Diabetologia (2010) 53:1331–1340
DOI 10.1007/s00125-010-1718-8

ARTICLE

Association of glucose metabolism with diastolic function along the diabetic continuum

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Received: 2 December 2009 / Accepted: 11 February 2010 / Published online: 13 April 2010

Abstract
Aims/hypothesis Hyperglycaemia and insulin resistance have been linked to diastolic dysfunction experimentally. We investigated the association between glucose metabolism and diastolic function along the whole spectrum of glucose metabolism states.

Methods In the observational Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart Failure (DIAST-CHF) study, patients with risk factors for heart failure were included. We analysed data including comprehensive echocardiography from a subgroup of patients classified by OGTT and history as normal (n=343), prediabetic (n=229) and non-insulin treated (n=335) or insulin-treated (n=178) type 2 diabetic.

Results While ejection fraction did not differ, markers of diastolic function significantly worsened across groups. Prediabetes represented an intermediate between normal glucose metabolism and diabetes with regard to echocardiography changes. Prevalence and severity of diastolic dysfunction increased significantly (p<0.001) along the diabetic continuum. Glucose metabolism status was significantly associated with prevalence of diastolic dysfunction on multivariate logistic regression analysis. In the whole cohort, HbA_{1c} correlated with early diastolic mitral inflow velocity (E):early diastolic tissue Doppler velocity at mitral annulus (e′) ratio (E:e′) (r=0.20, p<0.001). HbA_{1c} was significantly associated with E:e′ on multivariate analysis. Similarly, glucose metabolism status was significantly associated with E:e′ on multivariate analysis. The distance walked in 6 min decreased along the diabetic spectrum and was significantly correlated with E:e′ and grade of diastolic dysfunction.

Conclusions/interpretation Glucose metabolism is associated with diastolic dysfunction across the whole spectrum. Our data extend previous observations into the prediabetic and normal range, and may be relevant to preventive approaches, as no effective treatment has been identified for diastolic heart failure once established.

Keywords Cross-sectional studies · Diabetes mellitus · Diastolic heart failure · Echocardiography · Exercise tolerance · Insulin resistance · Prediabetic state

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Abbreviations

A	Late diastolic mitral inflow velocity
a′	Late diastolic tissue Doppler velocity (at mitral annulus)
CHF	Chronic heart failure
DIAST-CHF	Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart Failure
E	Early diastolic mitral inflow velocity
e′	Early diastolic tissue Doppler velocity (at mitral annulus)
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
HFnEF	Heart failure with normal ejection fraction
1 h-PG	1 h plasma glucose
2 h-PG	2 h plasma glucose
2 h-PI	2 h plasma insulin
$ISI_{(0,120)}$	Insulin sensitivity index according to Gutt
LVMI	Left ventricular mass index
PVS	Systolic pulmonary vein flow velocity
PVD	Diastolic pulmonary vein flow velocity
QUICKI	Quantitative insulin sensitivity check index
S:D	Ratio of PVS to PVD

Introduction

Chronic heart failure (CHF) is an ongoing epidemic of growing dimensions in western societies [1]. It has been recognised [2] and recently confirmed [3] that a large percentage of patients presenting with the clinical syndrome of heart failure have a normal left ventricular ejection fraction. These cases are therefore termed 'heart failure with normal ejection fraction' (HFnEF) and left ventricular diastolic dysfunction is believed to be common in these patients [4]. Once hospitalised for heart failure, their prognosis is similarly grim to that of patients with 'classic' systolic heart failure [2, 3]. Randomised trials looking for specific therapeutic interventions have been few and notoriously unsuccessful [5, 6]. Prevention therefore is of the essence if HFnEF is to be dealt with at a population level.

Diabetes mellitus has also reached epidemic proportions worldwide, with a further 50% increase in worldwide prevalence projected to occur by 2025 [7]. While well known as a strong risk factor for atherosclerotic disease, the relationship between diabetes and incident heart failure has as yet attracted less attention. Preclinical studies have linked diabetes to abnormalities in left ventricular relaxation and compliance [8]. Clinically, a large proportion of diabetic patients has been shown to have diastolic dysfunction [9] and diabetes is prevalent in patients with HFnEF [10]. Insulin resistance, a state that is generally present before the onset of type 2 diabetes, also seems to play a major role [11].

Given the proposed association of insulin resistance with diastolic dysfunction and the importance of preventive approaches for HFnEF, we sought to better define the link between glucose metabolism and diastolic dysfunction across a wide spectrum of metabolic statuses ranging from normal glucose metabolism through to prediabetes and type 2 diabetes mellitus treated either less intensively, i.e. without insulin (oral glucose-lowering therapy only), or more intensively with a regimen including insulin. Insulin treatment was used as a surrogate for more advanced disease requiring more intensive treatment.

