi = mechano-energetic efficiency per gram of LVM

BMI < 25 kg/m² ($n = 250$), between 25 and 29.9 kg/m² ($n = 378$), and > 30 kg/m² ($n = 446$). After adjustment for sex, the association between HGI levels and myocardial MEEi remained statistically significant in participants with BMI < 25 kg/m² ($\beta = -0.215$, $P < 0.001$), with BMI between 25 and 29.9 kg/m² ($\beta = -0.140$, $P = 0.008$), and with BMI > 30 kg/m² ($\beta = -0.206$, $P < 0.001$). Additionally, the study cohort was stratified into two glucose tolerance categories: individuals with NGT ($n = 668$) and those with prediabetes ($n = 406$). After adjustment for sex, the association between HGI levels and myocardial MEEi remained statistically significant in participants with NGT ($\beta = -0.207$, $P < 0.001$) and those with prediabetes ($\beta = -0.142$, $P = 0.004$).

Significant variables from the univariate analysis were subsequently included in a multivariate linear regression model to identify independent determinants of MEEi (Table 4). Collinearity diagnostics using the variance

Table 3 Multiple regression analysis evaluating the association between anthropometric and metabolic variables and myocardial MEEi as dependent variable

Variables	Myocardial MEEi (mL/sec*g^{-1})		
	β regression coefficient	95% confidence interval	*P*
Sex[a]	− 0.16	− 0.049 to − 0.023	< 0.001
Age *(years)*	− 0.25	− 0.002 to − 0.001	< 0.001
BMI (*kg/m^2*)	− 0.15	− 0.003 to − 0.001	< 0.001
Waist circumference (*cm*)	− 0.19	− 0.002 to − 0.001	< 0.001
Smoking status	− 0.06	− 0.016 to − 0.00002	0.04
Systolic blood pressure *(mmHg)*	− 0.30	− 0.0023 to − 0.0015	< 0.001
Diastolic blood pressure *(mmHg)*	− 0.26	− 0.003 to − 0.002	< 0.001
Total cholesterol (*mg/dL*)	− 0.07	− 0.00036 to − 0.000038	0.06
HDL-C (*mg/dL*)	0.15	− 0.001 to − 0.002	< 0.001
Triglycerides (*mg/dL*)	− 0.19	− 0.056 to − 0.029	< 0.001
Glucose tolerance status	− 0.20	− 0.027 to − 0.015	< 0.001
2-h post-load glucose (*mg/dl*)	− 0.20	− 0.0009 to − 0.0005	< 0.001
Fasting Insulin (*μU/ml*)	− 0.23	− 0.054 to − 0.031	< 0.001
HOMA-IR	− 0.24	− 0.054 to − 0.032	< 0.001
hsCRP (*mg/l*)	− 0.17	− 0.023 to − 0.011	< 0.001
HGI	− 0.21	− 0.090 to − 0.050	< 0.001
ACE inhibitor or Angiotensin receptor blocker therapy	− 0.20	− 0.037 to − 0.020	< 0.001
Beta blocker therapy	− 0.04	− 0.002 to 0.00034	0.20
Diuretic therapy	− 0.13	− 0.003 to − 0.001	< 0.001
Calcium channel blocker therapy	− 0.14	− 0.017 to − 0.007	< 0.001
Lipid-lowering therapy	− 0.09	− 0.053 to − 0.012	0.002

BMI = body mass index, HDL: high density lipoprotein, HOMA-IR = homeostasis model assessment for insulin resistance, MEEi: LVM-normalized mechano-energetic efficiency, HGI: hemoglobin glycation index, hsCRP: high sensitivity C reactive protein

