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Glycemic status and left atrial structure and function in adults with metabolic syndrome and overweight-obesity

Angel M. Alonso-Gómez [a,b,*], Leire Goicolea-Güemez [a,b], Dora Romaguera [b,c], Estefania Toledo [b,d], Aniqa B. Alam [e], Lucas Tojal-Sierra [a,b], Luis López Rodriguez [f], Raúl Ramallal [g], María Garrido Uriarte [a], Inés Gonzalez-Casanova [h], Jordi Salas-Salvadó [b,i], Montserrat Fitó [b,j], Alvaro Alonso [e]

[a] Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba. University Hospital, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain
[b] CIBER Consortium, Physiopathology of Obesity and Nutrition (CIBERObn), Carlos III Health Institute (ISCIII), Madrid, Spain
[c] Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain
[d] University of Navarra, Department of Preventive Medicine and Public Health, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain
[e] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[f] Cardiology Service, Hospital de Manacor, Manacor, Spain
[g] Cardiology Service, Hospital Universitario de Navarra, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain
[h] Department of Applied Health Science School of Public Health, Indiana University-Bloomington, Bloomington, IN, USA
[i] Human Nutrition Unit, Department of Biochemistry and Biotechnology, Rovira i Virgili University, Reus, Spain
[j] Cardiovascular Risk and Nutrition Group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

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1. Introduction

Metabolic syndrome (MetS) and obesity represent an important public health problem, due to their high prevalence, their association with cardiovascular risk factors, and their demonstrated association with higher risk of numerous cardiovascular complications, such as heart failure (HF), coronary artery disease, atrial fibrillation (AF), and cardiovascular mortality, and other chronic conditions [1]. Both MetS and obesity have been related with anomalies in left atrium (LA) structure and function, leading to an enlargement of the LA and a reduction in atrial mechanics parameters [2,3].

Diabetes is frequently associated with these two pathologies since both disorders have been shown to represent a risk factor for developing prediabetes and type 2 diabetes. The prevalence of glucose metabolism disorders is high in the population suffering from MetS and obesity, and, when both conditions are present, more than half of patients are estimated to have prediabetes or type 2 diabetes [4]. Diabetes is a key risk factor in the development of HF with preserved ejection fraction (HFpEF) and AF, where alterations in the structure and function of LA are not only present but can also predict their onset [5]. Adequate glycemic control helps reduce the likelihood of developing cardiovascular complications. Although blood glucose and hemoglobin A1c are the most commonly used parameters for this purpose, the triglyceride-glucose index has recently been shown to be an independent predictor of major adverse cardiovascular events in individuals with high cardiovascular risk [6].

LA evaluation has been classically obtained through echocardiography, by two-dimensional (2D) echocardiography (diameters, area and volumes) and spectral Doppler flow velocities assessment. However, with the introduction of 2D speckle-tracking echocardiography (2DSTE)

* Corresponding author. Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba. University Hospital, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain

E-mail addresses: angelmago13@gmail.com, angelmaria.alonsog@ehu.eus (A.M. Alonso-Gómez), leiregoiko@gmail.com (L. Goicolea-Güemez), mariaadoracion.romaguera@ssib.es (D. Romaguera), etoledo@unav.es (E. Toledo), abalam@emory.edu (A.B. Alam), lutojal@hotmail.com (L. Tojal-Sierra), lt_lr@hotmail.com (L. López Rodriguez), raulramallal@hotmail.com (R. Ramallal), mgarur@hotmail.com (M. Garrido Uriarte), inegonza@iu.edu (I. Gonzalez-Casanova), jordi.salas@urv.cat (J. Salas-Salvadó), mfito@researchmar.net (M. Fitó), alvaro.alonso@emory.edu (A. Alonso).

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techniques, a direct and angle-independent analysis of myocardial deformation can be obtained, providing sensitive and reproducible indexes of atrial function. Feasibility and reproducibility of 2DSTE for the study of LA mechanics have been validated and LA strain (LAS) has emerged as the most widely used parameter [7].