Methods

Participants The ongoing non-interventional DIAST-CHF (Diagnostic Trial on prevalence and clinical course of diastolic dysfunction and diastolic heart failure) study, which is part of the nationwide German Competence Network Heart Failure project, included patients aged 50 to 85 years with risk factors for diastolic heart failure (defined as history of hypertension, diabetes mellitus, sleep apnoea syndrome or atherosclerotic disease) or manifest CHF, defined as a history of CHF or presence of at least one major and two minor criteria according to the Framingham diagnostic criteria at presentation [12]. Candidates were referred by primary care physicians. As a population-based study, the only exclusion criterion was inability to participate or consent due, for example, to language problems, concomitant diseases or geographic reasons. Participants underwent a comprehensive non-invasive diagnostic workup at baseline, including history and physical examination, laboratory analyses, echocardiography, ECG, 6 min walk test and completion of several psychosocial and quality of life questionnaires, with additional tests performed in subsets of patients.

At the two study sites with the vast majority of participants (Goettingen and Berlin, 1,728 participants included out of 1,935 in the overall study), all patients without a history of diabetes mellitus were offered an OGTT. For the analyses presented here, all participants who underwent OGTT at baseline were included, as well as those who had been diagnosed with type 2 diabetes mellitus before inclusion and/or were being treated with glucose-lowering medication. Patients who were diagnosed with diabetes before the age of 40 and who became insulin-dependent within less than 1 year were considered to have a high probability of suffering from type 1 diabetes and were excluded from analyses.

The study complied with the Declaration of Helsinki, the protocol was approved by the responsible Ethics Committee and all patients gave written informed consent.

Oral glucose tolerance test A simplified protocol was used for the OGTT. Fasting plasma glucose (FPG) was determined immediately before ingestion of 75 g of solubilised glucose, followed 1 and 2 h later by determination of 1 h plasma glucose (1 h-PG) and 2 h plasma glucose (2 h-PG). Insulin levels were determined as fasting plasma insulin (FPI) and 2 h after glucose load as 2 h plasma insulin (2 h-PI). Patients were considered to have: (1) normal glucose metabolism at fasting glucose <5.6 mmol/l and 2 h glucose <7.8 mmol/l; (2) prediabetes when fasting glucose was 5.6 to 7.0 mmol/l or 2 h glucose 7.8 to 11.1 mmol/l; and (3) diabetes mellitus at fasting glucose >7.0 mmol/l or 2 h glucose >11.1 mmol/l, as currently recommended by the American Diabetes Association [13]. No OGTT was performed on insulin-treated type 2 diabetic participants and very few participants with stable type 2 diabetes treated by oral glucose-lowering medication underwent testing.

Insulin was measured with a commercially available immunoassay on an automated analyser (ADVIA Centaur; formerly Bayer Diagnostics, now part of Siemens Health Care Diagnostics, Eschborn, Germany). HbA_{1c} was measured in EDTA blood on an automated analyser (Integra 800; Roche Diagnostics, Mannheim, Germany) with a reference range of 2.9% to 4.2% according to recommendations of the International Federation of Clinical Chemistry.

Echocardiography Echocardiography was performed on a Sonos 5500 (Hewlett-Packard, Andover, MA, USA) according to the guidelines of the American Society of Echocardiography, including comprehensive evaluation of diastolic function with Doppler and tissue Doppler techniques. All examinations were performed by physicians experienced in the technique. As DIAST-CHF is part of the nationwide German Competence Network for Heart Failure project, randomly chosen echo examinations were reviewed by the echo core lab at the University of Essen for quality assurance.

Dimensions were recorded by standard techniques. Interventricular septum, left ventricular posterior wall thickness, left ventricular end-diastolic diameter, and end-systolic and left atrial diameter were measured by M-mode or anatomically, as appropriate. Left ventricular end-diastolic and end-systolic volumes, and ejection fraction were determined by the modified uniplanar Simpson's rule in the majority of patients. Transmitral peaks of early diastolic mitral inflow velocity (E), and late diastolic mitral inflow velocity (A) and E wave deceleration time were recorded at the tips of the mitral valve leaflets. Isovolumetric relaxation time was obtained in the apical five chamber view. Doppler signals of systolic pulmonary vein flow velocity (PVS), diastolic pulmonary vein flow velocity (PVD) and atrial reverse pulmonary vein flow velocity were recorded in the right upper pulmonary vein. Peak tissue velocities were derived by tissue Doppler analysis at the lateral margin of the mitral annulus for early diastolic tissue Doppler velocity (e′) and late diastolic tissue Doppler velocity (a′) inflow.

Calculations and statistical analyses As an estimate of global glucose tolerance, the AUC for glucose over the 2 h interval of the OGTT was calculated using a trapezoidal approach for integration ($AUC_{Glu0–120}$). To correct for FPG, we normalised AUC by indexing to the integral of fasting glucose over 2 h ($AUC_{Glu0–120}/[FPG \times 2]$), reflecting the relative increase in plasma glucose over the 2 h interval. As surrogates for insulin sensitivity, HOMA and quantitative insulin sensitivity check index (QUICKI) were calculated, as well as the insulin sensitivity index according to Gutt ($ISI_{0,120}$), all as described and recommended previously [14].

