# Cardiac Insulin Resistance in Subjects With Metabolic Syndrome Traits and Early Subclinical Atherosclerosis

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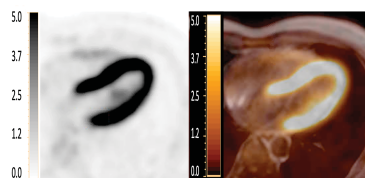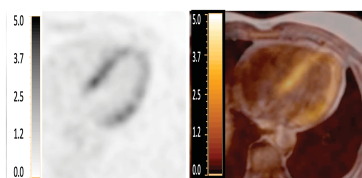
Cardiac metabolic phenotypes. Three myocardial phenotypes are observed in apparently healthy individuals: *1*) high myocardial ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake, associated with a healthy cardiometabolic profile and low prevalence rates of early atherosclerosis and bone marrow activation; *2*) intermediate myocardial ^{18}F-FDG uptake, associated with an intermediate cardiometabolic profile and intermediate prevalence of early subclinical atherosclerosis; and *3*) low myocardial ^{18}F-FDG uptake, associated with a poor cardiometabolic profile and high prevalence rates of early subclinical atherosclerosis and bone marrow activation.

ARTICLE HIGHLIGHTS

- Metabolic syndrome and cardiovascular risk factors are associated with myocardial substrate utilization in apparently healthy individuals.
- Lower myocardial ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake (i.e., myocardial glucose consumption) is associated with worse cardiovascular risk profile, early atherosclerosis, and bone marrow activation.
- Improved cardiometabolic profile is associated with normalization of myocardial ^{18}F-FDG uptake.
- The implications of reduced myocardial ^{18}F-FDG uptake (a surrogate for cardiac insulin resistance) on cardiac function warrant further studies; these data can explain, to some extent, the high prevalence of heart failure with preserved ejection fraction in subjects with long exposure to cardiovascular risk factors.

Cardiac Insulin Resistance in Subjects With Metabolic Syndrome Traits and Early Subclinical Atherosclerosis

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ORIGINAL ARTICLE

OBJECTIVE

Experimental evidence suggests that metabolic syndrome (MetS) is associated with changes in cardiac metabolism. Whether this association occurs in humans is unknown.

RESEARCH DESIGN AND METHODS

821 asymptomatic individuals from the Progression of Early Subclinical Atherosclerosis (PESA) study (50.6 [46.9–53.6] years, 83.7% male) underwent two whole-body ^{18}F-fluorodeoxyglucose positron emission tomography-magnetic resonance (^{18}F-FDG PET-MR) 4.8 ± 0.6 years apart. Presence of myocardial ^{18}F-FDG uptake was evaluated qualitatively and quantitatively. No myocardial uptake was grade 0, while positive uptake was classified in grades 1–3 according to target-to-background ratio tertiles.

RESULTS

One hundred fifty-six participants (19.0%) showed no myocardial ^{18}F-FDG uptake, and this was significantly associated with higher prevalence of MetS (29.0% vs. 13.9%, *P* < 0.001), hypertension (29.0% vs. 18.0%, *P* = 0.002), and diabetes (11.0% vs. 3.2%, *P* < 0.001), and with higher insulin resistance index (HOMA-IR, 1.64% vs. 1.23%, *P* < 0.001). Absence of myocardial uptake was associated with higher prevalence of early atherosclerosis (i.e., arterial ^{18}F-FDG uptake, *P* = 0.004). On follow-up, the associations between myocardial ^{18}F-FDG uptake and risk factors were replicated, and MetS was more frequent in the group without myocardial uptake. The increase in HOMA-IR was associated with a progressive decrease in myocardial uptake (*P* < 0.001). In 82% of subjects, the categorization according to presence/absence of myocardial ^{18}F-FDG uptake did not change between baseline and follow-up. MetS regression on follow-up was associated with a significant (*P* < 0.001) increase in myocardial uptake.

CONCLUSIONS

Apparently healthy individuals without cardiac ^{18}F-FDG uptake have higher HOMA-IR and higher prevalence of MetS traits, cardiovascular risk factors, and early atherosclerosis. An improvement in cardiometabolic profile is associated with the recovery of myocardial ^{18}F-FDG uptake at follow-up.

The myocardium is an omnivore organ that can generate energy from different substrates: fatty acids, carbohydrates, and ketone bodies (1). The flexibility in substrate utilization is essential, and an optimal cardiac function depends on the myocardium's ability to combine the intake of the different substrates (2).

Experimental studies suggest that cardiovascular risk factors are associated with changes in cardiac metabolism. Mouse models of metabolic syndrome (MetS) have demonstrated that there is a cardiac metabolic inflexibility associated with MetS, characterized by impaired insulin-induced glucose uptake and oxidation that leads to cardiomyocyte's mitochondrial energetics impairment (3–5). The hypothesis that MetS is associated with an abnormal cardiac substrate utilization has been recently highlighted in a pig model of MetS, in which a severely reduced availability of glycolytic cycle pathway metabolites has been shown (6). Cardiac metabolism abnormalities have also been observed in mouse models of diabetic cardiomyopathy, in which cardiac uptake and oxidation of fatty acids is increased because of impaired glucose transport (7,8).

In humans, molecular imaging techniques allow the evaluation of cardiac metabolism by means of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging (9). However, most clinical studies testing myocardial ^{18}F-FDG uptake are performed after strict preparation of the patient before the PET imaging (long fasting, high-fat low-carbohydrate diet) that alters cardiac metabolism and precludes its study under physiological conditions (10). Only a few retrospective studies performed in oncologic patients have provided some inconsistent data about myocardial ^{18}F-FDG uptake, which might not be applicable to healthy populations (11,12). Regarding cardiovascular risk factors, diabetes has been associated with a reduced myocardial ^{18}F-FDG uptake, and insulin resistance has been postulated as a potential mechanism (13–18). However, clinical data regarding the associations between MetS and cardiac metabolism are limited.