The impact of diabetes on LA structure and function has previously been studied in different scenarios: in cardiovascular disease [8], in HFpEF [9], in patients with prediabetes [10], in adolescents with diabetes [11], in population following lifestyle interventions [12], and in patients diagnosed with diastolic dysfunction [11,12]. A common finding in these studies is that atrial mechanics parameters in individuals with diabetes or prediabetes are reduced compared to healthy controls, but glycemic status effect on LA structure and function is yet to be determined in a population presenting with a baseline condition, MetS and obesity, that can in itself alter LA mechanics. The primary purpose of the present study was to assess whether glycemic status is related to LA function and structure in individuals with obesity and MetS. A secondary objective was to determine the frequency of echocardiographic criteria of diastolic dysfunction in this population and determine whether this prevalence was different from that in a reference population.

2. Methods

2.1. Study population

Participants in this analysis were selected from the PREDIMED-Plus study (ISRCTN89898870), a multi-center randomized trial for the primary prevention of cardiovascular disease in overweight/obese individuals with MetS. Between 2013 and 2016, 3574 men (aged 55–75 years) and 3300 women (aged 60–75 years) with a body mass index (BMI) ≥27 and < 40 kg/m^2 meeting ≥3 criteria for the MetS [13], were recruited from 23 centers in Spain. The primary endpoints of the trial are (i) a composite of non-fatal myocardial infarction, non-fatal stroke, or CVD death and, (ii) weight loss and long-term weight-loss maintenance [14,15]. Exclusion criteria are listed in the supplementary material (Table S1). The study protocol is available at: https://www.predimedplus.com/wp-content/uploads/2018/1.

For this analysis, we included a subsample of 574 PREDIMED-Plus participants from 3 recruiting centers (University of Navarra-Preventiva, Araba University Hospital and Son Espases University Hospital) who underwent prospectively transthoracic echocardiography at baseline according to a uniform protocol, which has been previously detailed [16]. After excluding participants with missing values of diabetes status (n = 8) and participants with baseline AF (n = 13), 553 participants were distributed according to their diabetic status so that they were classified into three groups: 68 normal, 287 with prediabetes and 198 with diabetes (Fig. 1).

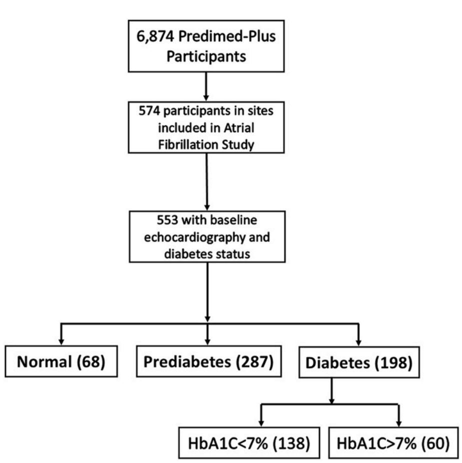

Fig. 1. Flowchart of participants included for this analysis.

The institutional review boards at each of the associated study centers have approved the current study protocol: University of Navarra-Preventiva: Comité de Ética de la Investigación con medicamentos del Gobierno de Navarra (EC_2013/23), Araba University Hospital: Comité Etico de Investigación Clínica Hospital Universitario Araba (EC_2014/002), Son Espases University Hospital: Comité de Ética de la Investigación de las Illes Balears (EC_2015/03).

All participants provided written informed consent, and the study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki by all the participating institutions.

2.2. Glucose metabolism status and glycemic measurements

Prediabetes and diabetes were defined following the American Diabetes Association criteria [4]. Diabetes was defined as a previous diagnosis of diabetes, hemoglobin A1c (HbA1c) ≥48 mmol/mol (≥6.5 %), use of antidiabetic medication, or having fasting plasma glucose ≥126 mg/dl in both the screening and baseline visits. Prediabetes status was defined as HbA1c between 39 mmol/mol (5.7 %) and 47 mmol/mol (6.4 %), or fasting plasma glucose between 100 mg/dl and 125 mg/dl. Participants who did not meet any of these parameters were categorized into the no-diabetes category. Glycated hemoglobin was used to categorize participants into those having “good” or “poor” diabetic control [HbA1c < 53 mmol/mol or ≥53 mmol/mol (7 %)], respectively [17]. Diabetes treatment was assessed at baseline using self-reported data on insulin, sulfonylureas, metformin, dipeptidyl peptidase-4 inhibitors (IDPP-4) or other antidiabetic medication use.