Left ventricular mass index (LVMI) was calculated by the Devereux formula indexed to body surface area [15]. For evaluation of diastolic function, we calculated the ratios of E to A (E:A), of PVS to PVD (S:D), of E to e′ (E:e′) and of e′ to a′ (e′:a′). Diastolic dysfunction was classified as follows: (1) normal diastolic function with $1 \leq$E:A, E:e′ <10, S:D ≥1, E:A with Valsalva manoeuvre ≥1; (2) mild diastolic dysfunction with E:A<1; (3) moderate diastolic dysfunction with $1 \leq$E:A<2, and one of E:e′ ≥10, S:D <1 and E:A Valsalva <1; and (4) severe diastolic dysfunction with E:A ≥2, and one of E:e′ ≥10 and S:D <1.

Descriptive statistics were performed stratified by glucose metabolism status. Several variables were not normally distributed. Therefore, data are expressed as median (interquartile range) for continuous variables or absolute number (per cent) for categorical. Log-transformed values were used for some analyses as appropriate. Non-parametric tests for group differences between categories of glucose tolerance were performed. The Jonckheere–Terpstra test is most sensitive for detection of effects across ordered categories. For comparison of proportions, Armitage's test for trend was applied. To investigate relations between variables, bivariate correlations were calculated. We used multivariate analysis of covariances and logistic regression to unravel multivariate relationships.

Statistical analyses were performed with SPSS Statistics 15.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics Of 1,935 patients included in DIAST-CHF, 1,085 patients were analysed, of whom 637 had an OGTT. A minority of these (13 patients) had a previous diagnosis of type 2 diabetes mellitus and were being treated with glucose-lowering medication. Overall, 465 patients had a history of diabetes mellitus at inclusion,

of whom four with probable type 1 diabetes were excluded from analyses. Of the remaining 461 patients with known type 2 diabetes mellitus, 178 were treated with insulin and 283 with diet and/or oral glucose-lowering drugs.

Among those undergoing glucose tolerance testing, 343 participants (55.0%) had normal glucose metabolism, 229 (36.7%) had prediabetes and 52 (8.3%) had newly diagnosed diabetes mellitus (Fig. 1).

Clinical characteristics for patients with normal, prediabetic and diabetic glucose metabolism are shown in Table 1. Glucose and lipid metabolism variables are shown in Table 2. Overall, prediabetes tended to be an intermediate stage between normal and diabetic groups with regard to many indicators of metabolic disturbance and end-organ disease, while patients with insulin-treated type 2 diabetes had the highest rates of end-organ disease or comorbidities. Groups did not differ with regard to age, systolic blood pressure and prevalence of hypertension. Patients with diabetes were treated more intensively than those with prediabetes or normal glucose metabolism. Treatments were with typical cardiovascular drugs with a significant trend towards ACE inhibitors, loop diuretics, aldosterone antagonists, statins, acetylic salicylic acid and vitamin K antagonists.

Consistent with the process of group allocation, prediabetic participants had significantly higher FPI and FPG than non-diabetic participants, as well as higher 1 h-PG and 2 h-PG, reflected also in $AUC_{Glu0–120}$ and normalised $AUC_{Glu0–120}$. Insulin resistance as approximated by HOMA was higher, and insulin sensitivity as approximated by QUICKI and Gutt index lower in prediabetic participants. Prediabetes also displayed an intermediate state in between normal and type 2 diabetic patients on oral glucose-lowering medication. LDL-cholesterol was paradoxically lower in this group and in insulin-treated type 2 diabetic patients, while HDL-cholesterol decreased with severity of glucose metabolism disturbance. This phenomenon is probably due to the fact that LDL-cholesterol is effectively lowered by statin therapy, which was more prevalent in diabetic patients, while low HDL-cholesterol is less amenable to pharmacological treatment.

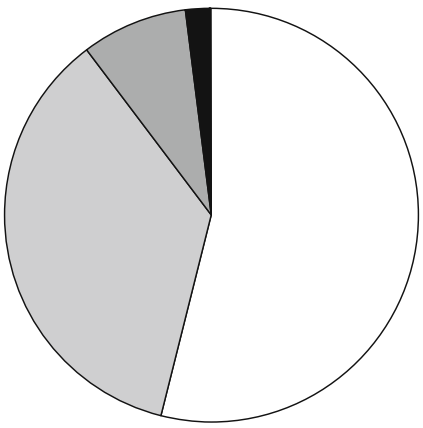

Fig. 1 Glucose metabolism among participants of OGTT. White, normal glucose; light grey, prediabetes; dark grey, newly diagnosed type 2 diabetes; black, known type 2 diabetes treated with oral glucose-lowering medication

Prevalence of diastolic dysfunction Diastolic function could not be analysed or classified in 61 participants (5.6%) due to presence of atrial fibrillation or missing echocardiographic variables critical for classification. Accordingly, 1,024 participants were included in the analysis of diastolic function. Echocardiographic variables are listed in Table 3.

