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Worsening diastolic function is associated with elevated fasting plasma glucose and increased left ventricular mass in a supra-additive fashion in an elderly, healthy, Swedish population ☆

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ABSTRACT

Aims: To examine whether increasing fasting plasma glucose (FPG) levels were associated with worsening left ventricular (LV) diastolic function, independently of LV mass index (LVMI) in elderly, otherwise healthy subjects.
Methods and results: We tested cross-sectional associations between echocardiographically determined averaged E/é ratio/diastolic function, LVMI, cardiovascular risk factors, and FPG categorized as normal (NFG), impaired (IFG), and new-onset diabetes mellitus (DM), in 483 men and 208 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%. Median E/é was significantly higher among subjects with diabetes than those without (8 vs. 7; $p = 0.03$), as was the prevalence of grade 2 or 3 diastolic dysfunction (25% vs. 16%; $p = 0.02$). E/é and diastolic function were significantly associated with LVMI ($p \leq 0.002$), but not FPG category, on multivariable analysis. However, interaction analyses revealed that increasing LVMI was primarily associated with worsening diastolic function (higher E/é) in subjects with FPG > 6 mmol/L ($\beta = 0.005$ for IFG and DM vs. 0.001 for NFG; $p = 0.02$), whereas increasing systolic blood pressure was primarily associated with worsening diastolic function (higher E/é) in subjects with FPG ≤ 6.9 mmol/L ($\beta = 0.005$ for NFG and 0.003 for IFG vs. −0.001 for DM; $p = 0.001$).
Conclusion: Diastolic dysfunction was significantly more prevalent among patients with DM than those without. The importance of LVMI increased, but the importance of systolic blood pressure decreased with higher FPG category.
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1. Introduction

Diastolic dysfunction (DD) is the inability of the cardiac myofibrils to rapidly or completely return to their resting length and is characterized by delayed active relaxation and increased left ventricular (LV) stiffness [1]. The condition is most often caused by ischemic heart disease and/or hypertension with subsequent concentric remodeling or hypertrophy of LV [2]. LV hypertrophy and DD are common findings among patients with diabetes mellitus (DM), with the presence and severity of LV DD being directly correlated to the duration of DM [3–5]. The associations are independent of concomitant hypertension and ischemic heart disease. Therefore, it seems that patients with DM are predisposed to

Abbreviations: DD, diastolic dysfunction; LV, left ventricular/left ventricle; DM, diabetes mellitus; HF, heart failure; $HbA1_c$, hemoglobin $A1_c$ (glycosylated hemoglobin); LVMI, left ventricular mass index; MPP, Malmö Preventive Project; MPP-RES, Malmö Preventive Project Re-examination Study; FPG, fasting plasma glucose; ICD, International Classification of Diseases; NFG, normal fasting glucose; IFG, impaired fasting glucose; WHO, World Health Organization; LVEF, left ventricular ejection fraction; ASE, American Society of Echocardiography; LAA, left atrial area; DT, E-wave deceleration time; EAE, European Association of Echocardiography; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; IQR, interquartile range; ANOVA, analysis of variance; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; CFR, coronary flow reserve.

☆ 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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a primary myocardial disease, diabetic cardiomyopathy, defined as ventricular dysfunction occurring in a diabetic patient, independently of a recognized cause [3].

DD in patients with DM is associated with both subsequent development of heart failure (HF) and increased mortality [4,5]. The mechanisms through which DD develops and progresses to overt HF in patients with DM are not clearly understood, but may be partially associated with increased LV mass [3]. Keeping in mind the negative results of recent clinical trials regarding the management of HF with preserved ejection fraction [6,7], a better understanding of the pathogenesis of DD is essential for development of novel therapeutic strategies that can prevent or delay this process.

LV diastolic function can be non-invasively evaluated by Doppler echocardiography, and a wide range of specific echocardiographic indicators of diastolic function exist [8]. The combination of assessing mitral annulus motion with tissue Doppler during early diastole (é) and early passive mitral inflow velocity (E) provides an acceptable estimate of LV filling pressure, with E/é < 8 being associated with normal filling pressure, whereas values >12–15 are associated with elevated filling pressures. Moreover, studies have demonstrated a reduction of é in type 2 DM and an independent correlation between increased E/é and glycosylated hemoglobin ($HbA1_c$), mortality, and the risk of development of overt HF [4,5,9–12]. Therefore, the E/é ratio may be used to detect and follow the progression of LV DD in patients with DM.

The purpose of this study was: 1) To examine whether worsening glucometabolic status was associated with worsening LV diastolic function, independently of increased LV mass index (LVMI); and 2) To identify other risk factors independently associated with worsening LV diastolic function.

2. Methods

The study was a cross-sectional study.

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 in Malmö, Sweden, born 1921–1949 [13]. A re-examination study (MPP-RES, n = 18,238) was conducted between 2002 and 2006, during which the participants answered a 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, and 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 was 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. 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 (n = 864), anti-diabetic (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, HF, stroke, or atrial fibrillation and/or flutter.

2.3. Glucometabolic status

The definitions of normal fasting glucose (NFG), IFG, and DM were based on the *World Health Organization* (WHO) criteria [14]: NFG was defined as a single FPG ≤ 6.0 mmol/L; IFG was defined as a single FPG between 6.1 and 6.9 mmol/L, or one measurement 7.0–11.0 mmol/L and a separate measurement ≤ 6.9 mmol/L; and new-onset 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. LV mass calculations were based on 2-dimensional images in the parasternal long-axis view at the level of the mitral valve tips during end-diastole, using the formula recommended by the *American Society of Echocardiography* (*ASE*), and indexed for body surface area, obtaining LVMI [15]. Left atrial area (LAA) during end-systole was obtained by planimetri in the apical four-chamber view. 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 variabilities are reported elsewhere [16]. Diastolic function was graded according to the recommendations of the *European Association of Echocardiography* (*EAE*) and *ASE*, using age-appropriate cut-off values of septal é, lateral é, E-wave DT, E/A, and averaged E/é [8]. 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 DD, and the values of E-wave DT, E/A, and E/é were used for grading subjects into grade 1, 2 or 3 DD (Table 1). If E/é was ≥9 and ≤12, subjects were only classified as having either grade 1 or 2 DD if the values of both E-wave DT and E/A fitted the same category. Equivocal cases, i.e. subjects who were in a transitional state between grade 1 and 2 DD with E/é ≥ 9 and ≤12, but E/A and E-wave DT pointing in the opposite directions, were classified as undetermined DD. If E/é was >12, subjects were classified as having either grade 2 or 3 DD. 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 DD (all other subjects), even if they did not strictly fulfill the primary é criteria for normal diastolic function. Grade 2 DD and grade 3 DD were grouped together, since only one individual fulfilled the criteria for grade 3 DD. Subjects with LVEF ≤ 50% were excluded in the present study (n = 29). Moreover, 43 subjects were excluded due to missing echocardiographic variables.

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.

2.6. Statistical analysis

Continuous variables were summarized by means and standard deviations (approximately normally distributed variables) and medians

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