2.3. Echocardiography study

Transthoracic echocardiography was performed at each site following a defined acquisition protocol using an ultrasound scanner Vivid 7 or Vivid 9 (General Electric Healthcare) according to guidelines from the European Association of Echocardiography (EACVI) and the American Society of Echocardiography (ASE) [18]. The study included a comprehensive conventional assessment, including mitral flow velocity, tissue Doppler measurements of the lateral and septal mitral annulus and detection of the tricuspid velocity gradient from various echocardiographic planes. M-mode, Doppler imaging, and 2D cine loops for three heartbeats of standard views were obtained from each patient. All images were digitally stored, and an offline ultrasound software EchoPAC 204 (GE Healthcare) was used for analysis. Images were obtained at each center by cardiologists with expertise in cardiac imaging, but they were assessed in a blind fashion by two independent expert cardiologists (core lab evaluators) not involved in obtaining the images [16]. To avoid interobserver variability, each measure was performed by the same reader across all echocardiographic studies.

2.4. Assessment of left atrial structure and function

Data collected included LA volumetric and functional data, mitral inflow and tissue Doppler. The LA volume index—defined as LA volume indexed to body surface area—was included as a marker of LA structure. LA volume was calculated by 2D echocardiography in the apical four and two-chamber views using the biplane methods of disk. All markers of LA atrial function were measured in non-foreshortened four and two-chamber apical views [19] using a dedicated software package for 2DSTE analysis of left atrial longitudinal strain (AFI LA, EchoPAC 204, GE Vingmed, Horten, Norway). The algorithm then calculates LA strain values for the reservoir, conduit, and contractile functions, plus the maximum LA Volume [19]. Supplementary Fig. S1 illustrates the three phases of left atrial mechanical function assessed by speckle tracking echo. Markers of LA function included: LA emptying fraction, peak LA longitudinal strain, LA conduit strain and contractile strain, LA stiffness index and LA function index. LA emptying fraction was calculated as (LA

Volume max – LA Volume min)/LA Volume max, where LA Volume were obtained by 2DSTE. The peak atrial longitudinal strain (PALS) was measured at the end of the reservoir phase. The LA stiffness index was calculated as E/e' ratio divided by peak LA systolic longitudinal strain, where E represents the early mitral inflow velocity (E wave) and e' represents the medial and lateral mitral annular velocity. The LA function index was calculated as (LA emptying fraction x left ventricular outflow tract – velocity time integral)/indexed LA end-systolic volume [20].

2.5. Echocardiographic criteria for diastolic dysfunction

To define the presence of left ventricle diastolic disfunction by echocardiography, the diagnostic algorithm for diastolic dysfunction proposed by the 2016 ASE/EACVI guidelines was applied in patients with preserved ejection fraction [21]. The presence of the following criteria were considered [1]: mitral septal annulus velocity e' < 7 cm/s or mitral lateral annulus velocity <10 cm/s [2]; mitral E-wave velocity ratio and mean value of lateral e' and septal e' velocities of the mitral annulus >14 [3]; peak tricuspid regurgitation velocity (PTRV) > 2.8 m/s [4]; left atrial volume index (LAVI) > 34 ml/m^2.

2.6. Covariates

All covariates were obtained in the baseline visit, including demographic characteristics (age, sex), smoking status, adherence to energy-reduced Mediterranean diet [22], total physical activity [23], prevalence of hypertension or hyperlipemia, fasting blood glucose, glycated hemoglobin, creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol use of anti-hypertensive lipid-lowering, and antidiabetic drugs). Anthropometric evaluations (weight, height, and waist circumference) were measured according to the PREDIMED-Plus protocol. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

2.7. Statistical analysis

We described participants' characteristics by glycemic status (normal, prediabetes, diabetes) using means and standard deviations for continuous variables and proportions for categorical variables. Participants with diabetes were further categorized by HbA1c levels (<7 %, ≥7 %) in additional analyses. Echocardiographic characteristics were compared with reference values obtained in the World Alliance Societies of Echocardiography (WASE) and HUNT4 study [24–27]. Multiple linear regression models with glycemic status as the primary independent variable and echocardiographic measurements as the outcomes were run. Models were adjusted for age, sex, BMI, current smoking status, adherence to Mediterranean diet, physical activity, hypertension, hyperlipidemia, creatinine, lipid lowering medication, and antihypertensive medication. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA, www.sas.com).