Prevalence of any degree of diastolic dysfunction increased with impairment in glucose metabolism, i.e. the highest prevalence was found among insulin-treated type 2 diabetic patients (87.3%) or those on oral glucose-lowering therapy (88.4%) as compared with those with prediabetes (86.7%) or normal glucose metabolism (76.0%, $p<0.001$ test for trend). Participants with prediabetes represented an intermediate between normal ($p=0.009$ for difference) and diabetic patients with regard to diastolic dysfunction. This is also evidenced by trends in structural variables that are indicative of diastolic dysfunction, but not used as criteria for classification, e.g. left atrial diameter or LVMI. While prevalence of diastolic dysfunction of any grade was very similar between prediabetes and diabetes, the distribution across grades 1 to 3 of diastolic dysfunction was shifted to the right for diabetes as compared with prediabetes (Fig. 2), reflected by a statistically significant χ^2 test of the correspondent 3 × 4 table ($p<0.001$). Only a small number of patients were identified as having severe diastolic dysfunction, none of whom had normal glucose metabolism; therefore patients with moderate or severe diastolic dysfunction were placed in one group for the above analysis.

Status of glucose metabolism remained significantly associated with prevalence of diastolic dysfunction in logistic regression analysis adjusted for the significantly associated variables heart rate, systolic blood pressure, and presence or history of heart failure. Furthermore, an odds ratio of 1.77 (95% CI 1.10–2.86) for having diastolic dysfunction was estimated for the prediabetes group compared with the normal glucose metabolism group.

Impairment in glucose metabolism and severity of diastolic dysfunction As a functional variable indicative of left ventricular end-diastolic pressure, E:e′ was similar in prediabetes compared with normal glucose metabolism, but was significantly higher ($p=0.002$) in diabetes than in the other groups. In the whole cohort, E:e′ correlated significantly with HbA_{1c} ($r=0.20$, $p<0.001$), as well as

Table 1 Clinical characteristics of patients with normal, prediabetic or diabetic glucose metabolism

Variable	Normal	Prediabetes	DM2 oral	DM2 insulin	*p* value[a]
n	343	229	335	178	
Measured variables					
Age (years)	66.0 (61.2–71.0)	67.0 (62.0–72.0)	66.0 (61.0–72.0)	65.5 (61.0–71.0)	0.573
Female sex, *n* (%)	181 (52.8)	105 (45.9)	130 (38.8)	86 (48.3)	0.025
BMI (kg/m^2)	27.0 (24.8–29.4)	29.0 (26.7–31.7)	29.4 (27.1–33.2)	31.2 (27.5–34.7)	0.000[b]
WHR	0.92 (0.86–0.98)	0.95 (0.90–1.01)	0.96 (0.90–1.01)	0.95 (0.95–1.02)	3.80E−09[b]
Systolic BP (mmHg)	144 (132–160)	153 (139–168)	150 (136–165)	145 (130–161)	0.610
Diastolic BP (mmHg)	85 (76–92)	85 (79–94)	83 (78–90)	79 (70–85)	4.05E−05[b]
Heart rate (beats per min)	63 (56–69)	64 (58–73)	67 (60–77)	67 (61–76)	0.000[b]
6 min walk distance (m)	550 (496–600)	542 (485–600)	506 (425–570)	470 (394–537)	1.60E−20[b]
Cardiovascular risk factors					
Hypertension, *n* (%)	300 (87.5)	210 (91.7)	287 (85.7)	156 (87.6)	0.569
Hyperlipidaemia, *n* (%)	136 (39.7)	92 (40.2)	166 (49.6)	104 (58.4)	1.13E−05[b]
Smoker, *n* (%)	44 (12.8)	12 (5.2)	38 (11.3)	19 (10.4)	0.051
CHD, *n* (%)	57 (16.6)	41 (17.9)	75 (22.4)	63 (35.4)	3.68E−06[b]
Peripheral artery disease, *n* (%)	11 (3.2)	9 (3.9)	19 (5.7)	31 (17.4)	6.28E−08[b]
Cerebrovascular disease, *n* (%)	26 (7.6)	14 (6.1)	35 (10.4)	13 (7.3)	0.488
CHF, *n* (%)	34 (9.9)	36 (15.7)	64 (19.1)	54 (17.3)	9.51E−09[b]
Sleep apnoea, *n* (%)	20 (5.8)	14 (6.1)	24 (7.2)	23 (12.9)	0.011
Atrial fibrillation, *n* (%)	24 (7.0)	13 (5.7)	23 (6.9)	16 (9.0)	0.468
Medications					
ACE-inhibitor, *n* (%)	146 (42.9)	101 (44.3)	165 (50.0)	108 (60.7)	1.43E−04[b]
AT1 receptor antagonist, *n* (%)	50 (14.7)	33 (14.5)	58 (17.6)	43 (24.2)	0.009
Beta-blocker, *n* (%)	156 (45.9)	116 (50.9)	150 (45.5)	106 (59.6)	0.042
Thiazide diuretic, *n* (%)	129 (37.9)	106 (46.5)	138 (41.8)	73 (41.0)	0.510
Loop diuretic, *n* (%)	19 (5.6)	18 (7.9)	48 (14.5)	55 (30.9)	4.77E−15[b]
Other diuretic, *n* (%)	10 (2.9)	13 (5.7)	17 (5.2)	8 (4.5)	0.304
Aldosterone antagonist, *n* (%)	2 (0.6)	1 (0.4)	6 (1.8)	7 (3.9)	0.003[b]
Calcium antagonist, *n* (%)	63 (18.5)	41 (18.0)	85 (25.8)	47 (26.4)	0.007
Statin, *n* (%)	74 (21.8)	55 (24.1)	119 (36.1)	105 (59.0)	2.92E−17[b]
Acetylic salicylic acid, *n* (%)	112 (32.9)	66 (28.9)	115 (34.8)	93 (52.2)	1.49E−04[b]
Vitamin K antagonist, *n* (%)	13 (3.8)	12 (5.3)	27 (8.2)	17 (9.6)	0.003[b]
Oral glucose-lowering, *n* (%)	0 (0)	0 (0)	214 (64.8)	52 (29.2)	1.40E−51[b]

