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ORIGINAL RESEARCH

Burden of Uncontrolled Metabolic Risk Factors and Left Ventricular Structure and Function in Patients With Type 2 Diabetes Mellitus

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***Background*—**Type 2 diabetes mellitus is closely associated with metabolic risk factors that all contribute to impairment of the left ventricle. The implications of having type 2 diabetes mellitus with well-controlled metabolic risk factors compared to an increasing burden of uncontrolled metabolic risk factors on left ventricular structure and function are not known.

***Methods and Results*—**We compared patients with type 2 diabetes mellitus (n=751) with different degrees of uncontrolled metabolic risk factors present with a control group of individuals without present uncontrolled metabolic risk factors as recommended by the World Health Organization (n=80). In patients with well-controlled metabolic risk factors, only diastolic but neither structural nor systolic measures were impaired compared to the control group: the (early diastolic mitral inflow velocity)/(atrial diastolic mitral inflow velocity) ratio (median 0.94 [interquartile range 0.80, 1.08] versus 1.11 [0.85, 1.38], $P<0.001$), lateral early diastolic myocardial velocity at the level of the mitral annulus (mean 9.6 m/s [SD 2.5] versus 10.8 [3.5], $P<0.001$) and lateral (early diastolic mitral inflow velocity)/(early diastolic myocardial velocity at the level of the mitral annulus) (7.7 [6.5, 10.2] versus 6.3 [4.9, 7.8], $P<0.001$). With an increasing burden of uncontrolled metabolic risk factors, there were increased left ventricular mass index and wall thicknesses and impaired systolic function measured as global longitudinal strain: control group −15.9 (2.0); 0 uncontrolled risk factors −15.3 (2.4); 1 to 2 −14.6 (2.8); and ≥3 −14.0 (2.8), $P<0.001$. Within the diabetes mellitus group, there were uni- and multivariable associations of left ventricular measures and systolic blood pressure, body mass index, hemoglobin A_{1c}, and HDL-cholesterol.

***Conclusions*—**In patients with type 2 diabetes mellitus, having well-controlled metabolic risk factors was associated with only left ventricular diastolic impairment but not with either structural or even subtle measures of systolic function. Increasing burden of uncontrolled metabolic risk factors was associated with structural and functional impairments. **(*J Am Heart Assoc*. 2018;7: e008856. DOI: 10.1161/JAHA.118.008856.)**

Key Words: echocardiography • metabolic syndrome • remodeling • type 2 diabetes mellitus

A dominant feature of type 2 diabetes mellitus (T2D) is its association with the metabolic syndrome, which in the World Health Organization definition includes, beyond insulin resistance, the metabolic risk factors obesity, hypertension, increased triglycerides and high-density lipoprotein (HDL)-cholesterol, and albuminuria. Although there is firm evidence of an increased risk of cardiovascular disease in patients with metabolic syndrome,[1-3] there has been a strong debate about whether this is beyond the sum of the contributions of each of the metabolic risk factors that constitute the syndrome.[4] There is a clear association between the metabolic risk factors diabetes mellitus,[5-7] obesity,[8] hypertension[9,10] and albuminuria[11] and the risk of developing heart failure (HF). However, whether dyslipidemia is associated with HF is less well elucidated. Nevertheless, in a recent study including 113 554 individuals from the general population, increasing nonfasting triglyceride was associated with a stepwise increase in the risk of developing HF.[12] These findings suggest a relationship between dyslipidemia and the risk of HF. Hence, evidence indicates that all of the metabolic risk factors in the World Health Organization definition of the metabolic syndrome are associated with an increased risk of developing HF.

For patients with T2D, a distinct effect of diabetes mellitus on the myocardium, the diabetic cardiomyopathy, has been

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Clinical Perspective

What Is New?

- Even with well-controlled metabolic risk factors there is evidence of diastolic but not systolic or structural cardiac impairment in patients with type 2 diabetes mellitus.
- With increasing burden of metabolic risk factors, the risk of further cardiac impairment increases in patients with type 2 diabetes mellitus.

What Are the Clinical Implications?

- Patients with type 2 diabetes mellitus should be considered for echocardiography even when the metabolic risk factors are well controlled.
- In assessing patients with type 2 diabetes mellitus, the risk of cardiac impairment is higher in patients with concomitant uncontrolled metabolic risk factors.

suggested and characterized by a number of previous studies. They have demonstrated that patients with diabetes mellitus have increased left ventricular wall thicknesses, left ventricular hypertrophy,[13–15] and both decreased systolic and diastolic function.[16–21] We have previously shown that these changes were amplified with increasing duration of T2D, supporting the suggested causal relationship between T2D and left ventricular (LV) remodeling and functional measures.[22]