3. Results

Fig. 1 shows the selection of participants into the study. Overall, 553 participants were eligible, of whom 198 (36 %) had diabetes, 287 (52 %) prediabetes, and 68 (12 %) normal glycemic status. Mean age (standard deviation) was 65.1 (4.8) years and 40.3 % of the participants were female. Participants' characteristics according to diabetes status are presented in Table 1. Anthropometric variables and prevalence of most cardiovascular risk factors were similar across groups, with the exception of higher blood glucose, HbA1c, prevalence of hypercholesterolemia, use of antidiabetic medication and use of lipid lowering medication among those with diabetes. Diabetic participants showed lower physical activity, although this was not statistically significant. Adherence to the MedDiet was similar in all three groups.

3.1. Echocardiographic measurements by glycemic status

Table 2 shows values of echocardiographic measurements according to glycemic status. Number of participants with missing values for each measurement are shown in Supplementary Table S2. No significant differences were observed across groups. Supplementary Table S3 provides additional information categorizing participants with diabetes according to glycemic control (HbA1c <7 % or ≥7 %), with no meaningful between-group differences.

Proportions of participants meeting specific echocardiographic criteria for diastolic dysfunction are shown in Supplementary Fig. S2 and Supplementary Table S4. The most frequently met criterion was having a lateral e' velocity <10 cm/s, which was present in 72 % of participants with normal status, 71 % of participants with prediabetes and 73 % of participants with diabetes. The least frequently met parameter was E/e'>14 (<8 % in all groups). None of the criteria

Table 1
Clinical characteristics of the study participants.

Variable (% or mean (SD)	Normal (68)	Prediabetes (287)	Diabetes (198)	p
Age, years	64.5 (4.9)	65.1 (4.9)	65.4 (4.8)	0.43
Women, %	20 (29.4)	118 (41.1)	85 (42.9)	0.14
Weight, kg	89.1 (14.4)	86.8 (12.3)	86.7 (12.9)	0.38
Height, cm	165.3 (9.0)	164.2 (9.0)	163.5 (9.6)	0.38
Body-mass index, kg/m^2	32.7 (3.7)	32.3 (3.1)	32.6 (3.5)	0.60
Adherence to MedDiet, score	8.0 (3.6)	7.4 (2.9)	7.9 (2.7)	0.14
Physical activity, MET•min/sem	3062 (2953)	2576 (2220)	2297 (1971)	0.05
Hypertension, %	52 (76.5)	232 (80.8)	174 (87.9)	0.05
Current smoking, %	6 (8.8)	27 (9.4)	20 (10.1)	0.58
Hypercholesterolemia %	44 (64.7)	195 (67.9)	149 (75.3)	**.03**
Glucose, mg/dL	93.8 (4.1)	107.1 (8.5)	138.7 (34.0)	**<.0001**
Glycated hemoglobin, %	5.4 (0.2)	5.8 (0.3)	6.8 (0.9)	**<.0001**
Creatinine, mg/dL	0.82 (0.12)	0.84 (0.18)	0.85 (0.19)	0.48
Total cholesterol, mg/dL	211 (38)	206 (36)	187 (32)	**<.0001**
HDL-cholesterol, mg/dL	45 (10)	47 (11)	44 (11)	**.03**
LDL-cholesterol, mg/dL	137 (34)	130 (30)	111 (28)	**<.0001**
Triglycerides, mg/dL	150 (65)	149 (68)	161 (75)	0.14
Use of blood pressure lowering drugs, %	46 (67.7)	211 (73.5)	166 (83.8)	0.006
Use of lipid-lowering drugs, %	26 (38.2)	127 (44.3)	129 (65.2)	**<.0001**
Insulin use, %	0 (0)	0 (0)	20 (10.1)	**<.0001**
Metformin use, %	0 (0)	0 (0)	107 (54.0)	**<.0001**
Other antidiabetic medication, %	0 (0)	0 (0)	104 (52.5)	**<.0001**

Table 2
Echocardiographic characteristics of the patient population.