Values are median (interquartile range) or *n* (%)

[a] Jonckheere–Terpstra test or Armitage's test of trend for proportions, as appropriate; [b] significant after Bonferroni–Holm adjustment (m=72)

DM2 insulin, insulin-treated type 2 diabetes; DM2 oral, type 2 diabetes on oral glucose-lowering medication

with several other markers of glucose metabolism, namely 2 h-PI, normalised $AUC_{Glu0–120}$ and $ISI_{0,120}$. Importantly, the association between E:e′ and HbA_{1c} remained significant when including only patients with HbA_{1c} in the normal range, i.e. ≤4.2% (r=0.16, p<0.05).

In multivariate linear analysis including sex, CHD, CHF, history of myocardial infarction, age, log(BMI), heart rate, systolic and diastolic blood pressure, cardiovascular medications and HbA_{1c} as predictors, HbA_{1c} remained significantly (p<0.001) associated with log(E:e′). When modelling status of glucose metabolism in place of HbA_{1c} in a general linear model with log (E:e′) as dependent variable, status of glucose metabolism was a significant predictor, together with sex, age, log (BMI), heart rate, systolic and diastolic blood pressure, and both beta blocker and aldosterone antagonist intake. These associations remained significant with Bonferroni–Holm adjustment for multiple testing.

LVMI and left atrial diameter as structural markers of diastolic function correlated significantly with HbA_{1c}

Table 2 Metabolic characteristics of patients with normal, prediabetic or diabetic glucose metabolism

Variable	Normal	Prediabetes	DM2 oral	DM2 insulin	*p* value[a]
n	343	229	335	178	
HbA_{1c} (%)	3.7 (3.1–4.1)	4.2 (3.8–4.6)	4.9 (4.4–5.5)	5.3 (4.9–6.1)	0.000[b]
FPI (pmol/l)	44.4 (31.9–72.2)	75.7 (43.8–111.8)	93.1 (43.8–136.1)	–	2.60E−14 [b]
2 h-PI (pmol/l)	374.3 (211.8–613.2)	598.7 (343.0–2,382.7)	898.0 (446.6–1,494.6)	–	4.21E−15 [b]
FPG (mmol/l)	5.1 (4.8–5.3)	5.7 (5.6–6.0)	7.0 (6.1–7.5)	–	0.000[b]
1h-PGe (mmol/l)	7.7 (6.3–9.0)	10.2 (8.9–11.6)	14.3 (12.8–15.5)	–	0.000[b]
2h-PG (mmol/l)	5.6 (4.8–6.4)	7.8 (6.3–8.8)	12.2 (11.3–13.9)	–	0.000[b]
Glucose AUC (mmol $l^{-1}\times h$)	12.9 (11.3–14.7)	16.9 (15.0–18.6)	23.8 (21.5–25.7)	–	0.000[b]
Glucose AUC normalised	1.30 (1.14–1.45)	1.50 (1.29–1.65)	1.73 (1.58–1.92)	–	0.000[b]
HOMA-IR index	1.40 (0.99–2.41)	2.62 (1.59–4.22)	3.77 (1.88–6.00)	–	0.000[b]
QUICKI	0.36 (0.33–0.38)	0.33 (0.31–0.36)	0.31 (0.30–0.35)	–	1.52E−23[b]
Gutt $ISI_{1,20}$	4.4 (3.6–5.5)	3.1 (2.6–3.7)	1.9 (1.7–2.4)	–	2.94E−55[b]
Diabetes duration (years)	–	–	4 (1–7.3)	13 (6.8–20.0)	0.000[b]
Insulin-dependent for (years)	–	–	–	4 (2.0–8.5)	–
Daily total dose insulin (IE)	–	–	–	48 (34–76)	–
Total cholesterol (mmol/l)	5.4 (4.7–6.0)	5.3 (4.8–6.1)	4.9 (4.3–5.6)	4.7 (3.9–5.1)	6.09E−16[b]
LDL-cholesterol (mmol/l)	3.3 (2.8–3.9)	3.4 (3.0–4.0)	3.0 (2.6–3.7)	2.7 (2.1–3.1)	2.97E−22[b]
HDL-cholesterol (mmol/l)	1.4 (1.2–1.7)	1.4 (1.1–1.6)	1.2 (1.0–1.5)	1.1 (1.0–1.5)	2.88E−16[b]
Uric acid (mmol/l)	5.8 (4.9–6.7)	6.3 (5.4–7.2)	6.3 (5.5–7.2)	6.1 (5.2–7.3)	3.19E−05[b]
eGFR (ml min^{-1} 1.73 m^{-2})	71.2 (63.3–78.9)	74.6 (64.2–86.5)	71.6 (63.5–88.0)	71.4 (60.1–78.5)	0.484

