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Association between liver fibrosis severity and impaired myocardial glucose metabolism in subjects with different degrees of glucose tolerance

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ABSTRACT

Introduction Increasing evidence suggests that liver fibrosis is an independent risk factor for cardiovascular disease. However, the mechanisms underlying this increased risk are still unsettled. The aim of this study was to explore the relationship between myocardial glucose metabolism and the severity of liver fibrosis.

Research design and methods We evaluated insulin-stimulated myocardial glucose metabolic rate (MrGlu) using cardiac dynamic positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) combined with a euglycemic-hyperinsulinemic clamp and liver fibrosis severity, estimated by the fibrosis-4 (FIB-4) index, in 57 individuals with varying degrees of glucose tolerance. According to the FIB-4 index, subjects were stratified into three groups: low risk of fibrosis (<1.3; n=37), intermediate risk of fibrosis (≥1.3 to <2.67; n=16), and high risk of fibrosis (≥2.67; n=4).

Results Subjects with a high risk of advanced fibrosis exhibited an age-adjusted decrease of myocardial MrGlu compared with both individuals with a low FIB-4 index category (4.6±4.3 µmol/min/100 g vs 21.7±11.2 µmol/min/100 g; p=0.009) and intermediate FIB-4 index category (20.±11.03 µmol/min/100 g; p=0.01, respectively). No significant differences in glycemic and anthropometric parameters, whole-body insulin sensitivity, or blood pressure were found between groups.
In a multivariable regression analysis, the only variable significantly associated with advanced liver fibrosis risk was myocardial MrGlu (β=−0.286; p=0.003), explaining 28.6% of the variation.

Conclusions These data suggest that impairment of insulin-stimulated myocardial glucose metabolism is associated with a high risk of advanced liver fibrosis in individuals with varying degrees of glucose tolerance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Advanced liver fibrosis, as estimated by the fibrosis-4 (FIB-4) index, is a well-established predictor of incident coronary events and cardiovascular mortality. However, the mechanisms underlying this increased risk are still unsettled. An impaired myocardial glucose metabolism is an early alteration strongly correlated with whole-body insulin resistance and has been shown to be an independent predictor of cardiovascular events.

WHAT THIS STUDY ADDS

⇒ An impaired insulin-stimulated myocardial glucose metabolism, assessed by dynamic cardiac ^{18}F-fluorodeoxyglucose-positron emission tomography with euglycemic-hyperinsulinemic clamp, is associated with a higher risk of advanced liver fibrosis across different glucose tolerance states.

⇒ Myocardial glucose metabolism is the main independent contributor to advanced fibrosis in individuals with varying degrees of glucose tolerance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Prospective longitudinal studies are needed to clarify the role of cardiac insulin resistance in determining the liver fibrosis-related cardiovascular risk.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), represents the most common chronic liver disorder worldwide, affecting approximately 30%–38% of the adult population, and its prevalence is expected to increase further in the near future.[1–3] MASLD encompasses a broad spectrum, ranging from simple steatosis in the presence of at least one cardiometabolic risk factor to more severe stages such as metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, and cirrhosis.[1–5] MASLD not only increases the risk of adverse liver-related health outcomes but is also increasingly acknowledged as a multisystem condition closely associated with insulin resistance,

obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD).[2–5]

Several studies and large meta-analyses reported a close association between MASLD and myocardial infarction, CVD mortality, and heart failure.[5–9] Mostly, in people with MASLD, the presence of liver fibrosis, the hallmark of advanced chronic liver injury, is a strong predictor not only of liver-related morbidity and mortality but also of all-cause mortality and cardiovascular (CV) mortality.[8 10–12] The increased risk of mortality may, moreover, increase with the stage of fibrosis.[10 12 13] However, the mechanisms by which MASLD and liver fibrosis confer an increased risk of CV events are still unsettled.