Variable (mean (SD))	Normal (n = 68)	Prediabetes (n = 287)	Diabetes (n = 198)	p
General Echocardiographic measures				
LVEDD (mm)	52.2 (6.7)	51.8 (6.2)	50.9 (6.2)	0.19
LVESD (mm)	30.6 (7.9)	30.7 (7.1)	31.0 (7.1)	0.83
Septum (mm)	10.2 (1.1)	10.2 (1.1)	10.1 (1.0)	0.85
Posterior wall (mm)	9.7 (1.0)	9.8 (1.0)	9.8 (1.0)	0.85
Mass index (g/m^2)	100 [33]	103 [32]	99 [31]	0.50
LV Ejection Fraction (%)	64.4 (6.5)	65.2 (7.1)	65.5 (6.3)	0.48
LV longitudinal strain (%)	17.2 (2.0)	17.9 (2.6)	17.5 (2.4)	0.07
LV longitudinal strain <16 % [n (%)]	18 (26 %)	71 (25 %)	51 (26 %)	0.94
Diastolic echocardiographic measures				
E-wave mitral flow (cm/s)	0.67 (0.18)	0.68 (0.15)	0.68 (0.14)	0.91
A-wave mitral flow (cm/s)	0.78 (0.15)	0.79 (0.16)	0.82 (0.17)	0.06
Deceleration time (ms)	241 (49)	235 (51)	236 (58)	0.67
E/A ratio	0.87 (0.17)	0.87 (0.21)	0.85 (0.24)	0.38
Septal e' velocity (cm/sec)	7.1 (1.5)	7.2 (1.6)	6.9 (1.5)	0.12
Lateral e' velocity (cm/sec)	8.6 (2.0)	8.7 (2.0)	8.7 (5.1)	1.00
Average E/e'ratio	8.7 (2.7)	8.8 (2.4)	9.2 (2.7)	0.23
PTRV (cm/s)	180 (60)	191 (56)	187 (57)	0.52
Left atrial substrate				
LA diameter (mm)	36.9 (5.8)	36.7 (5.9)	36.3 (4.8)	0.66
LA volume (mL)	53.6 (15.1)	55.5 (14.3)	54.6 (14.4)	0.57
LA volume index (mL/m^2)	27.3 (7.0)	28.8 (7.1)	28.4 (7.2)	0.29
Emptying fraction (%)	58.2 (9.9)	59.0 (8.9)	59.0 (9.9)	0.82
Peak systolic longitudinal strain (%)	27.5 (6.7)	27.7 (6.3)	27.4 (6.8)	0.87
Conduit strain (%)	11.8 (3.9)	12.1 (4.5)	11.8 (4.4)	0.72
Contractile strain (%)	15.8 (4.5)	15.6 (4.3)	15.6 (5.0)	0.97
Stiffness index (U)	0.35 (0.22)	0.34 (0.15)	0.36 (0.17)	0.47
Function index (U)	66.6 (34.6)	65.6 (27.5)	69.9 (29.5)	0.29

LA: Left atrial; LV: Left ventricle; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; PTRV: Peak tricuspid regurgitation velocity.

showed statistically significant differences across groups.

3.2. LA structure and function and diastolic dysfunction echocardiographic criteria by sex and glycemic status

Supplementary Table S4 shows the characteristics of the study population by sex and glycemic status, together with reference values from the WASE and HUNT4 cohorts. Measures of PALS were higher in the healthy reference population than in our cohort, while LA volume index was smaller in the healthy population of the WASE cohort. Measures obtained with tissue Doppler were similar in the reference population and our study sample.

3.3. Association between glycemic markers and LA strain

The correlation coefficients between LA reservoir strain and fasting plasma glucose and HbA1c were 0.01 ($p = 0.74$) and −0.02 ($p = 0.60$), demonstrating lack of an association between glycemic markers and LA longitudinal strain in crude analysis.

3.4. Association of glycemic status LA structure and function adjusting for confounders

We estimated the associations of glycemic status with measures of LA structure and function using multiple linear regression adjusting for potential confounders. Overall, there was no evidence of associations between glycemic status and echocardiographic measurements after adjustment for covariates (Table 3 and Supplementary Table S5).