Values are median (interquartile range) or *n* (%)

[a] Jonckheere–Terpstra test; [b] significant after Bonferroni–Holm adjustment ($m=72$)

DM2 insulin, insulin-treated type 2 diabetes; DM2 oral, type 2 diabetes on oral glucose-lowering medication; eGFR, estimated GFR; IR, insulin resistance

and also with $AUC_{Glu0–120}$, normalised $AUC_{Glu0–120}$, 1 h- and 2 h-PG, HOMA, QUICKI and $ISI_{0,120}$. In contrast to E:e′, these structural variables also correlated with FPG and FPI. However, in multivariate analysis associations of LVMI and left atrial diameter with HbA_{1c} lost significance. Interestingly, there was also a highly significant negative correlation of HDL-cholesterol with left atrial diameter and LVMI. No significant correlation of structural variables with HbA_{1c} was observed in patients with $HbA_{1c} \leq 4.2\%$. Nevertheless, when including only patients with normal glucose metabolism or prediabetes, the above-mentioned correlations remained statistically significant except those between left atrial diameter and HbA_{1c}, and LVMI and 2 h-PG or HbA_{1c}, respectively. While the two type 2 diabetes treatment groups (oral glucose-lowering medication, insulin) had a similar prevalence of diastolic dysfunction and similar distribution across grades of diastolic dysfunction, E:e′ was significantly higher in the insulin-treated than in the other group (10.7 vs 9.5, $p<0.05$).

E:e′, left atrial diameter or LVMI did not correlate with duration of diabetes or daily insulin dose.

Diabetes, diastolic dysfunction and physical impairment The distance walked in 6 min as a simple indicator of exercise capacity decreased along the diabetic continuum (Table 1). Both grade of diastolic dysfunction ($r=-0.29$, $p<0.001$) and E:e′ ($r=-0.17$, $p<0.001$) correlated significantly with the distance walked in 6 min. Ejection fraction did not differ significantly between groups and there was only a very weak correlation between ejection fraction and distance walked in 6 min ($r=0.09$, $p<0.01$).

Discussion

It has been reported previously that a large proportion of diabetic patients have diastolic dysfunction [9], which is believed to be a key component of diabetic cardiomyopathy [16].

Our data confirm and extend these observations, as prevalence of diastolic dysfunction was increased not only in type 2 diabetic, but also in prediabetes participants. Moreover, prevalence and severity of diastolic dysfunction

Table 3 Echocardiographic characteristics of patients with normal, prediabetic or diabetic glucose metabolism

Variable	Normal	Prediabetes	DM2 oral	DM2 insulin	*p* value[a]
n	343	229	335	178	
LVEDD (mm)	49 (45–52)	50 (46–53)	51 (46–53)	51 (46–54)	0.005
LVESD (mm)	30 (26–34)	30 (27–34)	31 (27–36)	32 (28–37)	3.16E−05[b]
LVEDV (ml)	88.0 (71–106)	92.0 (78–113)	94.0 (76–116)	90.0 (74–110)	0.057
LVESV (ml)	35.0 (27–43)	37.0 (29–47)	37.0 (28–50)	36.0 (28–49)	0.030
LV-EF (%)	60 (55–65)	60 (54–65)	60 (55–65)	60 (54–64)	0.179
IVS (mm)	12 (11–13)	12 (11–13)	13 (11–14)	13 (11–14)	9.14E−05[b]
LVPW (mm)	11 (10–12)	11 (10–12)	12 (11–13)	12 (11–13)	2.73E−08[b]
LVMI (g/m^2)	113.9 (97.8–130.9)	116.5 (101.3–133.2)	121.2 (102.0–141.6)	120.6 (100.2–140.0)	0.002
LAD (mm)	40 (37–45)	42 (38–45)	43 (38–46)	43 (40–47)	3.88E−08[b]
E (cm/s)	71 (59–83)	73 (60–84)	70 (58–82)	73 (62–89)	0.046
A (cm/s)	77 (65–89)	82 (69–93)	82 (70–95)	83 (69–102)	1.97E−05[b]
E:A ratio	0.88 (0.74–1.13)	0.86 (0.72–1.12)	0.83 (0.69–1.05)	0.83 (0.70–1.14)	0.008
Deceleration time (ms)	240 (202–298)	240 (195–300)	256 (201–305)	244 (195–300)	0.812
IVRT (ms)	100 (90–119)	100 (90–117)	105 (90–120)	97 (85–115)	0.559
e′ (cm/s)	7.9 (6.5–9.5)	7.9 (6.3–9.3)	7.6 (6.0–9.0)	7.0 (5.5–8.9)	0.008
a′ (cm/s)	11.2 (9.3–13.0)	11.0 (9.4–12.8)	11.0 (9.6–13.0)	11.0 (9.1–13.1)	0.760
e′:a′	0.70 (0.55–0.90)	0.70 (0.55–0.90)	0.64 (0.55–0.85)	0.63 (0.47–0.83)	0.009
E:e′	9.0 (7.3–11.2)	8.9 (7.3–11.5)	9.5 (7.4–11.8)	10.7 (8.3–13.7)	1.26E−04[b]
PVS (cm/s)	63 (54–73)	63 (55–71)	61 (54–69)	60 (51–70)	0.003
PVD (cm/s)	44 (37–52)	45 (37–53)	43 (37–51)	45 (37–54)	0.798
PVA (cm/s)	30 (27–33)	30 (27–33)	30 (26–33)	29 (26–32)	0.066
S:D ratio	1.41 (1.21–1.66)	1.41 (1.20–1.67)	1.40 (1.18–1.67)	1.38 (1.12–1.61)	0.118