In this study, we aimed to evaluate whether MetS traits and other cardiovascular risk factors are associated with changes in cardiac metabolism. With that purpose, we assessed myocardial ^{18}F-FDG uptake under physiological conditions in a large cohort of healthy middle-aged adults.

RESEARCH DESIGN AND METHODS
Study Population
The study population consisted of participants from the Progression of Early Subclinical Atherosclerosis (PESA-CNIC-Santander) study (19) who underwent whole-body ^{18}F-FDG PET-magnetic resonance (^{18}F-FDG PET-MR) (20) at baseline and at 5-year follow-up (21).

PESA is an observational, prospective cohort study of 4,184 asymptomatic employees at Santander Bank in Madrid. Exclusion criteria were previous cardiovascular disease, any condition reducing life expectancy or affecting study adherence, morbid obesity (BMI $\geq$40 kg/m^2), or chronic kidney disease (estimated glomerular filtration rate $<$60 mL/min/m^2). The main goal of the PESA study is to characterize atherosclerosis initiation and progression by means of serial multiterritory, multimodality, noninvasive imaging and paired biological sampling (21). At baseline, a subgroup of PESA participants showing atherosclerosis on vascular ultrasound and/or having any coronary artery calcification on computed tomography (CT) were studied by whole-body ^{18}F-FDG-PET-MR (20). Cardiovascular risk factor profiling and biochemical analysis in PESA have been explained in detail elsewhere (19,20,22–24). In this study, MetS was defined when a participant met at least three of the following conditions: central obesity (waist circumference $\geq$88 cm in women and $\geq$102 cm in men) (25), elevated fasting plasma triglycerides ($\geq$150 mg/dL), low plasma HDL cholesterol ($<$40 mg/dL in men or $<$50 mg/dL in women), elevated fasting plasma glucose ($\geq$100 mg/dL), and high blood pressure (systolic $\geq$130 mmHg and/or diastolic $\geq$85 mmHg) (26). The study protocol was approved by the Institutional Review Board at Instituto de Salud Carlos III, Madrid, Spain, and all participants provided written informed consent.

Hybrid PET-MR Acquisition Protocol and Image Analysis
The PET-MR protocol has been published previously (20). In brief, prescan preparation requirements included fasting for 6 h and refraining from exercise in the preceding 24 h. Plasma glucose was measured before the scan. Participants received a target dose of 270–300 MBq ^{18}F-FDG (27) and were asked to remain at rest in a quiet room for 30 min after radiolabel injection. Sequential whole-body PET-MR studies were performed with a Philips Ingenuity TF PET-MR hybrid system (Philips Healthcare, Cleveland, OH). MR was performed with a phased-array 16-channel torso XL coil for aorto-iliac and femoral arteries and a 16-channel neurovascular coil for carotid arteries, using peripheral pulse gating. The imaging protocol

and detailed MR parameters have been published previously (20).

Each scan was systematically assessed by two experts (A.D. and R.V.) blinded to the clinical data using dedicated software (IntelliSpace Portal; Philips Healthcare). Fused PET-MR axial images were assessed; the presence of visual myocardial ^{18}F-FDG uptake was defined as positive if an elevated signal was detected compared with blood pool. For semiquantitative assessment, regions of interest encompassing the left ventricular myocardium were drawn in a representative axial image (Supplementary Fig. 1). Maximum standard uptake values (SUVmax) were registered as well as maximum tissue-to-background ratio (TBRmax), where SUVmax was corrected for the mean activity of the blood pool (28). Participants with visual myocardial ^{18}F-FDG uptake were classified in three groups (grades 1–3) according to TBRmax tertiles; absence of uptake was defined as grade 0. Both qualitative and quantitative measurements were highly reproducible: κ index was 1 for both intrareader and interreader reliability on qualitative assessments; intraclass correlation coefficient was 0.98 for intrareader and 0.97 for interreader reliability on quantitative assessments.

Arterial ^{18}F-FDG uptake (a proxy of early atherosclerosis) was assessed in five vascular territories (two carotid arteries, two ilio-femoral arteries, and aorta) (20). Bone marrow ^{18}F-FDG uptake (a proxy of bone marrow activation) was assessed in lumbar vertebrae (L3 and L4) (24).

Statistical Analysis
Normally distributed continuous variables are expressed as mean ± SD, whereas nonnormally distributed variables are expressed as median [Q1–Q3]. Categorical variables are expressed as n (%). Differences between myocardial ^{18}F-FDG uptake and nonuptake groups were assessed as appropriate by the Student t test or Mann-Whitney two-sample statistic for continuous variables and by χ^2 or Fisher exact test for categorical variables. Linear trends across groups according to degree of myocardial ^{18}F-FDG uptake were assessed with an extension of the nonparametric Mann-Whitney two-sample statistic. For multivariate analysis, linear regression models were performed. To evaluate the association between MetS, HOMA-insulin resistance (IR), and myocardial ^{18}F-FDG uptake, several models were generated:

model 1, adjusting for blood glucose before injection and time from injection to imaging acquisition; and model 2, adjusting for age and sex. For all end points, differences were considered statistically significant at P values < 0.05. Statistical analyses were performed using Stata software version 15 (StataCorp, College Station, TX).

RESULTS

A total of 946 PESA participants underwent whole-body PET-MR at baseline. Reasons for noncompletion of the study were physical intolerance in 21 participants and technical issues with MR attenuation maps in 97 participants; 7 participants were excluded because of limited image quality. Finally, 821 participants constituted the population for the current study (86.8% of the total sample who underwent PET-MR); 706 participants underwent a follow-up PET-MR after a median time of 4.8 ± 0.6 years; 6 participants were excluded because of limited quality imaging; 700 participants (99.2%) constituted the follow-up cohort (Supplementary Fig. 2).