However, because of the marked association between metabolic risk factors and diabetes mellitus, and because both hypertension and obesity have been closely associated with changes in cardiac mechanics, the direct effect of diabetes mellitus on the myocardium is difficult to discern from the effect of the coexisting metabolic risk factors. The aim of the present study was to examine the association of the burden of uncontrolled metabolic risk factors with LV structure and function in patients with T2D receiving multifactorial treatment compared to a nondiabetic control group without or with well-controlled metabolic risk factors. Previously, we demonstrated an association between triglyceride level[23] and microalbuminuria[24] and LV remodeling and function in this population. Therefore, our aim here was in addition to examine this association with the remainder of the metabolic risk factors: obesity, hypertension, hemoglobin A_{1c} (HbA_{1c}), and HDL-cholesterol levels.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, researchers may request specific data and study materials for the purpose of reproducing the results by contacting the corresponding author.

Study Population

The Thousand&2 study recruited patients with T2D from 2 large, secondary care centers in Copenhagen, the Capital Region, Denmark: Steno Diabetes Center and Center for Diabetes Research, Gentofte Hospital. Details on study inclusion and study visit have been published previously.[24,25] In brief, a total of 2158 patients were invited and 1030 participated in the study. Before attending the examination the patients filled out a questionnaire with information on current medication, previous heart disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, congestive heart failure, and atrial fibrillation), previous stroke and peripheral artery disease, family history of coronary heart disease, smoking habits, height, and weight. The questionnaire was reviewed with the patient at the study visit by P.G.J. Blood pressure was measured in the supine position after at least 15 minutes of rest. Body mass index (BMI) was calculated (weight [kg]/height $[m]^2$) based on self-reported measurements.

Patients with atrial fibrillation during the echocardiographic examination, more than moderate valve disease, and/or previous heart valve surgery were excluded (n=96). Also, for the analyses of numbers of metabolic risk factors and relation to LV structure and function, patients with incomplete information on BMI, systolic blood pressure, HbA_{1c}, HDL-cholesterol, triglyceride levels, or albuminuria status were excluded (n=183).

The study was conducted in accordance with the Declaration of Helsinki, approved by The Danish National Committee on Biomedical Research Ethics, amendment to protocol no. H-3-2009-139.[26] All participants gave written informed consent.

The control group consisted of a sample of people from the Copenhagen City Heart Study, a prospective cohort study of cardiovascular risk factors in patients from the general population. Details on the sampling have been published previously.[22] In brief, patients from the Thousand&2 study were randomly matched 4:1 on age, sex, and systolic blood pressure with people from the Copenhagen City Heart Study without diabetes mellitus (n=252). The metabolic risk factors were measured in all patients with the exception of the presence of albuminuria. From the control group, people with known heart disease, atrial fibrillation at the time of the echocardiographic exam, or presence of any of the metabolic risk factors as defined above were excluded (n=172). Hence, the control group consisted of 80 people without diabetes mellitus, known heart disease, or any of the metabolic risk

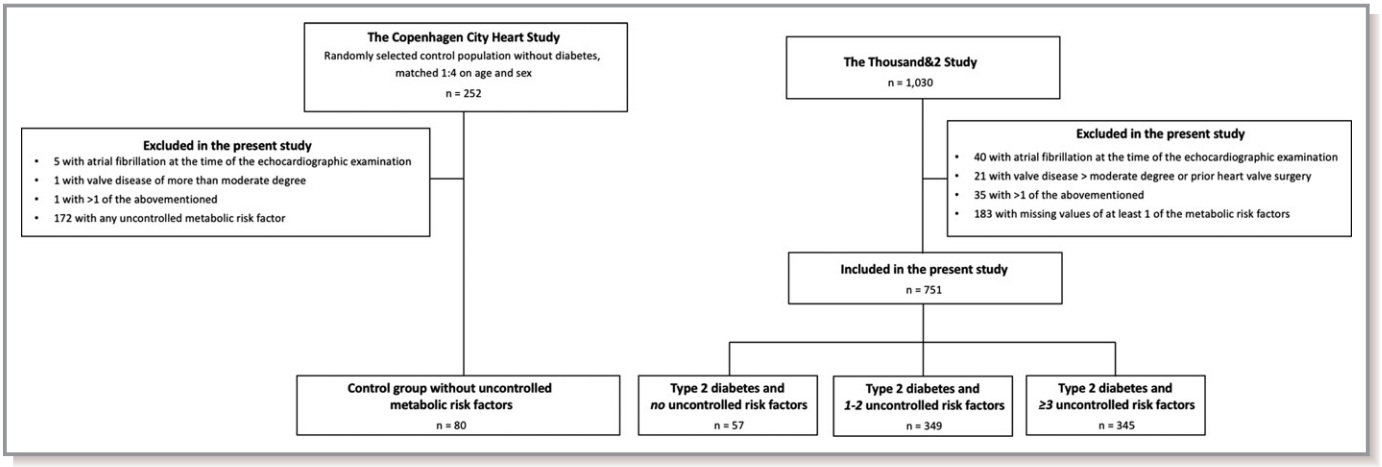

Figure 1. Flowchart of the derivation of the study sample.

factors. A flow chart of the derivation of the study population is provided in Figure 1.