Values are median (interquartile range)

[a] Jonckheere–Terpstra test; [b] significant after Bonferroni–Holm adjustment (m=72)

IVRT, isovolumetric relaxation time; IVS, interventricular septum; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LV-EF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVPW, left ventricular posterior wall; PVA, atrial reverse pulmonary vein flow velocity

were associated with degree of impairment of glucose metabolism along the whole spectrum of metabolic states. It is noteworthy that we found a very high absolute prevalence of diastolic dysfunction even in participants with normal glucose metabolism compared with older series [9, 17]. This, however, is not so surprising, considering the design of DIAST-CHF, which includes only patients with a risk factor for diastolic heart failure or (a minority) with manifest CHF. The high prevalence may also be due to the higher sensitivity of current echocardiographic techniques, as well as to our classification, which applies rather sensitive criteria for low-grade diastolic dysfunction. Even so, we were able to show an association between glucose metabolism and diastolic dysfunction.

With comprehensive echocardiographic characterisation of a large group of participants with prediabetes, we were able to show that prediabetes represents a morphological intermediate between normal and diabetic states. Also, we found significant trends for several indicators of diastolic dysfunction along the type 2 diabetic continuum, pointing to a graded effect of impaired glucose metabolism on diastolic function, although such an interpretation is limited by the cross-sectional nature of our analysis. Several mechanisms for a conditional relationship between glucose metabolism and diastolic function have been proposed. Hyperinsulinaemia can lead to increased myocardial mass through its growth-stimulating function and probably differential organ-specific levels of insulin resistance [18]. Furthermore, hyperinsulinaemia leads to chronic sympathetic nervous system activation with detrimental consequences on the heart [19]. These observations suggest a theoretical basis for our observation of subtle changes in myocardial, specifically diastolic, function in prediabetes. Recently, it was shown that insulin resistance was a predictor for incident heart failure independently of diabetes [11]. Impaired insulin sensitivity and hyperinsulinaemia are often

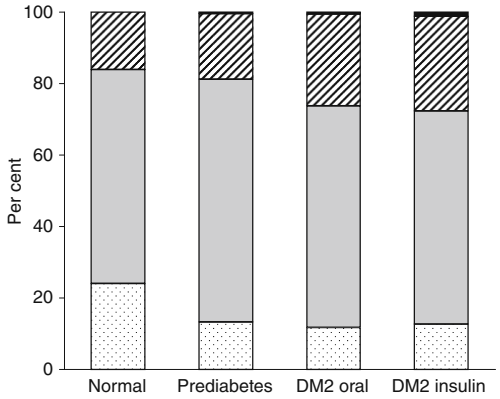

Fig. 2 Severity of diastolic dysfunction (DD) among patients with normal glucose metabolism, prediabetes, and type 2 diabetes (DM2) treated by insulin or by oral glucose-lowering medication. Dotted white bars, normal DD; light grey, mild DD; hatched, moderate DD; black, severe DD

present before full manifestation of type 2 diabetes mellitus. Also, insulin sensitivity and levels are continuous (rather than discrete) traits, making a continuous and graded effect intuitively more plausible than a threshold constellation. Similarly, hyperglycaemia has been linked to alterations in myocardial calcium handling and extracellular matrix modifications, leading to increased ventricular stiffness and impaired relaxation [8]. Indeed, across the whole cohort, HbA_{1c} was independently associated with E:e′, a variable that strongly correlates with left ventricular end diastolic pressure [20] and with the presence of diastolic dysfunction. We even found some evidence for such an association in the subgroup with normal glucose metabolism. HbA_{1c} as a continuous variable incorporates glucose levels over a longer period of time and can therefore be considered a more stable indicator of plasma glucose status, which is less vulnerable to acute perturbations around the time of testing. In fact, for these very reasons HbA_{1c} has recently been suggested for use as a primary variable on which to base the diagnosis of diabetes [21]. The correlation of E:e′ with HbA_{1c} complements data showing that in diabetic patients a 1% increase in HbA_{1c} is associated with an increase in the risk of heart failure of between 8 and 32% [22–24]. Similarly, FPG has recently been shown to be prognostic of incident heart failure in a very large randomised trial of patients at high cardiovascular risk [25]. Our data strengthen the experimentally based assumption that a considerable part of the increased risk of heart failure in diabetes is due to impaired diastolic function linked to hyperinsulinaemia and hyperglycaemia.

