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Untreated diabetes mellitus, but not impaired fasting glucose, is associated with increased left ventricular mass and concentric hypertrophy in an elderly, healthy, Swedish population☆

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ABSTRACT

Background/objectives: To examine whether higher fasting plasma glucose (FPG) levels were independently associated with left ventricular (LV) mass and/or geometry in elderly, otherwise healthy subjects.
Methods: We tested cross-sectional associations between echocardiographically determined LV mass/geometric patterns, cardiovascular risk factors, and FPG categorized as normal fasting glucose (NFG), impaired fasting glucose (IFG), and untreated diabetes mellitus (DM), in 486 men and 207 women aged 56–79 years without overt cardiovascular disease, who received no cardiovascular, anti-diabetic, or lipid-lowering drugs and had a preserved LV ejection fraction >50%.
Results: Unadjusted mean LV mass index (LVMI) was significantly greater among subjects with DM than those without (90 +/− 26 g/m^2 vs. 85 +/− 20 g/m^2, p = 0.01), as were both relative wall thickness (RWT) (0.43 +/− 0.09 vs. 0.40 +/− 0.08, p = 0.01) and prevalence of concentric LV hypertrophy (LVH) (11% vs. 6%, p = 0.03). However, only RWT remained significantly associated with the presence of DM after multivariable adjustment (p = 0.04). Interaction analyses revealed that greater LVMI/LVH was predominantly associated with higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) among subjects with IFG or DM, but not NFG.
Conclusions: Subjects with untreated DM had higher values of LVMI and a greater prevalence of concentric LVH, but the associations were not independent of other risk factors. NT-proBNP was primarily associated with greater LV size in subjects with IFG or DM.
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1. Introduction

Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular morbidity and mortality in subjects both with and without diabetes mellitus (DM) [1–3]. The increase in cardiovascular risk is directly related to the magnitude of increase in LV mass (LVM) [4,5]. Furthermore, the LV geometric pattern determined by the combination of LV mass index (LVMI) and relative wall thickness (RWT) may

Abbreviations: ANOVA, analysis of variance; ASE, American Society of Echocardiography; BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; DT, E-wave deceleration time; DUST, discrete upper septal thickening; EACVI, European Association of Cardiovascular Imaging; EAE, European Association of Echocardiography; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin $A1_c$ (glycosylated hemoglobin); HDL, high-density lipoprotein; ICD, International Classification of Diseases; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; IVS, interventricular septum thickness; LDL, low-density lipoprotein; LV, left ventricular/left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVID, left ventricular internal diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; MPP, Malmö Preventive Project; MPP-RES, Malmö Preventive Project Re-Examination Study; NFG, normal fasting glucose; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OGTT, oral glucose tolerance test; PW, posterior wall thickness; RWT, relative wall thickness; SBP, systolic blood pressure; WHO, World Health Organization.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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provide additional prognostic information beyond assessment of LVM alone [6,7].

The pathogenesis of LVH is presumably multifactorial and driven by both hemodynamic and non-hemodynamic factors [8–13]. LVMI and possibly also RWT are significantly greater among patients with DM than those without, and the case may be the same for subjects with impaired glucose tolerance (IGT) [14–20]. However, only few studies have investigated the association between DM and LVM after adjusting for body size and other traditional risk factors [14–19], and whether a graded association between fasting plasma glucose (FPG) category and LVM and geometry exists, has not been clearly established.

Given these knowledge gaps, a comprehensive evaluation of LV size and geometry and their relation to fasting glucometabolic status is justified and may reveal putative mechanisms for the development of LVH in subjects with impaired glucose metabolism. Therefore, the purpose of this cross-sectional study was: 1) To examine whether worse glucometabolic status (i.e. higher FPG category) was associated with greater LVMI, independently of other hemodynamic and non-hemodynamic risk factors; 2) To describe the association between FPG category and LV geometric pattern based on LVMI and RWT; and 3) To identify other risk factors independently associated with greater LVMI and LV geometric pattern.

2. Methods

2.1. Study population

The study subjects were derived from the Malmö Preventive Project (MPP, 1974–1992, n = 33,346), a population-based cohort study with the aim of screening for cardiovascular risk factors, alcohol abuse, and breast cancer among inhabitants of Malmö, Sweden, born 1921–1949 [21]. A re-examination study (MPP-RES, n = 18,238) was conducted between 2002 and 2006, during which the participants answered a self-administered questionnaire on lifestyle, medical history, and medication. Blood pressure and pulse rate were recorded twice in the supine position after 5 min of rest (with the values averaged for the analyses), and height, weight, waist and hip circumferences were measured. Moreover, blood samples were drawn after overnight fasting for analysis of plasma glucose, serum lipids, and storage in a biobank. In a subsample of 1792 individuals from MPP-RES, an echocardiography and a 12-lead ECG recording were carried out. These subjects were randomly selected from groups defined by fasting plasma glucose (FPG), with oversampling in groups of subjects with impaired fasting glucose (IFG) and DM, in order to ensure a sufficient number of individuals in each category. Both MPP and MPP-RES were approved by the Ethics Committee of Lund University, Sweden, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Prevalent cardiovascular disease or diabetes mellitus