Baseline Characteristics of Participants in Relation to Myocardial ^{18}F-FDG Uptake

The median age of the study population at baseline ^{18}F-FDG PET-MR was 50.6 years [46.9–53.6], and 83.7% of the population were male. Baseline characteristics are presented in Table 1. Within the study population, 156 participants (19.0%) had no myocardial ^{18}F-FDG uptake (grade 0). Myocardial ^{18}F-FDG uptake was present in the remaining 665 participants (81.0%) and was classified in grades 1 to 3 according to TBRmax tertiles (Supplementary Table 1).

Absence of myocardial ^{18}F-FDG uptake was associated with higher rates of hypertension (29.0% in participants without uptake versus 18.0% in those with any degree of uptake, $P = 0.002$), diabetes (11.0% vs. 3.2%, $P < 0.001$), and MetS (29% vs. 13.9%, $P < 0.001$) (Table 1). Greater levels of myocardial ^{18}F-FDG uptake were associated with lower rates of MetS ($P < 0.001$) (Supplementary Table 1). To better evaluate the associations between MetS traits and cardiac metabolism, participants were stratified in three groups according to the number of MetS components: 0 components, 1 or 2 components, or >2 components. Myocardial ^{18}F-FDG uptake assessed by TBRmax significantly decreased with the

increase in the number of MetS components ($P < 0.001$) (Supplementary Fig. 3). The grade 0 myocardial ^{18}F-FDG uptake group also had higher plasma triglycerides (111.0 mg/dL vs. 95.0 mg/dL $P = 0.022$) (Table 1), higher fasting blood glucose (94 mg/dL vs. 90 mg/dL, $P < 0.001$), higher hemoglobin A_{1c} (5.6% vs. 5.4%, $P = 0.001$), a higher insulin resistance index (HOMA-IR, 1.64% vs. 1.23%, $P < 0.001$), and higher plasma insulin (7.0 μU/mL vs. 5.6 μU/mL, $P = 0.001$). There was no difference between the no-uptake and uptake groups in family history of cardiovascular disease, smoking, or total and HDL cholesterol.

Participants with no myocardial ^{18}F-FDG uptake had higher counts of leukocytes (6.22×10^3 cells/μL vs. 5.80×10^3, $P = 0.002$), neutrophils (3.50×10^3 cells/μL vs. 3.30×10^3, $P = 0.022$), and lymphocytes (1.97×10^3 cells/μL vs. 1.83×10^3 cells/μL, $P = 0.009$). Absence of myocardial ^{18}F-FDG uptake was associated with higher erythrocyte sedimentation rates at 1 h (6 mm vs. 5 mm, $P = 0.01$).

When assessed using an exclusively quantitative evaluation (myocardial ^{18}F-FDG uptake divided into quartiles of TBRmax), the same results were observed (Supplementary Table 2). To better evaluate the associations between MetS, insulin resistance, and myocardial ^{18}F-FDG uptake, several models were performed. The associations between MetS and myocardial ^{18}F-FDG uptake (TBRmax) remained significant after adjusting for blood glucose levels before injection and time from injection to imaging (model 1; $P = 0.001$); these associations were also maintained after adjusting for age and sex (model 2; $P < 0.001$) (Supplementary Table 3). A similar trend was observed for the association between HOMA-IR and myocardial ^{18}F-FDG uptake when adjusted for model 1 ($P = 0.059$); the association between HOMA-IR and myocardial ^{18}F-FDG uptake remained significant when adjusted by model 2 ($P = 0.003$) (Supplementary Table 3).

Associations Between Myocardial ^{18}F-FDG Uptake and Uptake in the Arteries and Bone Marrow

Vascular and bone marrow ^{18}F-FDG uptake patterns in the different myocardial uptake groups are summarized in Supplementary Tables 4 and 5. Participants without myocardial ^{18}F-FDG uptake had a higher prevalence of early atherosclerosis (i.e., arterial

^{18}F-FDG uptake, 58.1% vs. 45.4% in the myocardial ^{18}F-FDG uptake group, $P = 0.004$), and had more arterial segments with vascular ^{18}F-FDG uptake (1 vs. 0, $P = 0.003$) and a higher overall arterial SUVmax (1.43 vs. 1.37, $P = 0.019$). Bone marrow activation was significantly more prevalent in participants without myocardial ^{18}F-FDG uptake (60.3% vs. 47.5%, $P = 0.007$), and these participants tended to have higher SUVmax values in the bone marrow (1.97 vs. 1.88 in individuals with myocardial ^{18}F-FDG uptake, $P = 0.051$).

Characteristics at Follow-up in Relation to Myocardial ^{18}F-FDG Uptake

Characteristics of the population at follow-up are summarized in Supplementary Table 6. Seventy participants (10.0%) had no myocardial ^{18}F-FDG uptake (grade 0). Myocardial ^{18}F-FDG uptake in the remaining participants ($n = 630$, 90.0%) was classified in grades 1–3 according to TBRmax tertiles (Supplementary Table 7).

Most of the associations observed at baseline were replicated at follow-up. Absence of myocardial ^{18}F-FDG uptake was associated with higher rates of diabetes (22.7% vs. 3.9% in those with any degree of uptake, $P < 0.001$), higher BMI (28.5 kg/m^2 vs. 27.1 kg/m^2, $P = 0.004$), and larger waist circumference (98.9 cm vs. 95.6 cm, $P = 0.024$) and with a trend to higher rates of MetS (24.2% vs. 15.0%, $P = 0.051$) (Supplementary Table 6). Greater levels of myocardial ^{18}F-FDG uptake were associated with lower rates of MetS ($P = 0.001$) (Supplementary Table 7), and myocardial ^{18}F-FDG uptake assessed by TBRmax significantly decreased with the increase in the number of MetS components ($P = 0.005$) (Supplementary Table 8). The grade 0 myocardial ^{18}F-FDG uptake group also had higher plasma triglycerides (126.0 mg/dL vs. 91.0 mg/dL $P = 0.001$) (Supplementary Table 6), higher fasting blood glucose (96 mg/dL vs. 88 mg/dL, $P < 0.001$), higher hemoglobin A_{1c} (5.6% vs. 5.4%, $P < 0.001$), a higher insulin resistance index (HOMA-IR, 2.05% vs. 1.35%, $P < 0.001$), and higher plasma insulin (8.5 μU/mL vs. 6.3 μU/mL, $P < 0.001$). The group with no uptake showed lower levels of HDL-cholesterol (47.8 mg/dL vs. 51.4 mg/dL, $P = 0.032$). There was no difference between the no-uptake and uptake groups in family history of cardiovascular disease, smoking, or total and LDL cholesterol.