Metabolic Risk Factors

According to the World Health Orgnization definition of the metabolic syndrome,[27] the metabolic risk factors constitute T2D or impaired fasting glucose, impaired glucose tolerance, increased systolic or diastolic blood pressure or antihypertensive treatment, elevated plasma triglycerides, HDL levels, increased BMI or waist:hip ratio, and presence of albuminuria. Accordingly, we regarded metabolic risk factors as uncontrolled when systolic blood pressure was >140 mm Hg, body mass index was >30 kg/m^2, HbA_{1c} was >48 mmol/L, HDL-cholesterol was <1.0 mmol/L for women and <0.9 mmol/L for men, triglyceride was >1.7 mmol/L, and in the presence of micro- or macroalbuminuria.

Biochemistry

Lipid levels, HbA_{1c}, and creatinine were obtained from routine blood tests performed at either Steno Diabetes Center or the Center for Diabetes Research, Herlev and Gentofte Hospital. Urine albumin/creatinine ratio and/or 24-hour urine albumin excretion rate are evaluated at least annually at both centers. Microalbuminuria was defined as a urine albumin/creatinine ratio between 30 and 300 mg/g or urine albumin excretion rate between 30 and 300 mg/day, and macroalbuminuria as a urine albumin/creatinine ratio above 300 mg/g or urine albumin excretion rate above 300 mg/day on 2 consecutive measurements.

Echocardiography

Details on the echocardiographic examinations have been published previously.[22-25] In brief, chamber quantification was done in accordance with the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.[28] LV mass was indexed according to height,[27] which was chosen in line with our previous studies. Sphericity index was calculated in end-diastole as LV length in an apical 4-chamber view/left ventricular internal diameter in a parasternal long-axis view. LV ejection fraction was measured with the Simpson biplane method, and reduced ejection fraction was defined as an LV ejection fraction <50%. 2-Dimensional speckle tracking was performed using GE EchoPAC software, BT13. Midmyocardial global strain provided by the software algorithm was used for both longitudinal and circumferential strain. Global longitudinal strain (GLS) was the mean value of the GLS from all 3 standard projections. Global circumferential strain (GCS) was measured at the level of the papillary muscle. Strain rate was the rate of these deformations in either longitudinal or circumferential directions and measured in seconds^{-1}.

People from the Copenhagen City Heart study were examined with the same echocardiographic protocol as patients in the Thousand&2 study using Vivid E9 (GE Vingmed Ultrasound, Horten, Norway).

Statistical Analysis

Continuous variables are presented as mean (SD)/median (interquartile range) and compared using Welsh t tests or 1-way analysis of variance/Mann-Whitney U tests or Kruskall-Wallis tests where appropriate. Categorical values are presented as number (percentage) and compared using chi-squared tests. Systolic blood pressure, BMI, HbA_{1c}, and HDL-cholesterol were nonnormally distributed and transformed using the binary logarithm (log_2), after which they were normally distributed. Association of these and echocardiographic measures were examined using linear regression models. *P*-values less than 0.05 on 2-sided tests were

considered significant. Statistics were performed using R for Mac, version 3.4.2 (R Project for Statistical Computing, Vienna University of Economics and Business Administration, Vienna, Austria).

Results

We identified 751 patients from the diabetes mellitus cohort with all metabolic risk factors measured. The distribution of uncontrolled metabolic risk factors among the patients with T2D is found in Table 1. We identified 57 patients without any or all well-controlled metabolic risk factors after aggressive multifactorial treatment. Of these, 14% received β-blockers, 21% angiotensin-converting enzyme inhibitors, 32% angiotensin II receptor blockers, and 28% calcium antagonists. Also, 72% received metformin, 10% to 21% received other antidiabetic treatment, and 86% received statins.

Patients from the diabetes mellitus group were further divided into categories with, respectively, 0 (n=57), 1 to 2 (n=349), and ≥3 (n=345) uncontrolled metabolic risk factors and compared with the control group (n=80). The population demographics after this subdivision are shown in Table 2. Compared to the control group, patients with T2D were of similar age and sex regardless of the presence of uncontrolled metabolic risk factors. Blood pressure, both systolic and diastolic, was insignificantly higher in patients with T2D compared to the control group but was significantly higher in patients with T2D with any uncontrolled metabolic risk factor present. Similar results were seen with for triglyceride levels, but there were significantly higher BMI and lower LDL- and HDL-cholesterol in all patients with T2D compared with the control group. Patients with T2D were more often treated with antihypertensive drugs, diuretics, and statins regardless of the presence of uncontrolled metabolic risk factors compared with the control group.