Subjects with prevalent cardiovascular disease (n = 300) and/or those on cardiovascular (incl. antihypertensive) (n = 864), antidiabetic (n = 329) or lipid-lowering therapy (n = 464) were excluded in the present study (total excluded n = 1029). Prevalent cardiovascular disease was defined by the *International Classification of Diseases* (ICD-9 and ICD-10) codes gathered from the Swedish Hospital Discharge Registry as well as local hospital and study registries and encompassed previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, heart failure, stroke, or atrial fibrillation and/or flutter.

2.3. Fasting plasma glucose category

The definitions of normal fasting glucose (NFG), IFG, and DM were based on the *World Health Organization* (WHO) criteria [22]: NFG was defined as a single FPG ≤ 6.0 mmol/L; IFG was defined as a single FPG between 6.1–6.9 mmol/L, or one measurement 7.0–11.0 mmol/L and a separate measurement ≤6.9 mmol/L; and untreated DM was defined as a single FPG ≥ 11.1 mmol/L or two separate measurements ≥7.0 mmol/L.

2.4. Echocardiography

Echocardiography was conducted with a 3V2c transducer (Acuson Sequoia, Mountain View, CA) or an S3 transducer (Sonos 5500 Philips, Andover, MA). LV ejection fraction (LVEF) was quantified visually. LVM calculations were based on 2-dimensional linear measurements in the parasternal long-axis view at the tips of the mitral valve leaflets at end-diastole, perpendicular to the long axis of LV. The thickness of the interventricular septum (IVS), LV internal diameter (LVID), and the thickness of the posterior wall (PW) were obtained by placing the calipers on the interface between myocardial wall and cavity and the interface between myocardial wall and pericardium, respectively. LVM was then calculated using the Cube formula recommended by the *American Society of Echocardiography* (*ASE*) *and the European Association of Cardiovascular Imaging* (*EACVI*) [23], and indexed for BSA, obtaining LVMI. Cut-off values for LVH were LVMI >95 g/m^2 in women and >115 g/m^2 in men, respectively. Relative wall thickness (RWT) was calculated as (2 × PW) / LVID, allowing categorization of LV geometry into normal (normal LVMI and RWT ≤ 0.42), concentric remodeling (normal LVMI and RWT > 0.42), eccentric LVH (increased LVMI and RWT ≤ 0.42), and concentric LVH (increased LVMI and RWT > 0.42).

LV diastolic function was assessed in the apical four-chamber view using transmitral pulsed Doppler flow with a 1–3 mm sample volume placed between the tips of the mitral valve leaflets (obtaining E, A, and E-wave deceleration time (DT)) and tissue Doppler imaging with the sample volume positioned within 1 cm of the septal and lateral borders of the mitral annulus (obtaining both septal and lateral é and averaging the values for the analyses). A mean of 3–5 cycles was used. The intra- and interobserver variability is reported elsewhere [24]. Diastolic function was graded according to the recommendations of *ASE and EACVI* (*formerly known as the European Association of Echocardiography*) [25], using age-appropriate cut-off values of septal é, lateral é, E-wave DT, E/A, and averaged E/é. If septal é was ≥8 and/or lateral é was ≥10, subjects were classified as having normal diastolic function. If septal é was <8 and lateral é was <10, subjects were classified as having diastolic dysfunction, and the values of E-wave DT, E/A, and E/é were used for grading subjects into grade 1, 2 or 3 diastolic dysfunction (Table 1). If E/é was ≥9 and ≤12, subjects were only classified as having either grade 1 or 2 diastolic dysfunction if the values of both E-wave DT and E/A fitted the same category. If E/é ≥ 9 and ≤12, but E/A and E-wave DT were incompatible with each other, subjects were classified as having undetermined diastolic dysfunction [26]. If E/é was >12, subjects were classified as having either grade 2 or 3 diastolic dysfunction. Finally, all subjects with E/é < 9 were classified as either normal (E-wave DT < 240 ms and E/A ≥ 0.8) or grade 1 diastolic dysfunction (all other subjects), even if they did not strictly fulfill the primary é criteria for normal diastolic function. Subjects with LVEF ≤50% were excluded from the present study (n = 29). Moreover, 41 subjects were excluded due to missing echocardiographic variables. None of the remaining subjects had severe left-sided valvular stenosis or regurgitation.

2.5. Biomarkers

In the echocardiography subcohort, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was analyzed using an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland) at the Department of Clinical Chemistry, Akershus University Hospital, Lorenskog, Norway.

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