4. Discussion

Our study supports that individuals with MetS and overweight or obesity, but free of cardiovascular disease, have a certain degree of abnormalities in LA structure and function. The primary finding from our analysis is that glycemic status was not associated with impairment in LA structure or function (Graphical abstract). Similarly, prevalence of diastolic dysfunction criteria was similar across glycemic status groups.

Prevalence of MetS has been associated with abnormalities in cardiac mechanics, both in the left ventricle and the LA. In 399 Hispanic participants in the Echo-SOL Study, those participants with MetS had reduced left ventricular strain and had higher prevalence of diastolic dysfunction measurements compared to 861 participants without MetS [28]. We also know that MetS significantly elevates the incidence of atrial fibrillation. Cardiac chamber structural and electrical remodeling, autonomic imbalance, inflammation, oxidative stress, and fibrosis constitute the primary pathways through which metabolic syndrome contributes to atrial fibrillation. Similarly, obesity in the absence of MetS or diabetes has been associated with significant changes in LA function, detectable in adolescents and young adults [11], in persons 35–55 years of age [3], and in obese patients without heart disease or diastolic dysfunction [29]. Mechanisms through which obesity may affect LA function include chronic volume overload, systemic inflammation, increase of epicardial adipose tissue, adipose and fibrotic infiltration of atrial tissue, and other conditions linked to obesity such as hypertension

Table 3
Mean differences and their 95 % confidence interval for the association of diabetes status with echocardiographic parameters.

Parameter	Normal	Prediabetes	Diabetes
General echocardiographic measures			
Mass index (g/m^2)	0 (Ref.)	3.55 (−4.85, 11.96)	−0.34 (−9.27, 8.59)
LV Ejection Fraction (%)	0 (Ref.)	0.75 (−1.05, 2.55)	1.20 (−0.72, 3.11)
LV longitudinal strain (%)	0 (Ref.)	**.71 (.04, 1.38)**	0.48 (−0.23, 1.19)
Diastolic echocardiographic measures			
E-wave mitral flow (cm/s)	0 (Ref.)	0.01 (−0.03, 0.05)	0.00 (−0.04, 0.04)
E/A mitral ratio	0 (Ref.)	0.02 (−0.04, 0.08)	0.00 (−0.06, 0.06)
Septal e' velocity (cm/sec)	0 (Ref.)	0.22 (−0.19, 0.62)	0.01 (−0.42, 0.44)
Lateral e' velocity (cm/sec)	0 (Ref.)	0.22 (−0.70, 1.14)	0.25 (−0.73, 1.23)
Average E/e'ratio	0 (Ref.)	−0.11 (−0.77, 0.55)	0.04 (−0.67, 0.74)
PTRV (cm/s)	0 (Ref.)	6.36 (−11.51, 24.24)	−2.25 (−22.34, 17.84)
Left atrial substrate			
LA volume (mL)	0 (Ref.)	3.57 (−0.05, 7.19)	2.78 (−1.08, 6.64)
LA volume index (mL/m^2)	0 (Ref.)	**1.83 (.01, 3.65)**	1.45 (−0.49, 3.39)
Emptying fraction (%)	0 (Ref.)	1.17 (−1.30, 3.64)	1.15 (−1.47, 3.77)
Peak systolic longitudinal strain (%)	0 (Ref.)	0.52 (−1.21, 2.25)	0.41 (−1.42, 2.25)
Conduit strain (%)	0 (Ref.)	0.56 (−0.64, 1.75)	0.35 (−0.92, 1.62)
Contractile strain (%)	0 (Ref.)	0.03 (−1.26, 1.31)	0.17 (−1.19, 1.53)
Stiffness index (U)	0 (Ref.)	−0.02 (−0.06, 0.02)	−0.01 (−0.06, 0.03)
Function index (U)	0 (Ref.)	−1.43 (−9.37, 6.51)	2.78 (−5.62, 11.17)

Results from multiple linear regression adjusted for age, sex, BMI, smoking status, hypertension, hyperlipidemia, creatinine, lipid lowering medication use, antihypertensive treatment, antidiabetic treatment, adherence to Mediterranean diet, and physical activity.

and sleep apnea. These pathways result in the development of atrial myopathy, facilitating occurrence of atrial fibrillation and diastolic dysfunction (as a precursor to HFpEF development). Thus, it is expected that participants affected by both MetS and excessive body weight, as in the PREDIMED-Plus population, have, on average, abnormal values for LA structure and function.