Impaired myocardial glucose metabolism is an early alteration that is strongly correlated with whole-body insulin resistance. It has been observed in patients with T2DM, with or without coronary heart disease (CHD) or heart failure, as well as in conditions associated with an increased risk of T2DM, including pre-diabetes and metabolic syndrome.[14–19] Furthermore, myocardial insulin resistance is an independent predictor of CV events in individuals with CHD and has been associated with atherosclerosis.[20 21]

Only a few studies have investigated myocardial glucose metabolism in individuals with liver steatosis.[21 22] Tang *et al* reported an independent association between reduced myocardial glucose uptake and both NAFLD and coronary atherosclerosis.[21] Consistently, Lee *et al* demonstrated that liver steatosis and fibrosis were associated with decreased myocardial glucose uptake in subjects with T2DM.[22] However, a major limitation of these studies is that myocardial glucose uptake was assessed using ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) performed exclusively in the fasting state. In contrast, myocardial insulin resistance in terms of glucose disposal should be evaluated under dynamic insulin-stimulated conditions.[23] Indeed, dynamic myocardial ^{18}F-FDG-PET combined with an euglycemic-hyperinsulinemic clamp is considered the gold standard for assessing myocardial glucose metabolism, as it enables measurements under standardized conditions of euglycemia and physiological hyperinsulinemia.[14 23–25]

In this context, we sought to investigate the relationship between insulin-stimulated myocardial glucose metabolic rate (MrGlu), assessed by dynamic cardiac ^{18}F-FDG-PET combined with an euglycemic-hyperinsulinemic clamp, and the severity of liver fibrosis. Liver fibrosis was estimated using one of the most widely applied non-invasive fibrosis scores, the fibrosis-4 (FIB-4) index,[26] in individuals without a history of CHD and spanning a broad spectrum of glucose tolerance.

RESEARCH DESIGN AND METHODS

Study participants

The study cohort consisted of 57 subjects participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI), an observational study recruiting adult individuals with one or more cardiometabolic risk factors recruited at a referral hospital of the University 'Magna Graecia' of Catanzaro.[15 27] Inclusion criteria were age between 30 and 70 years and the presence of at least one cardiometabolic risk factor, including family history of diabetes, dysglycemia, hypertension, dyslipidemia, or overweight/obesity. Exclusion criteria included type 1 diabetes, end-stage renal disease, previous CVD on the basis of medical history, resting ECG and stress test or myocardial scintigraphy for individuals with T2DM, history of atrial fibrillation or other arrhythmias, right and left bundle branch block, dyssynchrony in ventricular contraction, valvular heart disease, liver cirrhosis, history of malignant or autoimmune diseases, acute or chronic infections, positivity for antibodies to hepatitis C virus or hepatitis B surface antigen, history of alcohol or drug abuse, and treatment with drugs known to affect glucose tolerance such as steroids and estro-progestins, induce liver injury, or influence cardiac function, including beta blockers and antiarrhythmic drugs. All subjects underwent anthropometrical evaluation, including measurements of body mass index (BMI), waist circumference, and body composition by bioelectrical impedance. Readings of blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of rest, using a standard sphygmomanometer. BP values were calculated as the average of three measurements after a 10-minute rest period in the supine position. After an overnight fast, biochemical determinations and a 75 g oral glucose tolerance test (OGTT) were performed in individuals with fasting plasma glucose (FPG) <126 mg/dL, hemoglobin A1c (HbA1c) <6.5%, and no history of T2DM. According to the American Diabetes Association (ADA) criteria,[28] individuals were classified as having normal glucose tolerance (NGT) when FPG was <100 mg/dL (5.5 mmol/L), 2-hour postload glucose was <140 mg/dL (<7.77 mmol/L), and HbA1c was <5.7%, pre-diabetes when FPG was 100–125 mg/dL (5.5–6.9 mmol/L), 2-hour postload glucose was 140–199 mg/dL (7.77–11.0 mmol/L), or HbA1c was 5.7%–6.4%, and T2DM when FPG was ≥126 mg/dL (>7 mmol/L), 2-hour postload glucose was ≥200 mg/dL (>11.1 mmol/L), HbA1c was ≥6.5%, or they were in treatment with antidiabetic drugs.

On the second day, after 12 hours of fasting, all subjects underwent an ^{18}F-FDG-PET scan combined with an euglycemic-hyperinsulinemic clamp in the morning.

^{18}F-FDG-PET scan combined with euglycemic-hyperinsulinemic clamp

Myocardial MrGlu was measured by ^{18}F-FDG-PET acquired during an euglycemic-hyperinsulinemic clamp as previously described.[15 29] Subjects received a priming dose of insulin (100 UI/mL) (Humulin R; Eli Lilly) during the initial 10 min to raise the serum insulin concentration acutely (80 mU/m^2×min), and then it was maintained by continuous insulin infusion fixed at 40 mU/m^2×min.[30] The blood glucose level was maintained constant at 90 mg/dL for the next 120 min

by infusing 20% glucose at varying rates according to blood glucose measurements performed at 5-minute intervals (mean coefficient of variation of blood glucose was <4%). Glucose metabolized by the whole body (M) was calculated as the mean rate of glucose infusion measured during the last 60 min of the clamp examination (steady state) and was expressed as milligrams per minute per kilogram fat-free mass (M_{FFM}).