inflation factor (VIF) indicated multicollinearity between glucose tolerance status and 2-hour post-load glucose (VIF values were 2.679 and 2.810, respectively); consequently, these variables were included separately in the regression model. A comparison of standardized coefficients revealed the relative strength of association with MEEi, ranked from strongest to weakest as follows: age, HOMA-IR, HGI, sex, hs-CRP, calcium channel blocker therapy, and ACE inhibitor/angiotensin receptor blocker therapy (Table 3). The R^2 value of the regression model was 0.174, the F-value was 13.570, with $P < 0.001$. The independent association between HGI and MEEi remained statistically significant even when BMI was substituted by waist circumference (Model 2, Table 4), HOMA-IR was replaced by fasting insulin levels (Model 3, Table 4), and when glucose tolerance status was exchanged for 2-hour post-load glucose (Model 4, Table 4). Additionally, the association persisted (β = − 0.114, $P < 0.001$) when beta-blocker therapy was incorporated into the regression model (Model 5, Table 4). The independent association between HGI and MEEi remained statistically significant even when HGI levels, as a continuous variable, were substituted by quartiles of HGI as a categorical variable (Model 6, Table 4).

Discussion

Our cross-sectional study demonstrates that subjects with elevated HGI levels exhibit a significant reduction in myocardial MEEi compared to those with lower HGI values. The inverse association between myocardial MEEi and the main explanatory variable, HGI levels, remained significant after adjusting for numerous potential confounders, including sex, age, BMI, waist circumference, smoking status, triglycerides, HDL cholesterol, 2-hour post-load glucose, glucose tolerance status, fasting insulin, HOMA-IR, hsCRP, and the use of antihypertensive and lipid-lowering medications. A possible explanation for the observed relationship is that the measured HbA1c reflects both fasting and postprandial glycemia, while the predicted HbA1c, calculated solely from fasting glucose, fails to capture postprandial excursions. Subjects with higher HGI also had elevated 2-hour post-load glucose levels, which have been linked to reduced MEEi [39]. However, the persistence of the association between higher HGI levels and myocardial MEEi after adjustment for post-load glucose or glucose tolerance status argues against this possibility.

Another factor to consider is the more significant proportion of subjects with high HGI who were receiving beta-blocker therapy. Given their effects on heart rate, beta-blockers could lead to a higher calculated MEEi based on the formula used. However, increased beta-blocker usage would be expected to attenuate rather than exaggerate the observed association, pushing results toward the null hypothesis. Moreover, the fact that the significant association between HGI and MEEi persisted even after adjusting for beta-blocker use further supports the validity of our findings.

Previous investigations have shown that an elevated HGI may serve as an indicator of increased non-enzymatic protein glycation and the subsequent accumulation of advanced glycation end products (AGEs) within tissues [9, 40]. The potential biological mechanisms through which HGI influences MEE are likely to involve the accumulation of those products (AGEs) and their detrimental effects on myocardial function. When AGEs interact with their receptors (RAGE) on the cell membrane, they can alter cellular function through various mechanisms, including modification of intracellular proteins and stimulation of inflammatory mediator expression via

Table 4 Multiple regression analysis evaluating the association between anthropometric and metabolic variables and myocardial MEEi as dependent variable.