Consistent evidence shows that diabetes and prediabetes significantly affect LA structure and function [9,10]. This is a common finding when diabetes occurs with other conditions such as cardiovascular disease [8], HF [9] and diastolic dysfunction [12]. The mechanisms through which diabetes causes LA remodeling are not clear. Persistent hyperglycemia may induce collagen synthesis by cardiac fibroblasts, resulting in LA fibrosis and the development of the substrate for the onset of AF [5]. The finding of a significant association between prediabetes and major events (mortality, cardiac arrest and stroke) in patients with atrial fibrillation supports the hypothesis that both entities share common pathophysiological mechanisms with endothelial dysfunction and inflammation playing a key role [30].

Previous studies have compared obese and obese diabetic patients, but the novelty of our study is that the baseline population has two risk factors that impair LA function, the high number of patients studied and advanced age. The sample included in this study allows us to evaluate whether prediabetes or diabetes is associated with a worsening of the structural and functional substrate in LA in individuals with some previous involvement. To our knowledge, this goal has not been previously addressed. In our study, LA size (raw or indexed) did not show differences across groups. Similarly, LA emptying fraction, LA strain, and LA function index did not differ by glycemic status. This lack of association could be due to the underlying high cardiovascular risk in this population and the limited additional impact of abnormal glycemic status in the context of MetS and excessive body weight. In a study of 142 obese patients with a mean BMI of 32.7 kg/m^2, Chirinos et al. reported a LA volume index of 21.5 mL/m^2 and a reservoir strain of 30.9 % [3]. These values differ from those observed in our population, likely due to the substantial age difference between the two groups (47 vs. 65 years). In another study of 54 patients with obesity and diabetes (mean age 58 years, BMI 35 kg/m^2), the LA volume index was 27.6 mL/m^2—similar to the 28.2 mL/m^2 observed in our cohort. The LA emptying fraction was 64.8 %, slightly higher than the 58.4 % observed in our diabetic group, and the peak atrial longitudinal strain (PALS) was 30.5 %, also higher than the 26.8 % seen in our 155 diabetic patients [31]. The influence of age on atrial strain is well established; strain may remain preserved in younger adults, as demonstrated by Steele et al., who reported a reservoir strain of 46.6 % in 116 diabetic patients with a mean BMI of 35.8 kg/m^2 and a mean age of 22 years [11].

In our multivariate analysis, we did not identify any associations between glycemic status and echocardiographic measurements after adjusting for demographic variables, lifestyles, BMI and cardiovascular risk factors. Previous studies have identified associations between obesity and LA strain, highlighting the importance of adjusting for that variable [29].

4.1. Reference values for LA structure and function measurements

Increased LA volume and impaired LA function are associated with higher incidence of AF, stroke, HF, hospitalizations and mortality [32]. Thus, establishing reference values for normality in these measurements is key. The definition of a healthy population without disease does not depend solely on age and sex, as ethnic origin, the presence of risk factors, obesity, and the echocardiographic techniques used also have an influence. A recent study has shown that the LA volume index threshold would be 40 mL/m^2 instead of 34 mL/m^2 if we used three-dimensional echocardiography instead of 2D echocardiography [33]. In our analysis, we chose reference values used by WASE and HUNT4, that contain a significant number of older adults (≥65 years) distributed by sex (Table S4). The PALS threshold for our population is significantly lower than that found in the WASE study and somewhat lower than in the HUNT4 cohort. However, the threshold in the LA volume index is higher than the WASE values but lower than those found in the HUNT4 study. These differences can be explained by the fact that, unlike the WASE population, the HUNT 4 population included individuals with obesity, high blood pressure, and high cholesterol levels [26]. In our sample, LA volume was similar in both males and females, but functional measures (LA emptying fraction and LA strain measures) were higher in males than females. Observed values in our sample cohort are consistent with a pattern of diastolic dysfunction with abnormal relaxation, which is expected in an overweight/obese population with MetS, high blood pressure and high prevalence of glycemic dysfunction. The reference value for stiffness index was obtained from the Norre study, which evaluated 61 male individuals 60 and older [34]. In our sample, the mean stiffness index was in the abnormal range. However, analyses comparing these measurements across glycose status categories did not show differences.