The ^{18}F-FDG-PET imaging procedure was performed on a hybrid PET/CT scanner (GE Discovery ST8-2D PET scanner), starting 60 min after the insulin infusion. A 60-minute dynamic acquisition was started simultaneously with the intravenous injection of 370 MBq ^{18}F-FDG, according to the following time frame sampling: 8×15 s, 2×30 s, 2×120 s, 1×180 s, 6×300 s, and 2×600 s.[31] PET images were reconstructed in a 128×128 matrix using an ordered subset expectation maximization algorithm and corrected for decay and attenuation based on co-registered CT. The insulin-glucose infusion continued during the entire PET acquisition. The estimation of myocardial MrGlu was performed by Patlak compartmental modeling,[27 29] using the graphical tool specific for cardiac image analysis (PCARD) implemented in the PMOD Software platform (V.3.806).[31] In PCARD, the full dynamic study is used for MrGlu calculation, and the arterial input function is extracted from a volume of interest semiautomatically placed in the left ventricular cavity.[32]

Laboratory determinations

Plasma glucose, total and high-density lipoprotein (HDL) cholesterol, and triglycerides were assayed using enzymatic methods (Roche Diagnostics, Mannheim, Germany). HbA1c was measured with high-performance liquid chromatography using a National Grievance Service Portal-certified automated analyzer (Adams HA-8160 HbA1c analyzer, Menarini, Italy). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using the α-ketoglutarate reaction and gamma-glutamyltransferase (GGT) with the L-gamma-glutamyl-3-carboxy-4-nitroanilide rate method (Roche, Basel, Switzerland). An automated particle counter (Siemens Healthcare Diagnostics ADVIA 120/2120 Hematology System, Milan, Italy) was employed to measure platelet count.

Calculation of serum FIB-4 concentrations

FIB-4 index, an index related to liver fibrosis, was calculated by the following formula[26]:FIB-4=((Age (Years)×AST (IU/L))/(platelet counts (10^9/L)×ALT (IU/L))^{½}). Based on the FIB-4 index, participants were stratified into three categories according to the guidelines[33]: low risk of fibrosis (<1.3; <2.0 in subjects >65 years of age); intermediate risk of fibrosis (≥1.3 to <2.67); and high risk of fibrosis (≥2.67).

Statistical analyses

Variables with skewed distribution, including triglycerides and M_{FFM}, were natural log-transformed for statistical analyses. Continuous variables are presented as means±SD. Categorical variables were compared by χ^2 test. Between-groups comparisons were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons. In addition, polynomial linear contrasts were used to assess the linear trend in myocardial MrGlu across increasing FIB-4 categories. A stepwise multivariate regression analysis was performed to determine the independent contributors to the risk of advanced liver fibrosis.

Based on previous reports describing a 30%–42% reduction in myocardial glucose uptake in individuals with NAFLD,[21 22] a sample size of 56 participants was estimated to provide 80% power to detect a 30% difference in myocardial glucose metabolism between individuals at high risk of liver fibrosis and those at low risk, assuming a two-sided α level of 0.05.

For all analyses, a p value <0.05 was considered to be statistically significant. All analyses were performed using SPSS software V.29 for Mac.

RESULTS

Based on the FIB-4 index, participants were stratified into three categories[33]: low risk of fibrosis (<1.3; n=37; <2.0 in subjects >65 years of age=0); intermediate risk of fibrosis (≥1.3 to <2.67; n=16); and high risk of fibrosis (≥2.67; n=4).

The clinical characteristics of participants stratified according to FIB-4 categories are presented in table 1. No significant differences were observed across groups with respect to sex distribution or age.