	Independent contributors	Dependent variable: myocardial MEEi			
		Standardized coefficient β	Unstandardized coefficient B	*P*	VIF
Model 1 includes sex, age, BMI, smoking status, triglycerides, HDL, glucose tolerance status, HOMA-IR, hsCRP, HGI, ACE inhibitor or angiotensin receptor blocker therapy, diuretic therapy, calcium channel blocker therapy, and lipid-lowering therapy.	Age	− 0.162	− 0.001	< 0.001	1.538
	HOMA-IR	− 0.161	− 0.029	< 0.001	1.575
	HGI	− 0.115	− 0.039	< 0.001	1.170
	Sex	− 0.102	− 0.023	0.004	1.383
	hsCRP	− 0.096	− 0.010	0.006	1.314
	Calcium channel blocker therapy	− 0.082	− 0.007	0.009	1.084
	ACE inhibitor or angiotensin receptor blocker therapy	− 0.076	− 0.011	0.048	1.590
Model 2 includes sex, age, waist circumference, smoking status, triglycerides, HDL, glucose tolerance status, HOMA-IR, hsCRP, HGI, ACE inhibitor or angiotensin receptor blocker therapy, diuretic therapy, calcium channel blocker therapy, and lipid-lowering therapy	Age	− 0.163	− 0.001	< 0.001	1.520
	HOMA-IR	− 0.160	− 0.029	< 0.001	1.591
	HGI	− 0.115	− 0.039	< 0.001	1.175
	Sex	− 0.103	− 0.023	0.004	1.520
	hsCRP	− 0.094	− 0.010	0.006	1.291
	Calcium channel blocker therapy	− 0.082	− 0.007	0.009	1.084
	ACE inhibitor or angiotensin receptor blocker therapy	− 0.077	− 0.011	0.044	1.591
Model 3 includes sex, age, BMI, smoking status, triglycerides, HDL, glucose tolerance status, fasting insulin, hsCRP, HGI, ACE inhibitor or angiotensin receptor blocker therapy, diuretic therapy, calcium channel blocker therapy, and lipid-lowering therapy.	Age	− 0.174	− 0.001	< 0.001	1.559
	Fasting insulin	− 0.171	− 0.033	< 0.001	1.520
	HGI	− 0.109	− 0.037	< 0.001	1.170
	Sex	− 0.106	− 0.024	0.003	1.379
	hsCRP	− 0.095	− 0.010	0.006	1.314
	Calcium channel blocker therapy	− 0.082	− 0.007	0.009	1.084
	ACE inhibitor or angiotensin receptor blocker therapy	− 0.076	− 0.011	0.04	1.590
	Glucose tolerance status	− 0.068	− 0.007	0.04	1.180
Model 4 includes sex, age, BMI, smoking status, triglycerides, HDL, 2-h post-load glucose, HOMA-IR, hsCRP, HGI, ACE inhibitor or angiotensin receptor blocker therapy, diuretic therapy, calcium channel blocker therapy, and lipid-lowering therapy.	HOMA-IR	− 0.167	− 0.030	< 0.001	1.562
	Age	− 0.165	− 0.001	< 0.001	1.552
	HGI	− 0.113	− 0.039	< 0.001	1.190
	Sex	− 0.105	− 0.024	0.004	1.375
	hsCRP	− 0.094	− 0.009	0.00	1.318
	Calcium channel blocker therapy	− 0.081	− 0.007	0.01	1.084
	ACE inhibitor or angiotensin receptor blocker therapy	− 0.076	− 0.011	0.05	1.590
Model 5 includes sex, age, BMI, smoking status, triglycerides, HDL, glucose tolerance status, HOMA-IR, hsCRP, HGI, ACE inhibitor or angiotensin receptor blocker therapy, diuretic therapy, calcium channel blocker therapy, beta blocker therapy, and lipid-lowering therapy.	Age	− 0.173	− 0.001	< 0.001	1.571
	HOMA-IR	− 0.164	− 0.030	< 0.001	1.577
	HGI	− 0.114	− 0.039	< 0.001	1.170
	Sex	− 0.098	− 0.022	0.006	1.385
	hsCRP	− 0.094	− 0.009	0.007	1.315
	Calcium channel blocker therapy	− 0.083	− 0.007	0.009	1.084
	ACE inhibitor or angiotensin receptor blocker therapy	− 0.082	− 0.012	0.03	1.601
	Beta blocker therapy	0.068	0.001	0.04	1.157
Model 6 includes sex, age, BMI, smoking status, triglycerides, HDL, glucose tolerance status, HOMA-IR, hsCRP, quartiles of HGI, ACE inhibitor or angiotensin receptor blocker therapy, diuretic therapy, calcium channel blocker therapy, and lipid-lowering therapy.	Age	− 0.166	− 0.001	< 0.001	1.529
	HOMA-IR	− 0.160	− 0.029	< 0.001	1.575
	Quartiles of HGI	− 0.103	− 0.010	0.002	1.149
	Sex	− 0.101	− 0.023	0.005	1.383
	hsCRP	− 0.097	− 0.010	0.005	1.313
	Calcium channel blocker therapy	− 0.079	− 0.007	0.01	1.080
	ACE inhibitor or angiotensin receptor blocker therapy	− 0.075	− 0.011	0.05	1.590