Association of Burden of Uncontrolled Metabolic Risk Factors and Echocardiographic Findings

The associations of numbers of uncontrolled metabolic risk factors and echocardiographic findings are found in Table 3. There was a highly significant difference between the control group, patients with 0, 1 to 2, and ≥3 uncontrolled metabolic risk factors, and all the structural and diastolic findings except LV end-diastolic diameter and left atrial volume index. The association was less pronounced in the systolic measures because this was only the case for the proportion with LV ejection fraction <50% and GLS. Thus, GLS rate, GCS, and GCS rate were not affected by an increasing number of uncontrolled metabolic risk factors present.

When the control group is compared with the patients with T2D without any uncontrolled metabolic risk factor present, there were no significant differences in any structural or systolic measure, but there was clear evidence of reduced diastolic function expressed as decreased lateral and septal early diastolic myocardial velocity at the level of the mitral annulus and (early diastolic mitral inflow velocity)/(early diastolic myocardial velocity at the level of the mitral annulus), (early diastolic mitral inflow velocity)/(atrial diastolic mitral inflow velocity) ratio, and increased peak early and atrial diastolic mitral inflow velocities. With increasing numbers of uncontrolled metabolic risk factors present, there was increasing evidence of both structural remodeling with increasing LV wall thicknesses and relative wall thicknesses but no changes in LV end-diastolic diameter or left atrial volume index. Regarding diastolic measures, there was an increase in diastolic dysfunction with increasing number of uncontrolled metabolic risk factors present. With respect to the systolic measures, GLS was decreased when ≥1 uncontrolled risk factor was present and more so when ≥3 were present, and GLS rate was not affected unless ≥3 uncontrolled risk factors were present. There were no differences in

Table 1. Distribution of the Metabolic Risk Factors Present Among Patients With Type 2 Diabetes Mellitus

	Number of Uncontrolled Metabolic Risk Factors Present						
	0 (n=57)	1 (n=137)	2 (n=212)	3 (n=170)	4 (n=120)	5 (n=43)	6 (n=12)
Elevated systolic blood pressure, n (%)	0 (0)	8 (6)	46 (22)	63 (37)	61 (51)	31 (72)	12 (100)
Elevated BMI, n (%)	0 (0)	17 (12)	75 (35)	99 (58)	91 (76)	40 (93)	12 (100)
Elevated HDL-cholesterol, n (%)	0 (0)	7 (5)	13 (6)	34 (20)	44 (37)	30 (70)	12 (100)
Elevated triglyceride, n (%)	0 (0)	24 (18)	87 (41)	122 (72)	102 (85)	43 (100)	12 (100)
Albuminuria, n (%)	0 (0)	7 (5)	35 (17)	47 (28)	66 (55)	30 (70)	12 (100)
Elevated hemoglobin A_{1c}, n (%)	0 (0)	74 (54)	168 (79)	145 (85)	116 (97)	41 (95)	12 (100)

Criteria for metabolic risk factors: hemoglobin A_{1c} >48 mmol/L, systolic blood pressure >140 mm Hg, body mass index >30 kg/m^2, HDL-cholesterol <1.0 mmol/L for women and <0.9 mmol/L for men, triglycerides >1.7 mmol/L, and presence of micro- or macroalbuminuria. BMI indicates body mass index; HDL, high-density lipoprotein.