CV risk factors and metabolic parameters according to FIB-4 categories

As shown in table 1, no significant differences across FIB-4 categories were observed for BMI, waist circumference, systolic or diastolic BP, fasting plasma glucose, HbA1c, HDL cholesterol, or triglycerides. Participants in the high FIB-4 category exhibited higher age-adjusted total cholesterol levels compared with those in the intermediate (p=0.003) fibrosis risk category. In addition, low-density lipoprotein cholesterol levels were significantly higher, after age adjustment, in individuals with high FIB-4 compared with both those in the low (p=0.04) and intermediate FIB-4 categories (p=0.003). As expected, increasing fibrosis risk was associated with a progressive age-adjusted increase in serum AST, ALT, and GGT concentrations (all p<0.0001).

Although differences did not reach statistical significance, individuals with intermediate and high fibrosis risk showed numerically lower whole-body insulin-stimulated glucose disposal compared with those in the low fibrosis risk category. Similarly, no significant differences in glucose tolerance status were observed across groups. However, all participants in high FIB-4 categories had either pre-diabetes or T2DM, whereas individuals in the low FIB-4 categories included a comparable proportion of subjects with NGT or T2DM. No differences in antihypertensive, lipid-lowering, and glucose-lowering

Table 1 Clinical characteristics of the study population stratified according to the risk of advanced fibrosis

	Subjects with low risk of fibrosis (<1.3; n=37)	Subjects with intermediate risk of fibrosis (≥1.3 to < 2.67; n=16)	Subjects with high risk of fibrosis (≥2.67; n=4)	P value
Gender (M/F)	22/15	5/11	3/1	0.1
Age (years)	48±8	52.9±12	54.5±1	0.3
Body mass index (kg/m^2)	29.2±4	31.1±6	31.7±5	0.3
Waist circumference (cm)	101±11	105±12	111±12	0.1
Systolic BP (mm Hg)	123±16	120±15	134±5	0.2
Diastolic BP (mm Hg)	77±11	73±19	79±6	0.3
Fasting glucose (mg/dL)	110±32	118±34	144±83	0.2
Hemoglobin A1c (%/)	6.4±1.2	6.6±1.2	6.9±1.4	0.7
Total cholesterol (mg/dL)	191±40	175±26	227±35	0.04
High-density lipoprotein cholesterol (mg/dL)	49±11	45±10	42±10	0.3
Low-density lipoprotein cholesterol (mg/dL)	123±33	116±24	165±37	0.02
Triglycerides (mg/dL)	122±75	144±50	180±52	0.2
Aspartate aminotransferase (UI/L)	18±5	26±16	75±36	<0.0001
Alanine aminotransferase (UI/L)	22±11	20±10	51±23	<0.0001
Gamma-glutamyltransferase (UI/L)	27±20	23±13	66±22	<0.0001
Platelet counts (U/mm^3)	233±51	208±32	168±45	0.01
Normal glucose tolerance/pre-diabetes/type 2 diabetes mellitus (%)	15/7/15	5/2/9	0/2/2	0.4
Insulin-stimulated glucose disposal (mg/min × kg fat-free mass)	6.1±4.4	5.15±7.5	2.1±0.5	0.3
Antihypertensive therapy (%)	35.1	31.3	25	0.9
Glucose-lowering therapy (%)	40.5	56.3	50	0.5
Lipid-lowering therapy (%)	24.2	33	25	0.4

Data are means±SD, unless otherwise indicated. Categorical variables were compared by χ^2 test. Comparisons between groups were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons. §The p values refer to results after analyses with adjustment for age.
BP, blood pressure.

therapies were observed between subjects in the three FIB-4 categories in the study (table 1). All the subjects with T2DM were treated with metformin.

Myocardial glucose metabolism according to FIB-4 categories

Individuals at high risk of advanced liver fibrosis exhibited a significantly lower age-adjusted insulin-stimulated myocardial MrGlu compared with individuals in the low FIB-4 category (4.6±4.3 vs 21.7±11.2 µmol/min/100 g; p=0.009; figure 1). This difference remained significant also after further adjustment for antidiabetic, lipid-lowering, and antihypertensive therapies (p=0.003). Furthermore, subjects at high risk of advanced liver fibrosis showed a significantly lower age-adjusted myocardial glucose metabolism as compared with subjects in the intermediate FIB-4 category (4.6±4.3 vs 20.6±11.03 µmol/min/100 g; p=0.01; figure 1). This difference remained significant also after further adjustment for antidiabetic, lipid-lowering, and antihypertensive therapy (p=0.005, respectively).