activation of nuclear factor κ-B [41]. Additionally, there is evidence suggesting that in human coronary artery endothelial cells, AGEs may induce endothelial dysfunction by reducing endothelial nitric oxide synthase expression, a process mediated by increased production of reactive oxygen species [42]. Therefore, the resulting impaired endothelial-mediated vasodilation may contribute to a decline in MEE, as the heart becomes less efficient in converting metabolic energy into mechanical work [43], while the increased formation of AGEs can promote inflammatory processes and endothelial dysfunction, further contributing to cardiovascular impairment. Of course, further studies are necessary to confirm this pathophysiological mechanism conclusively.

Overall, the results of our study align with previously published data demonstrating that HGI is associated with cardiovascular organ damage, including increased carotid intima-media thickness (IMT) [38], the incidence of coronary artery calcification (CAC) [44], subclinical myocardial injury [45], and cardiovascular diseases such

as coronary artery disease, stroke, and peripheral artery disease [18] in non-diabetic individuals. These observations reinforce the concept that excessive non-enzymatic glycation of intracellular proteins could be a key contributor to cardiovascular diseases, even in subjects without diabetes.

A key strength of our study is the inclusion of a relatively large sample size of ethnically homogeneous (White) subjects who were carefully characterized, with anthropometric and metabolic data collected by trained personnel following a standardized protocol. Additionally, the inclusion of both sexes, the use of OGTT and HbA1c data to rigorously exclude type 2 diabetes, the elimination of confounding conditions that might affect HbA1c levels (e.g., anemia, hemoglobinopathies, or the use of antiplatelet/anticoagulant medications), and the utilization of a standardized HbA1c assay on fresh blood samples all contribute to the robustness of the study.

Nonetheless, this study has certain limitations. First, due to its cross-sectional design, the study cannot establish a causal relationship between elevated HGI and reduced MEEi; prospective longitudinal studies will be needed to verify these findings. Second, all metabolic parameters, including plasma glucose during the OGTT and HbA1c, were measured only once. Although this is common in large observational studies, intra-individual variability in glycemic measures might have resulted in some misclassification of subjects. Furthermore, because only fasting plasma glucose was used to derive the predicted HbA1c, the analysis could not account for diurnal fluctuations in glucose levels. In future studies, the use of continuous glucose monitoring (CGM) may provide more detailed information about interindividual glycemic fluctuations, offering a more comprehensive understanding of glucose variability and how it could impact on myocardial function. Additionally, residual confounding by unmeasured factors such as socioeconomic status, education, occupation, living conditions, dietary habits, and physical activity levels might have impacted the present results. Moreover, since this study is not a randomized trial but rather an observational study recruiting participants at increased risk for cardio-metabolic disease from a referral university hospital, we cannot exclude the possibility of collider bias due to selection bias. Finally, since all participants were White, the generalizability of these findings to other ethnic groups, such as Black, Hispanic, or Native American populations, who tend to exhibit higher HbA1c levels [46], remains uncertain.

Conclusions

In conclusion, our study provides evidence that elevated HGI is linked to a significant decline in myocardial MEEi in non-diabetic individuals. Further prospective studies and mechanistic research are needed to clarify the contributions of excessive non-enzymatic glycation, AGEs accumulation and related inflammatory pathways to myocardial performance.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02710-y.

Supplementary Material 1.

Author contributions

C.M.A.C. and T.V.F., contributed to conceive the study, critically reviewed and edit the manuscript, M.R., V.C., A.R., E.S., M.P., A.S., F.A. collected data and reviewed the manuscript; G.S. designed the study, analyzed data, and wrote the manuscript.

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Data availability

Raw data were generated at Magna Graecia University and analysed at Sapienza University. Derived data supporting the findings of this study are available from the corresponding author C.M.A.C. on request.

Declarations

Competing interests

The authors declare no competing interests.

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