Table 2. Population Demographics

	Control Group	Type 2 Diabetes Mellitus and			*P* Value (Across All Groups)	*P* Value (Control vs 0 Risk Factors)	*P* Value (Control vs 1 to 2 Risk Factors)	*P* Value (Control vs ≥3 Risk Factors)
		0 Uncontrolled Risk Factors	1 to 2 Uncontrolled Risk Factors	≥3 Uncontrolled Risk Factors				
	n=80	n=57	n=349	n=345				
Clincal								
Age, y	63 [57, 68]	65 [59, 72]	65 [59, 71]	65 [57, 70]	0.03	0.17	0.005*	0.11
Male sex, %	52 (65.0)	32 (56.1)	233 (66.8)	231 (67.0)	0.44	0.38	0.87	0.84
Diabetes mellitus duration, y		7 [2, 15]	11 [5, 17]	13 [8, 20]				
Body mass index, kg/m^2	24.1 [22. 8, 26.1]	26.0 [23.5, 27.8]	27.7 [25.3, 30.4]	32.3 [29.0, 35.5]	<0.001*	0.004*	<0.001*	<0.001*
Systolic blood pressure, mm Hg	123 (9)	126 (10)	132 (16)	142 (18)	<0.001*	0.09	<0.001*	<0.001*
Diastolic blood pressure, mm Hg	76 (10)	77 (8)	78 (10)	82 (11)	<0.001*	0.37	0.05*	<0.001*
Coronary heart disease, %		10 (17.5)	58 (16.6)	63 (18.3)				
Laboratory values								
LDL-cholesterol, mmol/L	3.1 [2.6, 3.5]	1.9 [1.6, 2.3]	2.0 [1.6, 2.6]	2.0 [1.5, 2.6]	<0.001*	<0.001*	<0.001*	<0.001*
HDL-cholesterol, mmol/L	1.7 [1.5, 2.0]	1.5 [1.2, 1.8]	1.2 [1.0, 1.5]	1.0 [0.9, 1.3]	<0.001*	0.006	<0.001*	<0.001*
Triglyceride, mmol/L	1.0 [0.8, 1.3]	1.1 [0.8, 1.3]	1.4 [1.0, 2.0]	2.3 [1.8, 3.1]	<0.001*	0.45	<0.001*	<0.001*
Albuminuria, %			42 (12.0)	155 (44.9)				
Microalbuminuria, %			37 (10.6)	100 (29.0)				
Macroalbuminuria, %			5 (1.4)	55 (15.9)				
Hemoglobin A_{1c}, mmol/mol		43 [40, 46]	54 [46, 62]	60 [53, 73]				
Hemoglobin A_{1c}, %		6.1 (0.4)	7.3 (1.3)	8.0 (1.5)				
Creatinine, μmol/L	78 [71, 87]	72 [63, 84]	77 [66, 92]	82 [65, 103]	0.01	0.06	0.72	0.19
Medication								
Metformin, %		41 (71.9)	251 (71.9)	252 (73.0)				
DPP4 inhibitors, %		7 (12.3)	30 (8.6)	35 (10.1)				
Sulfonylurea, %		6 (10.5)	58 (16.6)	51 (14.8)				
Glucagon-like peptide 1-receptor agonist, %		11 (19.3)	63 (18.1)	103 (29.9)				
Insulin, %		12 (21.1)	159 (45.6)	201 (58.3)				
β-Blockers, %	8 (10.0)	8 (14.0)	80 (22.9)	94 (27.2)	<0.001*	0.002*	<0.001*	<0.001*

Continued

Table 2. Continued

	Control Group	Type 2 Diabetes Mellitus and			*P* Value (Across All Groups)	*P* Value (Control vs 0 Risk Factors)	*P* Value (Control vs 1 to 2 Risk Factors)	*P* Value (Control vs ≥3 Risk Factors)
		0 Uncontrolled Risk Factors	1 to 2 Uncontrolled Risk Factors	≥3 Uncontrolled Risk Factors				
	n=80	n=57	n=349	n=345				
Angiotensin-converting enzyme inhibitors, %	5 (6.2)	12 (21.1)	144 (41.3)	128 (37.1)	<0.001*	0.12	<0.001*	<0.001*
Angiotensin II receptor blockers, %	8 (10.0)	18 (31.6)	125 (35.8)	163 (47.2)	<0.001*	<0.001*	<0.001*	<0.001*
Calcium antagonists, %	8 (10.0)	16 (28.1)	111 (31.8)	120 (34.8)	<0.001*	0.01*	<0.001*	<0.001*
Diuretics, %	8 (10.0)	23 (40.4)	155 (44.4)	204 (59.1)	<0.001*	<0.001*	<0.001*	<0.001*
Statins, %	8 (10.0)	49 (86.0)	278 (79.7)	263 (76.2)	<0.001*	<0.001*	<0.001*	<0.001*

Criteria for uncontrolled metabolic risk factors include hemoglobin A_{1c} >48 mmol/L, systolic blood pressure >140 mm Hg, body mass index >30 kg/m^2, HDL-cholesterol <1.0 mmol/L for women and <0.9 mmol/L for men, triglycerides >1.7 mmol/L, and presence of micro- or macroalbuminuria. Continuous traits are reported as mean (SD) or median [interquartile range] in case of nonnormal distribution. DPP4 indicates dipeptidyl peptidase-4; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*P<0.05.

LV ejection fraction, GCS, or GCS rate with increasing number of uncontrolled metabolic risk factors present.

Figure 2 shows how LV structural, diastolic, and systolic measures were affected with increasing numbers of uncontrolled metabolic risk factors present. Here, these patterns are repeated: there was diastolic but not structural or systolic impairment without concomitant metabolic risk factors. Structural and systolic impairment emerged as numbers of uncontrolled metabolic risk factors increased.