Table 1—Characteristics by presence of myocardial ^{18}F-FDG uptake at baseline

	Total population	No uptake (grade 0)	Uptake (grades 1–3)	P value
n	821	156	665	
Age, years	50.6 [46.9–53.6]	50.8 [48.0–53.5]	50.5 [46.4–53.6]	0.196
Male	684 (83.7)	120 (77.4)	564 (85.2)	0.018
TBRmax	5.10 [2.75–8.04]	1.68 [1.36–2.15]	5.97 [3.91–8.79]	<0.001
Blood glucose before injection, mg/dL	89 [84–95]	92 [85–99]	89 [83–94]	0.001
Time injection to imaging, min	132 [124–142]	134 [124–146]	131 [124–141]	0.082
Cardiovascular risk factors				
Hypertension	164 (20.1)	45 (29.0)	119 (18.0)	0.002
Dyslipidemia	479 (58.6)	86 (55.5)	393 (59.4)	0.377
Diabetes	38 (4.7)	17 (11.0)	21 (3.2)	<0.001
Current smoking	217 (27.1)	45 (29.4)	172 (26.5)	0.466
Family history of CV disease	169 (20.7)	36 (23.2)	133 (20.1)	0.386
BMI, kg/m^2	27.2 ± 3.6	27.6 ± 4.1	27.1 ± 3.5	0.096
Body weight, kg	81.6 ± 13.7	81.3 ± 15.3	81.6 ± 13.3	0.782
Waist circumference, cm	93.9 ± 11.1	94.4 ± 13.3	93.8 ± 10.5	0.558
Metabolic syndrome and its components				
Metabolic syndrome	137 (16.8)	45 (29.0)	92 (13.9)	<0.001
Number of components				
0 components	261 (32.0)	44 (28.4)	217 (32.8)	0.286
1 or 2 components	418 (51.2)	66 (42.6)	352 (53.2)	0.017
>2 components	137 (16.8)	45 (29.0)	92 (13.9)	<0.001
Central obesity	214 (26.2)	50 (32.3)	164 (24.8)	0.056
HDL cholesterol, mg/dL	46.4 ± 11.4	46.6 ± 12.9	46.3 ± 11.0	0.810
Triglycerides, mg/dL	97 [71–131]	111 [69–157]	95 [72–127]	0.022
Fasting glucose, mg/dL	91 [85–97]	94 [87–104]	90 [84–96]	<0.001
Systolic blood pressure, mmHg	120.6 ± 12.8	120.5 ± 15.2	120.7 ± 12.2	0.851
Diastolic blood pressure, mmHg	75.0 ± 9.3	75.9 ± 10.6	74.8 ± 9.0	0.209
Treatment				
Antihypertensive therapy	113 (13.8)	34 (21.8)	79 (11.9)	0.001
Lipid-lowering therapy	120 (14.6)	26 (16.7)	94 (14.1)	0.421
Antidiabetic therapy	31 (3.8)	14 (9.0)	17 (2.6)	<0.001
Biochemistry				
Total cholesterol, mg/dL	208.3 ± 34.8	204.8 ± 30.1	209.1 ± 35.8	0.161
LDL cholesterol, mg/dL	139.7 ± 30.9	133.4 ± 27.8	141.2 ± 31.4	0.004
Hemoglobin A$_{1c}$, %	5.5 [5.2–5.7]	5.6 [5.3–5.8]	5.4 [5.2–5.7]	0.001
HOMA-IR, %	1.27 [0.85–1.98]	1.64 [0.95–2.67]	1.23 [0.83–1.88]	<0.001
Insulin, μU/mL	5.7 [3.9–8.3]	7.0 [4.3–10.8]	5.6 [3.8–8.0]	0.001
Inflammatory markers				
hs-CRP, mg/dL	0.11 [0.06–0.20]	0.11 [0.05–0.20]	0.10 [0.06–0.19]	0.467
Ferritin, ng/mL	122.1 [63.0–202.8]	107.7 [53.6–199.9]	123.4 [66.4–202.8]	0.377
Erythrocyte sedimentation rate (1 h), mm	5 [4–8]	6 [4–9]	5 [4–7]	0.010
Fibrinogen, mg/dL	264.7 [236.0–295.3]	266.1 [231.8–298.1]	264.4 [236.5–295.1]	0.990
P-selectin, ng/mL	135.2 [107.0–165.0]	136.7 [114.0–169.6]	134.4 [106.7–164.5]	0.347
Vascular cell adhesion molecule-1, ng/mL	644.8 [519.6–820.0]	640.8 [512.7–814.5]	646.9 [522.3–822.9]	0.569
Blood count				
Red blood cell count, 10^6 cells/μL	5.86 [5.01–7.02]	6.22 [5.28–7.38]	5.80 [4.96–6.92]	0.002
Hemoglobin, g/dL	15.0 [14.3–15.6]	14.8 [14.1–15.6]	15.0 [14.3–15.7]	0.053
Platelet count, 10^3 cells/μL	225 [199–256]	227 [197–263]	225 [199–255]	0.500
Leukocytes, 10^3 cells/μL	5.86 [5.01–7.02]	6.22 [5.28–7.38]	5.80 [4.96–6.92]	0.002
Segmented neutrophils, 10^3 cells/μL	3.33 [2.72–4.21]	3.50 [2.83–4.51]	3.30 [2.68–4.13]	0.022
Lymphocytes, 10^3 cells/μL	1.85 [1.56–2.20]	1.97 [1.66–2.34]	1.83 [1.54–2.17]	0.009
Monocytes, 10^3 cells/μL	0.42 [0.33–0.52]	0.42 [0.34–0.53]	0.41 [0.33–0.52]	0.542
Eosinophils, 10^3 cells/μL	0.13 [0.08–0.20]	0.13 [0.09–0.21]	0.12 [0.08–0.20]	0.180
Basophils, 10^3 cells/μL	0.05 [0.03–0.06]	0.05 [0.03–0.07]	0.05 [0.03–0.06]	0.139