Overall, insulin-stimulated myocardial glucose metabolism differed significantly across FIB-4 categories after adjustment for age (p=0.026) (figure 1). A significant

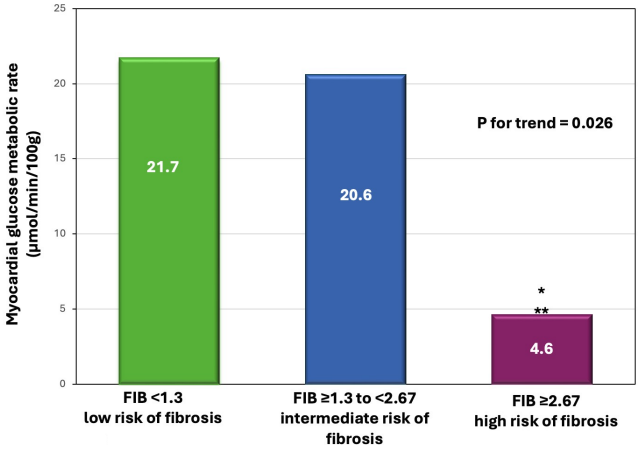

Figure 1 Comparisons in insulin-stimulated myocardial glucose metabolic rate (µmol/min/100 g) performed using a general linear model with adjustment for age in subjects stratified according to FIB-4 categories. *p=0.009 between high versus low risk of fibrosis categories; **p=0.01 between high versus intermediate risk of fibrosis categories. FIB-4, fibrosis-4.

linear trend was also observed across increasing FIB-4 categories, indicating a progressive decline in insulin-stimulated myocardial MrGlu with increasing liver fibrosis risk (p for trend=0.017). This association remained significant after further adjustment for CV risk factors (p=0.042).

To identify independent determinants of the FIB-4 index, we performed a multivariable linear regression analysis including age, sex, BMI, waist circumference, BP, lipid profile, fasting plasma glucose, HbA1c, whole-body insulin-stimulated glucose disposal, and insulin-stimulated myocardial MrGlu as independent variables, with FIB-4 index categories as the dependent variable. Among these, only myocardial insulin-stimulated MrGlu was significantly associated with a high FIB-4 index (β=–0.286; p=0.003), accounting for 28.6% of its variance (table 2).

DISCUSSION

The main finding of this study is that advanced liver fibrosis is associated with myocardial insulin resistance across a broad spectrum of glucose tolerance. Individuals with higher FIB-4 index values, indicative of high risk of advanced fibrosis, exhibited a significant age-adjusted reduction in insulin-stimulated myocardial MrGlu, assessed using the gold standard technique of dynamic cardiac ^{18}F-FDG-PET combined with euglycemic-hyperinsulinemic clamp.

These results are consistent with previous studies showing an independent association between liver steatosis and fibrosis and decreased glucose uptake, assessed by fasting ^{18}F-FDG-PET.[21 22] Liver fibrosis is a well-established predictor of CV mortality, with risk increasing with fibrosis stage.[8 10–13] Advanced fibrosis, as estimated by FIB-4, is associated with a higher incidence of CV events and CV mortality.[12 13]

The mechanisms linking MASLD and liver fibrosis to adverse CV outcomes remain incompletely understood. Proposed contributors include peripheral insulin resistance, chronic inflammation, and endothelial dysfunction.[34] Indeed, previous studies have shown that insulin resistance leads to the release of free fatty acids from adipocytes and their delivery to the liver, contributing to the accumulation of hepatic triglycerides.[33 35 36] Furthermore, liver inflammation, characterized by the presence of inflammatory leukocytes and increased cytokine production, associated with endoplasmic reticulum stress and reactive oxygen species formation, is closely linked to the progression of steatosis to steatohepatitis and also increases the risk of CVD.[5 33 34 36–38] Our findings suggest that myocardial insulin resistance may represent an additional pathophysiological link between liver fibrosis and increased CV risk. Impaired myocardial glucose metabolism is closely related to whole-body insulin resistance[15 28] and is an independent predictor of CV events, associated with reduced systolic function, impaired myocardial mechano-energetic efficiency, and increased cardiac workload across different glucose tolerance states.[14 20 21 30]