Association of Systolic Blood Pressure, BMI, HbA_{1c}, and HDL-Cholesterol With Echocardiographic Findings in Patients With T2D

Univariable and multivariable associations of systolic blood pressure, BMI, HbA_{1c}, HDL-cholesterol, and echocardiographic findings are found in Tables 4 and 5. In general, there was an overall association with LV structural measures (LV mass index [not for HbA_{1c}], LV wall thicknesses, and relative wall thickness [not for HDL-cholesterol]). This, however, was attenuated overall for HbA_{1c} and HDL-cholesterol but persisted for systolic blood pressure and BMI after adjustment for the other metabolic risk factors. Regarding diastolic measures, they were consistently associated with systolic blood pressure and BMI, in particular evidence of elevated filling pressures expressed as (early diastolic mitral inflow velocity)/(early diastolic myocardial velocity at the level of the mitral annulus) and decreased LV relaxation expressed as lateral early diastolic myocardial velocity at the level of the mitral annulus. On the other hand, there was no consistent pattern of association between either HbA_{1c} or HDL-cholesterol and diastolic measures. For the systolic measures, all metabolic risk factors were univariably associated with GLS, but after adjustment for the other metabolic risk factors, there was a significant association only with BMI. Interestingly, after adjusting, where BMI was associated with both GLS and GCS and not their corresponding rates, the opposite was the case for systolic blood pressure. Other than that, there was no clear pattern of associations between either and the systolic LV measures except LV ejection fraction, which increased with HDL-cholesterol in both uni- and multivariable analyses.

Discussion

The primary findings in this study were that in patients with T2D with well-controlled metabolic risk factors, there was evidence of cardiac impairment characterized only by diastolic dysfunction with neither structural changes nor systolic dysfunction. Furthermore, with an increasing number of uncontrolled metabolic risk factors present, there was also a progressive impairment of LV structure and LV systolic (longitudinal) function. Hence, despite reaching treatment goals in patients with T2D and eliminating the contribution of the metabolic risk factors, we were still able to identify an effect on the myocardium characterized only by impaired diastolic functional measures.

Table 3. Association of Number of Uncontrolled Metabolic Risk Factors and Echocardiographic Findings

	Control Group	Type 2 Diabetes Mellitus and			*P* Value (Across All Groups)	*P* Value (Control vs 0 Risk Factors)	*P* Value (Control vs 1 to 2 Risk Factors)	*P* Value (Control vs ≥3 Risk Factors)
		0 Uncontrolled Risk Factors	1 to 2 Uncontrolled Risk Factors	≥3 Uncontrolled Risk Factors				
	n=80	n=57	n=349	n=345				
Structural measures								
Left ventricular mass index, g/m$^{2.7}$	35.5 (8.0)	35.5 (9.6)	37.1 (11.7)	41.1 (11.1)	<0.001*	0.99	0.26	<0.001*
Interventricular septum thickness, mm	10.0 (1.3)	9.9 (1.4)	10.4 (1.8)	11.2 (1.7)	<0.001*	0.87	0.06	<0.001*
End-diastolic internal diameter, mm	46.8 (4.8)	46.0 (6.8)	45.6 (6.3)	45.9 (6.0)	0.51	0.43	0.13	0.21
Posterior wall thickness, mm	9.4 (1.3)	9.5 (1.2)	10.1 (1.5)	10.8 (1.6)	<0.001*	0.76	<0.001*	<0.001*
Relative wall thickness	0.41 (0.07)	0.42 (0.07)	0.45 (0.09)	0.48 (0.10)	<0.001*	0.26	<0.001*	<0.001*
Sphericity index	0.17 (0.02)	0.17 (0.02)	0.18 (0.03)	0.18 (0.03)	0.17	0.60	0.11	0.05*
Left atrial end-systolic volume index, mL/m^2	26 [22, 32]	26 [21, 31]	25 [20, 32]	25 [20, 31]	0.81	0.82	0.79	0.56
Diastolic measures								
Peak E velocity, m/s	0.67 [0.55, 0.78]	0.74 [0.63, 0.87]	0.75 [0.63, 0.87]	0.76 [0.65, 0.88]	<0.001*	0.01*	<0.001*	<0.001*
Peak A velocity, m/s	0.60 (0.16)	0.79 (0.19)	0.85 (0.19)	0.86 (0.20)	<0.001*	<0.001*	<0.001*	<0.001*
E/A ratio	1.11 [0.85, 1.38]	0.94 [0.80, 1.08]	0.86 [0.75, 1.07]	0.87 [0.75, 1.06]	<0.001*	0.005*	<0.001*	<0.001*
E deceleration time, ms	191 [164, 219]	209 [168, 247]	220 [183, 263]	220 [188, 269]	<0.001*	0.14	<0.001*	<0.001*
Lateral e′ (per second)	10.8 (3.5)	9.6 (2.5)	8.7 (2.6)	8.5 (2.5)	<0.001*	0.03*	<0.001*	<0.001*
Septal e′, m/s	8.4 (2.7)	7.2 (1.8)	6.8 (1.9)	6.5 (1.8)	<0.001*	0.002*	<0.001*	<0.001*
E/e′$_{lateral}$	6.3 [4.9, 7.8]	7.7 [6.5, 10.2]	8.6 [6.9, 10.6]	9.0 [7.2, 12.1]	<0.001*	<0.001*	<0.001*	<0.001*
E/e′$_{septal}$	7.7 [6.6, 9.9]	10.5 [8.6, 12.4]	10.9 [9.2, 13.3]	11.6 [9.6, 14.9]	<0.001*	<0.001*	<0.001*	<0.001*
Systolic measures								
Ejection fraction, %	61 [56, 65]	62 [57, 66]	61 [57, 65]	60 [55, 65]	0.14	0.52	0.96	0.24
Reduced ejection fraction (<50%), %	5 (6.5)	2 (3.6)	34 (9.9)	48 (14.4)	0.03*	0.73	0.48	0.09
Global longitudinal systolic strain, %	−15.9 (2.0)	−15.3 (2.4)	−14.6 (2.8)	−14.0 (2.8)	<0.001*	0.13	<0.001*	<0.001*
Global longitudinal systolic strain rate (per second)	−0.81 (0.11)	−0.80 (0.14)	−0.79 (0.17)	−0.77 (0.18)	0.09	0.53	0.37	0.04*
Global circumferential systolic strain, %	−18.1 (4.1)	−18.7 (4.8)	−18.0 (5.2)	−17.4 (5.3)	0.34	0.49	0.87	0.35
Global circumferential systolic strain rate (per second)	−0.97 (0.22)	−0.99 (0.28)	−1.05 (0.33)	−1.03 (0.34)	0.27	0.71	0.07	0.19