Data are presented as n (%) or median [Q1–Q3]. CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein.

When assessed using an exclusively quantitative evaluation (myocardial ^{18}F-FDG uptake divided into quartiles of TBRmax), the same results were observed (Supplementary Table 9). The associations between MetS and myocardial ^{18}F-FDG uptake were maintained after adjusting by model 1 ($P = 0.050$) and model 2 ($P = 0.012$), and so were the associations between HOMA-IR and myocardial ^{18}F-FDG uptake (model 1: $P = 0.001$; model 2: $P < 0.001$) (Supplementary Table 3).

Longitudinal Assessment of Myocardial FDG Uptake

PET-MR was available at both baseline and follow-up in 612 participants (87.4% of 700 PET-MR at follow-up). At follow-up, presence of myocardial ^{18}F-FDG uptake did not change in 82.0% of participants ($n = 502$); in 81 participants (13.2%) who did not have uptake at baseline, myocardial ^{18}F-FDG uptake was present at follow-up; finally, myocardial ^{18}F-FDG uptake disappeared in 29 participants (4.7%) at follow-up (Fig. 1A). Forty-six participants (7.9%) met MetS criteria both at baseline and follow-up; MetS had regressed in 45 participants (7.7%) and appeared de novo in 50 (8.6%) participants

at follow-up (Supplementary Table 10). MetS regression at follow-up was associated with an increase in myocardial ^{18}F-FDG uptake (TBRmax: 2.70 at baseline vs. 5.33 at follow-up, $P < 0.001$), while myocardial ^{18}F-FDG uptake did not significantly change when MetS was present at both baseline and follow-up (Fig. 1B and Supplementary Table 10). The presence of MetS at baseline was associated with less myocardial ^{18}F-FDG uptake at follow-up ($P = 0.015$), and this association was maintained after adjusting by model 1 ($P = 0.05$) and model 2 ($P = 0.012$) (Supplementary Table 3).

CONCLUSIONS

The current study evaluated cardiac metabolism by means of myocardial ^{18}F-FDG uptake in a population of apparently healthy individuals. Absence of myocardial ^{18}F-FDG uptake was associated with the presence of MetS and cardiovascular risk factors, as well as with bone marrow activation and early atherosclerosis. The same associations were observed when evaluated at 5-year follow-up, which allowed confirmation of the findings. At follow-up, presence of myocardial uptake

was unchanged in the great majority of participants; MetS regression at follow-up was associated with an increase in myocardial ^{18}F-FDG uptake.

The study of cardiac metabolism in humans is possible by means of myocardial ^{18}F-FDG uptake evaluation (9). Some studies using cardiac ^{18}F-FDG PET have been performed in oncology patients; however, the results are heterogenous and might not be extrapolated to healthy populations (11,12). Most cardiac ^{18}F-FDG PET studies are performed to evaluate different cardiac conditions, particularly inflammatory diseases, for which an aggressive preparation is required in order to annul myocardial physiological glucose uptake, and thus do not provide information on cardiac basal metabolism. In contrast, our study was performed in apparently healthy individuals with no modification of metabolic conditions before the study, thus reflecting homeostatic cardiac status.

Several preclinical studies have postulated that there is an association between MetS and an abnormal myocardial metabolism. The proposed mechanisms are impaired myocardial sensitivity to insulin, altered myocardial substrate utilization, and abnormal cardiac mitochondrial function (3,4,29). Experimental models of MetS have shown that the heart defends against MetS by severely altering glycolysis and activating alternative pathways for energy production (5,6). Clinical data regarding the associations between MetS and cardiac metabolism are limited; one small study using ^{18}F-FDG PET observed that, among subjects with type 2 diabetes, those with MetS showed a reduction in myocardial glucose metabolic rate as compared with those without MetS (30). The role of insulin resistance in altered myocardial metabolism has been previously suggested in clinical studies; indeed, one study using endomyocardial biopsies showed that myocardial mitochondrial oxidative capacity for different substrates was lower in a group with impaired glucose tolerance among subjects without apparent heart failure (31,32). Myocardial insulin resistance might also explain why studies in diabetes have shown a decrease in myocardial ^{18}F-FDG uptake in patients with diabetes compared with subjects without diabetes (13–18). Our results support these observations, as they demonstrate that variations in myocardial ^{18}F-FDG uptake are associated with MetS traits and diabetes in the PESA cohort
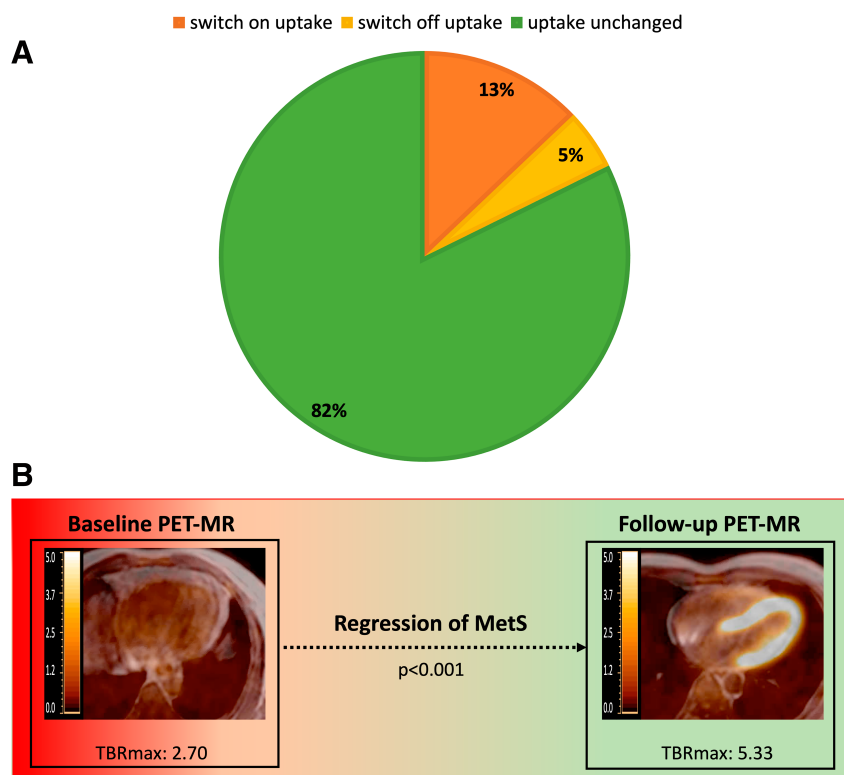