In keeping with our findings, previous studies showed an association between high hepatic triglyceride content, assessed by magnetic resonance spectroscopy, and a decrease of myocardial glucose uptake, an impaired myocardial energetic state, and a reduced myocardial perfusion in subjects with T2DM.[38 39] Furthermore, the degree of hepatic and epicardial fat accumulation is associated with cardiac contractile dysfunction, fibroinflammatory liver disease, and insulin resistance in individuals with T2DM.[38] In insulin-resistant conditions, reduced glucose transporter type 4 activity decreases myocardial glucose uptake and shifts myocardial energy utilization toward fatty acid oxidation, leading to impaired cardiac energy efficiency, mitochondrial dysfunction, increased susceptibility to ischemia, cardiomyocyte death, and potentially the development of CHD.[14 19–21 28 34 40 41]

The significant linear trend observed across increasing FIB-4 categories further supports the association between increasing liver fibrosis risk and impaired insulin-stimulated myocardial glucose metabolism. In multivariable linear regression including established cardiometabolic risk factors, such as age, sex, BMI, waist circumference, BP, lipid profile, fasting plasma glucose, and HbA1c, only myocardial insulin-stimulated glucose metabolism remained significantly associated with the FIB-4 index (β=–0.286; p=0.003), accounting for 28.6% of its variance. These data support the hypothesis that impaired myocardial glucose metabolism may be an independent predictor of advanced liver fibrosis and a potential mechanistic link to increased CV risk. Prospective studies are required to establish causality.

This study has some strengths. First, myocardial glucose metabolism was assessed using the gold standard dynamic ^{18}F-FDG-PET combined with the euglycemic-hyperinsulinemic clamp, allowing evaluation under controlled conditions of euglycemia and physiological hyperinsulinemia.[14 23–25] Second, glucose tolerance was rigorously classified using FPG, 2-hour postload glucose, and HbA1c according to ADA criteria.[29] Third, all assessments—including anthropometry, OGTT, and PET–clamp studies—were performed by trained examiners blinded to participants' clinical data.

Nonetheless, several limitations should be acknowledged. First, liver fibrosis was not assessed by biopsy or

Table 2 Independent predictors of advanced liver fibrosis after stepwise multiple regression analysis

	Total r^2 (%)	β	T	P value
Myocardial glucose metabolic rate (µmol/min/100 g)	28.6	–0.286	–2.197	0.03

Model including age, sex, body mass index, waist circumference, blood pressure, lipid profile, fasting plasma glucose, glycated hemoglobin, insulin-stimulated glucose disposal, and myocardial glucose metabolic rate.

advanced imaging techniques such as magnetic resonance elastography or vibration-controlled transient elastography. Moreover, MRI or spectroscopy was not available for the quantification of liver fat. Although FIB-4 is a non-invasive and well-validated index recommended by the American Association for the Study of Liver Diseases guidelines as a first-line assessment due to its simplicity and low cost,[33 42] the lack of advanced imaging techniques may have introduced misclassification bias. Furthermore, the relatively small sample size, particularly in the higher fibrosis categories, may affect the robustness of regression analyses, and the adjustment for multiple covariates in a small cohort may lead to unstable estimates.[43] However, the planned sample size ensured adequate statistical power for the primary analyses, while increasing the sample further would have exposed additional participants to unnecessary radiation. The study population was restricted to White adults aged 30–70 years with ≥1 cardiometabolic risk factor from a referral hospital, limiting generalizability. Additionally, although statistical analyses were adjusted for a wide variety of covariates, residual unmeasured confounders such as dietary habits and physical activity may have affected the present results. Finally, due to its cross-sectional design, the study cannot establish a causal relationship between impaired myocardial glucose metabolism and high risk of advanced liver fibrosis.

CONCLUSIONS

Our study demonstrates that impairment of insulin-stimulated myocardial glucose metabolism, assessed by dynamic cardiac ^{18}F-FDG-PET with euglycemic-hyperinsulinemic clamp, is associated with a high risk of advanced liver fibrosis in individuals with varying degrees of glucose tolerance. Myocardial glucose metabolism was the main independent contributor to advanced fibrosis.

Prospective longitudinal studies are needed to clarify the role of cardiac insulin resistance in determining the liver fibrosis-related CV risk.

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Contributors ES designed the study, researched and analyzed data, and wrote and edited the manuscript. VM, IG, TVF, MP, GCM, AS, and FA researched data and reviewed the manuscript. PVi analyzed the data from the cardiac PET scans. GLC performed cardiac PET scans. PHG, PVe, and GLC contributed to the discussion and reviewed the manuscript. GS wrote and reviewed the manuscript. All authors have read and approved the final manuscript. ES is the guarantor of this work and, as such, accepts full responsibility for the finished work, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and controlled the decision to publish.

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