Criteria for uncontrolled metabolic risk factors include hemoglobin A_{1c} >48 mmol/L, systolic blood pressure >140 mm Hg, body mass index >30 kg/m^2, HDL-cholesterol <1.0 mmol/L for women and <0.9 mmol/L for men, triglyceride >1.7 mmol/L, and presence of micro- or macroalbuminuria. Continuous traits are reported as mean (SD) or median [interquartile range] in case of nonnormal distribution. A indicates atrial diastolic mitral inflow velocity; E, early diastolic mitral inflow velocity; e′, early diastolic myocardial velocity at the level of the mitral annulus.

*P<0.05.

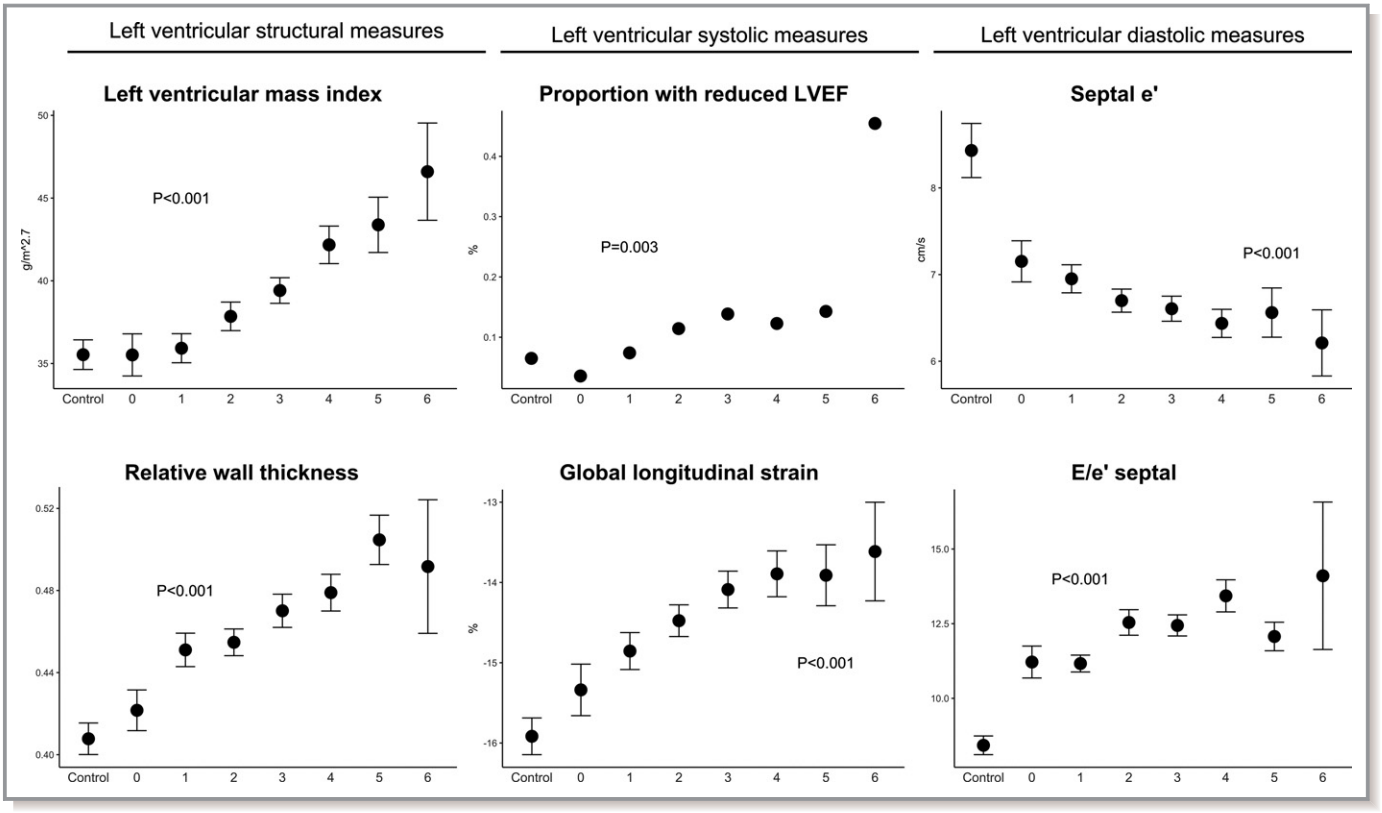

Figure 2. Association of number of uncontrolled metabolic risk factors and measures of left ventricular structural and systolic and diastolic measures. e′, early diastolic myocardial velocity; E/e′, ratio of early mitral inflow velocity and early diastolic myocardial velocity; LVEF, left ventricular ejection fraction.

Metabolic Risk Factors and LV Structure and Function in T2D

We found that in patients with well-controlled metabolic risk factors there was no evidence of structural or systolic impairment of the LV. This is in contrast to previous studies that have demonstrated the presence of both structural and systolic in addition to diastolic impairment in patients with T2D. The Strong Heart Study demonstrated increased LV wall thicknesses, LV mass index, and decreased fractional shortening in a population of American Indians with a high prevalence of T2D.[14] The same tendency was found in hypertensive patients in the HyperGEN study, in which T2D was associated with increased LV mass and wall thicknesses,[15] and in the *ARIC* study, in which increasing levels of HbA_{1c} were associated with LV mass, wall thicknesses, GLS, and diastolic measures including septal and lateral early diastolic myocardial velocity at the level of the mitral annulus and (early diastolic mitral inflow velocity)/(early diastolic myocardial velocity at the level of the mitral annulus).[29] Additionally, Ernande et al compared 144 patients with T2D without cardiac disease with 88 healthy controls without T2D, hypertension, low levels of total and LDL-cholesterol, high levels of HDL-cholesterol, and normal renal function and found that T2D was associated with decreased systolic function expressed as radial and longitudinal strain and strain rate.