Figure 1—Progression of myocardial ^{18}F-FDG uptake progression according to changes in cardiometabolic profile. A: Progression of myocardial ^{18}F-FDG uptake from baseline to follow-up. B: Regression of MetS is associated with an increase in myocardial ^{18}F-FDG uptake.

(apparently healthy individuals). As postulated by experimental models, MetS might alter cardiac metabolism and increase the utilization of alternative energy substrates other than glucose by the myocardium, which might explain our findings (i.e., lower myocardial ^{18}F-FDG uptake in MetS). The contributory role of the different components of the MetS is well reflected by a progressive reduction in myocardial ^{18}F-FDG uptake as the number of components of the MetS increases (Supplementary Fig. 3). In our study, insulin resistance (assessed by HOMA-IR) also showed an association with cardiac metabolism; the increase in HOMA-IR was associated with a progressive decrease in myocardial ^{18}F-FDG uptake (Fig. 2).

In the present work, the study population comprised apparently healthy individuals with no history of heart failure or cardiomyopathy. The same population underwent a cardiac MRI study at a previous time point of the study (23), and no overt structural or functional cardiac abnormality was observed. Lower insulin-stimulated myocardial glucose metabolic rate evaluated by myocardial ^{18}F-FDG uptake has been associated with reduced cardiac mechano-energetic efficiency, which represents the capability of the myocardium to convert energy into mechanical work (33). A reduced myocardial energetic efficiency has, in turn, been associated with incident heart failure (34) and cardiovascular events (35). A reduction in myocardial ^{18}F-FDG uptake may

indicate a very early stage of myocardial energy disruption, although further studies are warranted to understand these mechanisms.

Moreover, myocardial ^{18}F-FDG uptake was associated with lower prevalence of bone marrow activation (indexed by elevated ^{18}F-FDG uptake in the bone marrow [24]) as well as with lower prevalence of early atherosclerosis, as indexed by elevated arterial metabolic activity (arterial ^{18}F-FDG uptake). Bone marrow activation is triggered by cardiovascular risk factors and metabolic syndrome, it is implicated in the atherosclerotic process long before the appearance of acute cardiovascular events, and it is considered an early phenomenon in the atherosclerosis development (24). As bone marrow activation progresses, it is accompanied by an increase in hematopoietic progenitor cells and inflammatory markers that leads to the very early stages of atherosclerosis (increased arterial ^{18}F-FDG uptake [20]) and, ultimately, to overt atherosclerotic plaque (24). Overall, our data suggest that greater ^{18}F-FDG uptake in the heart (as opposed to absence of uptake) in steady-state conditions is a marker of a healthy cardiovascular state.

In this study, we were able to replicate the results in a very large population at 5-year follow-up under similar conditions, which allowed the evaluation of cardiac metabolism at its physiological state at two time points. Since MetS and insulin resistance increase with age and male sex (36), we evaluated the associations between MetS, HOMA-IR, and myocardial ^{18}F-FDG

uptake after adjusting by age and sex, and we confirmed that they were maintained. As previous studies have reported (37), some intraindividual variability in myocardial ^{18}F-FDG uptake was observed between the baseline and follow-up scans (18%); however, these changes were associated with a change in the cardiometabolic risk profile. In the study population, blood glucose measured just before PET-MR was higher in the group with no myocardial ^{18}F-FDG uptake than in participants with any degree of uptake. Moreover, the associations between MetS, HOMA-IR, and myocardial ^{18}F-FDG uptake were maintained after adjusting by blood glucose before injection. Myocardial ^{18}F-FDG uptake is therefore not explained by elevated blood glucose before the procedure, which is in agreement with previous studies (38).

These results suggest that, as the cardiovascular risk profile worsens, myocardial ^{18}F-FDG uptake declines, being lost as the risk profile deteriorates further. Based on both qualitative and quantitative measurements of myocardial ^{18}F-FDG uptake, we identified three phenotypes. A healthy cardiometabolic risk profile is associated with low prevalence of early atherosclerosis and bone marrow activation and greater myocardial ^{18}F-FDG uptake (i.e., normal myocardial substrate utilization). At the other extreme is the phenotype characterized by no cardiac ^{18}F-FDG uptake (i.e., abnormal glucose consumption by the myocardium), which coincides with the poorest cardiometabolic profile and the highest prevalence rates of early atherosclerosis and bone marrow activation. Between these extremes is an intermediate phenotype characterized by intermediate grades of myocardial ^{18}F-FDG uptake (Graphical Abstract).