4.2. Echocardiographic criteria for diastolic dysfunction

As mentioned above, MetS, obesity and diabetes were associated with HF development, usually together with diastolic dysfunction in early stages. Echocardiography is key for the noninvasive diagnosis of diastolic dysfunction, with available criteria [21]. These criteria have some limitations, leading recently to the addition of peak atrial longitudinal strain (PALS) from 2DSTE as an additional criterion [7]. Our study sample had a very high prevalence of diastolic dysfunction echocardiographic parameters. Consistent with other studies, reduced velocity of the e wave using issue Doppler was the most frequent finding. We did not classify our sample according to diastolic dysfunction categories (absent, undetermined, present), since the LA volume criterion tends to overestimate abnormalities. Also, current guidelines do not offer consistent thresholds to categorize PALS, with values ranging from −15 % to −23 %. Overall, we did not find differences in prevalence of diastolic dysfunction measurements by glycemic status.

4.3. Clinical implications

Abnormalities in LA structure and function are associated with worse outcomes, but we did not find differences in LA measurements by glycemic status. Due to the cross-sectional design, this analysis cannot answer whether diabetes or prediabetes affect LA measures over time, questions that will be addressed in future analyses, testing whether diabetes or prediabetes are associated with larger increases in LA volume and greater decline in LA function parameters [35]. Global longitudinal strain is the parameter most consistently associated with AF and HFpEF [36]. Although the optimal threshold for guiding changes in screening and prevention strategies remains uncertain in clinical practice, it is reasonable to consider that patients with more abnormal values (<18–20 %) may derive the greatest benefit. In this subgroup, intensified secondary prevention efforts—particularly weight loss—enhanced arrhythmia monitoring, and the use of pharmacologic agents that delay the onset of HF may be warranted. The role of catheter ablation in this population may offer an added benefit, as we know that this procedure improves left atrial remodeling, even immediately after the intervention [37], leading to a reduction in arrhythmia recurrences and a significant decrease in the development of heart failure in the future [38,39].

4.4. Limitations

The study included overweight or obese individuals with MetS aged 55–70 years in Spain, free of cardiovascular disease, and, therefore, results may not be generalizable to populations in other settings, to different age groups, or to those with preexisting cardiovascular conditions. We used 2D echocardiography, which is the most frequently used in clinical practice, but can underestimate LA volumes compared to other techniques such as 3D echocardiography. Also, magnetic resonance imaging has higher validity in individuals with high BMI. Our findings may not be applicable to studies using different echocardiographic platforms and software. The cross-sectional design is a limitation of the current analysis, which does not allow evaluation of temporal relationships and may have resulted in the lack of associations. Finally, we used a HbA1c value < 7 % to determine good glycemic control, but other studies have used different thresholds.

5. Conclusion

In this population of older adults with metabolic syndrome and overweight/obesity, and free of cardiovascular diseases, mean values of measures of LA structure and function were in the abnormal range. Measures of LA structure and function were similar in individual across the glycemic status (diabetes, prediabetes, normal). Prevalence of diastolic dysfunction parameters in this sample was high but, again, did not differ by glycemic status.

CRediT authorship contribution statement

Angel M. Alonso-Gómez: Writing – original draft, Validation, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Leire Goicolea-Güemez:** Writing – review & editing, Resources. **Dora Romaguera:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Estefania Toledo:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Aniqa B. Alam:** Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lucas Tojal-Sierra:** Writing – review & editing, Funding acquisition, Data curation. **Luis López Rodriguez:** Writing – review & editing, Formal analysis, Data curation. **Raúl Ramallal:** Writing – review & editing, Data curation. **María Garrido Uriarte:** Writing – review & editing, Visualization, Data curation. **Inés Gonzalez-Casanova:** Writing – review & editing, Supervision, Methodology. **Jordi Salas-Salvadó:** Writing – review & editing, Validation, Supervision, Funding acquisition. **Montserrat Fitó:** Writing – review & editing, Methodology, Formal analysis. **Alvaro Alonso:** Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Consent for publication

Not applicable.

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Appendix A. Supplementary data

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