The observed elevation in E:e′ can be assumed to be of prognostic relevance, as an E:e′ >15 resulted in an 11% relative increase in all-cause mortality rates in a recent retrospective analysis of diabetic patients from Olmsted county [26]. Similarly, degree of diastolic dysfunction was an independent predictor of all-cause mortality in a large epidemiological study [9].

Statistically speaking, the biological signal we found is not very strong against the ‘noise’ in our heterogeneous population-based cohort; the model fitting also leaves something to be desired. However, the observed association may still be of considerable importance at a population level, considering the epidemic proportions of diabetes and the persistent lack of effective treatments for diastolic dysfunction and diastolic heart failure.

Exercise capacity, as measured by 6 min walk test, decreased along the diabetic continuum. Although this may in part reflect more activity-limiting comorbidities, we also observed a highly significant negative correlation between E:e′ and distance walked in 6 min in our sample, indicating that impaired exercise capacity may be partly due to diastolic dysfunction. It has previously been demonstrated in a small sample that decreased exercise tolerance is associated with diastolic dysfunction in patients with diabetes, even when well controlled and without CHD, hypertension or heart failure [27, 28]. Our results extend these data to a broader population and a much larger sample. In contrast to diastolic dysfunction, left ventricular ejection fraction did not differ across groups of glucose metabolism and was only very weakly associated with distance walked in 6 min.

Our data show that diastolic dysfunction is partly determined by glucose metabolism even in participants with normal glucose and those with prediabetes, thus supporting early preventive measures to improve glucose metabolism on a population scale as one possible approach to combat diastolic dysfunction and diastolic heart failure. Although we cannot directly draw such conclusions from our cross-sectional and non-interventional study, improvements in diastolic function with intensified glucose control have been demonstrated in diabetic patients [29], providing the theoretical basis for such a demand. The relevance of glucose metabolism for diastolic dysfunction in a longitudinal setting will be the subject of future analyses from DIAST-CHF.

With regard to technicalities, clear strengths of our study include its well characterised sample of patients with all stages of impairment of glucose metabolism. As all non-diabetic participants underwent OGTT, allocation to the respective group was exact. In addition, the measurement of HbA_{1c} in the majority of patients adds further detail to the metabolic characterisation of our patients. Diastolic dysfunction was analysed with tissue Doppler techniques that were considered state-of-the-art at the time of data collection and indeed more advanced than those used by most published studies on the subject.

Several aspects of our report, however, merit critical review. As this analysis was cross-sectional, no conclusions

on causality can be drawn. We did not limit our analysis to participants without overt cardiovascular disease like coronary artery disease or CHF, as is often done in studies investigating diabetic cardiomyopathy. This approach was chosen to assess the overall relationship of glucose metabolism with diastolic function, be it independent or be it mediated through end-organ disease. The fact that the associations remained significant when including coronary artery disease and CHF as covariates in the respective models indicates that glucose metabolism plays a role independently of coronary artery disease and CHF as mediating factors. Grading of diastolic dysfunction is the subject of an ongoing debate and newer guidelines have been published [30], whose clinical value has yet to be prospectively validated. It would have been interesting to measure fasting triacylglycerol, considering the recently proposed role of myocardial triacylglycerol accumulation in diabetic cardiomyopathy [31]. We did, however, observe a significant correlation between markers of diastolic dysfunction and low HDL-cholesterol levels. As the latter are part of the typical pattern of dyslipidaemia with low HDL-cholesterol and elevated triacylglycerol most frequently observed in insulin resistance, this might provide some indirect evidence. Similarly, it would also have been interesting to include a larger group of patients with confirmed type 1 diabetes or to determine diabetes-associated antibodies for diagnosis of latent autoimmune diabetes in adults, as this might have allowed us to speculate on whether divergent underlying pathophysiologies could have had a differential impact on diastolic function. Given our observations, we were rather surprised that duration of type 2 diabetes did not correlate with E:e′ or other markers of diastolic function. We speculate that duration of type 2 diabetes does not necessarily reflect severity of disease. The latter might be more appropriately indicated by HbA_{1c}, which reflects glycaemia over a period of time, and by the use of insulin, which reflects the necessity for intensified treatment in most cases.

In summary, our data show an association between diastolic dysfunction and glucose metabolism along the diabetic continuum, which extends into the normal range. Diastolic dysfunction negatively correlates with exercise tolerance. Our analysis supports a relevant role for diastolic dysfunction in diabetic heart failure and also the initiation of early preventive measures to address diastolic heart failure in the community.

Acknowledgements This work was supported by grants from the German Federal Ministry of Education and Research (German Heart Failure Network, TP 7 [FKZ 01GI0205], clinical trial programme ALDO-DHF [FKZ 01KG0506]) and the German Diabetes Foundation.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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