Studies of the PESA cohort have confirmed that cardiovascular risk factors impact metabolism in distinct organs, establishing associations between a poor cardiovascular risk profile and vascular inflammation (20), global brain hypometabolism (39), and bone marrow reactive activation (24). The current study extends these findings, demonstrating the associations between cardiometabolic risk factors and the metabolism of the heart. Interestingly, the association between cardiometabolic profile and organ ^{18}F-FDG uptake does not always go in the same direction; our results show that risk factors are associated with increased bone
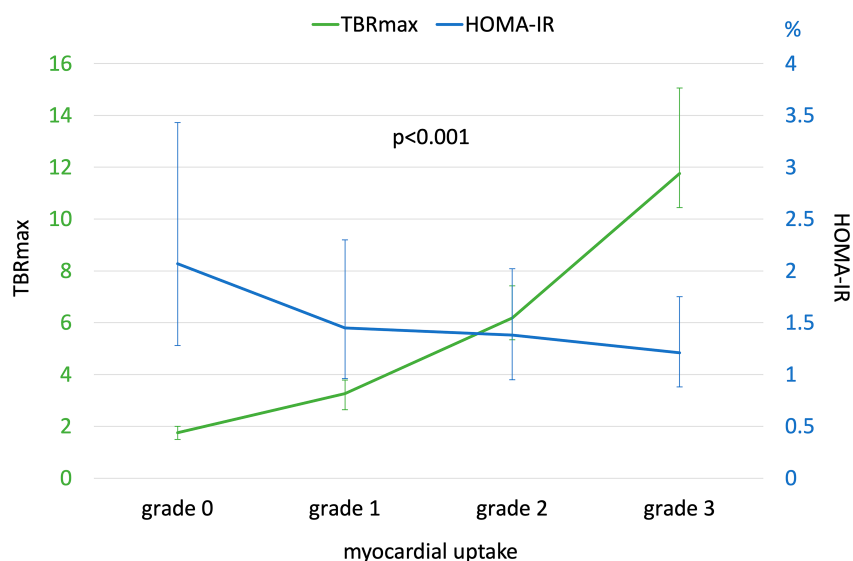

Figure 2—Myocardial ^{18}F-FDG uptake and insulin resistance.

marrow ^{18}F-FDG uptake but with decreased myocardial uptake.

Study Limitations

The selection of participants from the PESA cohort to undergo whole-body ^{18}F-FDG PET-MR was based on the presence of subclinical atherosclerosis on baseline vascular ultrasound. Around 20% of participants invited to participate declined enrollment or had MR contraindications, comparable to similar studies (40). As previously reported (20), the first 97 PET studies could not be used because of inaccuracies in MR-based attenuation and reconstruction; however, feasibility was almost 100% thereafter. This is, to our knowledge, the largest study to date of myocardial ^{18}F-FDG-PET-MR performed in healthy individuals. Unlike previous studies performed in cancer or cardiology patients, the current study provides information on an apparently healthy middle-aged population, without aggressive pre-exam preparation, thus allowing the study of cardiac metabolism under physiological conditions.

In conclusion, in apparently healthy individuals, absence of myocardial ^{18}F-FDG uptake is associated with a poorer cardio-metabolic risk profile (mainly metabolic syndrome and insulin resistance). Absence of myocardial ^{18}F-FDG uptake was further associated with higher prevalence of early atherosclerosis and bone marrow activation. Changes in myocardial ^{18}F-FDG uptake are associated with changes in the cardiometabolic risk profile.

References

1. Taegtmeyer H. Energy metabolism of the heart: from basic concepts to clinical applications. Curr Probl Cardiol 1994;19:59–113
2. Taegtmeyer H, Lubrano G. Rethinking cardiac metabolism: metabolic cycles to refuel and rebuild the failing heart. F1000Prime Rep 2014;6:90
3. Ilkun O, Wilde N, Tuinei J, et al. Antioxidant treatment normalizes mitochondrial energetics and myocardial insulin sensitivity independently of changes in systemic metabolic homeostasis in a mouse model of the metabolic syndrome. J Mol Cell Cardiol 2015;85:104–116
4. Landa-Galvan HV, Rios-Castro E, Romero-Garcia T, Rueda A, Olivares-Reyes JA. Metabolic syndrome diminishes insulin-induced Akt activation and causes a redistribution of Akt-interacting proteins in cardiomyocytes. PLoS One 2020;15:e0228115
5. Ren J, Pulakat L, Whaley-Connell A, Sowers JR. Mitochondrial biogenesis in the metabolic syndrome and cardiovascular disease. J Mol Med (Berl) 2010;88:993–1001
6. Karimi M, Petkova V, Asara JM, et al. Metabolomics and the pig model reveal aberrant cardiac energy metabolism in metabolic syndrome. Sci Rep 2020;10:3483
7. Ménard SL, Croteau E, Sarrhini O, et al. Abnormal in vivo myocardial energy substrate uptake in diet-induced type 2 diabetic cardiomyopathy in rats. Am J Physiol Endocrinol Metab 2010;298:E1049–E1057
8. Ouwens DM, Diamant M, Fodor M, et al. Cardiac contractile dysfunction in insulin-resistant rats fed a high-fat diet is associated with elevated CD36-mediated fatty acid uptake and esterification. Diabetologia 2007;50:1938–1948
9. Peterson LR, Gropler RJ. Radionuclide imaging of myocardial metabolism. Circ Cardiovasc Imaging 2010;3:211–222
10. Lu Y, Grant C, Xie K, Sweiss NJ. Suppression of myocardial ^{18}F-FDG uptake through prolonged high-fat, high-protein, and very-low-carbohydrate diet before FDG-PET/CT for evaluation of patients with suspected cardiac sarcoidosis. Clin Nucl Med 2017;42:88–94
11. Inglese E, Leva L, Matheoud R, et al. Spatial and temporal heterogeneity of regional myocardial uptake in patients without heart disease under fasting conditions on repeated whole-body ^{18}F-FDG PET/CT. J Nucl Med 2007;48:1662–1669
12. Maurer AH, Burshteyn M, Adler LP, Gaughan JP, Steiner RM. Variable cardiac 18FDG patterns seen in oncologic positron emission tomography computed tomography: importance for differentiating normal physiology from cardiac and paracardiac disease. J Thorac Imaging 2012;27:263–268
13. Ozguven MA, Karacalioglu AO, Ince S, Emer MO. Altered biodistribution of FDG in patients with type-2 diabetes mellitus. Ann Nucl Med 2014;28:505–511
14. Kim G, Jo K, Kim KJ, et al. Visceral adiposity is associated with altered myocardial glucose uptake measured by 18FDG-PET in 346 subjects with normal glucose tolerance, prediabetes, and type 2 diabetes. Cardiovasc Diabetol 2015;14:148
15. Yokoyama I, Yonekura K, Ohtake T, et al. Role of insulin resistance in heart and skeletal muscle F-18 fluorodeoxyglucose uptake in patients with non-insulin-dependent diabetes mellitus. J Nucl Cardiol 2000;7:242–248
16. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, Camici PG. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. Diabetes 2002;51:3020–3024
17. Hu L, Qiu C, Wang X, Xu M, Shao X, Wang Y. The association between diabetes mellitus and reduction in myocardial glucose uptake: a population-based ^{18}F-FDG PET/CT study. BMC Cardiovasc Disord 2018;18:203
18. Nielsen R, Jorsal A, Iversen P, et al. Heart failure patients with prediabetes and newly diagnosed diabetes display abnormalities in myocardial metabolism. J Nucl Cardiol 2018;25:169–176
19. Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, et al. The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: rationale and design. Am Heart J 2013;166:990–998
20. Fernández-Friera L, Fuster V, López-Melgar B, et al. Vascular inflammation in subclinical atherosclerosis detected by hybrid PET/MRI. J Am Coll Cardiol 2019;73:1371–1382
21. Ibanez B, Fernández-Ortiz A, Fernández-Friera L, García-Lunar I, Andrés V, Fuster V. Progression of Early Subclinical Atherosclerosis (PESA) study: JACC Focus Seminar 7/8. J Am Coll Cardiol 2021;78:156–179
22. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. Circulation 2015;131:2104–2113
23. de la Chica JA, Gómez-Talavera S, García-Ruiz JM, et al. Association between left ventricular noncompaction and vigorous physical activity. J Am Coll Cardiol 2020;76:1723–1733
24. Devesa A, Lobo-González M, Martínez-Milla J, et al. Bone marrow activation in response to metabolic syndrome and early atherosclerosis. Eur Heart J 2022;43:1809–1828
25. World Health Organization. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. Geneva, World Health Org., 2000 (Tech. Rep. Ser., no. 894)
26. Swarup S, Goyal A, Grigorova Y, Zeltser R. Metabolic syndrome. Accessed 2 May 2023. Available from Accessed 2 May 2023. https://www.ncbi.nlm.nih.gov/books/NBK459248/
27. Bucerius J, Mani V, Moncrieff C, et al. Optimizing ^{18}F-FDG PET/CT imaging of vessel wall inflammation: the impact of ^{18}F-FDG circulation time, injected dose, uptake parameters, and fasting blood glucose levels. Eur J Nucl Med Mol Imaging 2013;41:369–83
28. Maier A, Liao SL, Lescure T, et al. Pulmonary artery ^{18}F-fluorodeoxyglucose uptake by PET/CMR as a marker of pulmonary hypertension in sarcoidosis. JACC Cardiovasc Imaging 2022;15:108–120

29. Ilkun O, Boudina S. Cardiac dysfunction and oxidative stress in the metabolic syndrome: an update on antioxidant therapies. Curr Pharm Des 2013;19:4806–4817

30. Succurro E, Vizza P, Papa A, 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

31. Zweck E, Scheiber D, Schultheiss HP, et al. Impaired myocardial mitochondrial respiration in humans with prediabetes: a footprint of prediabetic cardiomyopathy. Circulation 2022;146:1189–1191

32. Zweck E, Scheiber D, Jelenik T, et al. Exposure to type 2 diabetes provokes mitochondrial impairment in apparently healthy human hearts. Diabetes Care 2021;44:e82–e84

33. Succurro E, Cicone F, Papa A, 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;22:4

34. Losi MA, Izzo R, Mancusi C, et al. Depressed myocardial energetic efficiency increases risk of incident heart failure: The Strong Heart Study. J Clin Med 2019;8:1044

35. de Simone G, Izzo R, Losi MA, et al. Depressed myocardial energetic efficiency is associated with increased cardiovascular risk in hypertensive left ventricular hypertrophy. J Hypertens 2016;34: 1846–1853

36. Kuk JL, Ardern CI. Age and sex differences in the clustering of metabolic syndrome factors: association with mortality risk. Diabetes Care 2010;33:2457–2461

37. Thut DP, Ahmed R, Kane M, Djekidel M. Variability in myocardial metabolism on serial tumor (18)F-FDG PET/CT scans. Am J Nucl Med Mol Imaging 2014;4:346–353

38. de Groot M, Meeuwis APW, Kok PJM, Corstens FHM, Oyen WJG. Influence of blood glucose level, age and fasting period on non-pathological FDG uptake in heart and gut. Eur J Nucl Med Mol Imaging 2005;32:98–101

39. Cortes-Canteli M, Gispert JD, Salvadó G, et al. Subclinical atherosclerosis and brain metabolism in middle-aged individuals: The PESA study. J Am Coll Cardiol 2021;77:888–898

40. Fayad ZA, Mani V, Woodward M, et al.; dal-PLAQUE Investigators. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet 2011;378:1547–1559