[18] The same group also concluded in a different analysis that the deformation changes were closely associated with increased LV wall thicknesses associated with T2D.[19] Common among these studies is that there were differences between the compared groups regarding BMI (Strong, ARIC, HyperGEN, and Ernande), systolic blood pressure (Strong, HyperGEN, and Ernande), and lipid levels (ARIC, HyperGEN, and Ernande), and although adjusted models were constructed, the complex interaction of obesity, blood pressure, and lipid levels is difficult to examine fully in any of these cohorts. Hence, our study indicates that the presence of other metabolic risk factors in T2D accounts for the structural changes found in T2D and possibly therefore for the changes in systolic function as suggested in the abovementioned study by Ernande et al.[19] Thus, our findings suggest that the previously found effect of diabetes mellitus on LV structural and systolic function may have been caused by the presence of confounding, concomitant metabolic risk factors. Recently, this complex interaction was addressed in a study that suggested cardiac phenotypes in patients with T2D. This was based on cluster analysis and found that obesity and hypertension were particularly associated with worse prognosis in women, whereas in the case of

Table 4. Univariable Association of Systolic Blood Pressure, BMI, HbA_{1c}, HDL-Cholesterol, and Echocardiographic Findings in Patients With T2D

	Log_2 (Systolic Blood Pressure)		Log_2 (BMI)		Log_2 (HbA_{1c})		Log_2 (HDL-Cholesterol)	
	β-Coefficient (SE)	*P* Value	β-coefficient (SE)	*P* Value	β-Coefficient (SE)	*P* Value	β-Coefficient (SE)	*P* Value
Structural measures								
Left ventricular mass index, $g/m^{2.7}$	11.5 (2.3)	<0.001*	15.3 (1.5)	<0.001*	−0.02 (1.2)	0.98	−3.8 (1.0)	<0.001*
Interventricular septum diameter, mm	1.3 (0.4)	<0.001*	1.6 (0.2)	<0.001*	0.5 (0.2)	0.003*	−0.7 (0.2)	<0.001*
End-diastolic internal diameter, mm	1.1 (1.3)	0.41	4.3 (0.9)	<0.001*	−1.6 (0.6)	0.01*	−2.1 (0.5)	<0.001*
Posterior wall diameter (mm)	1.3 (0.3)	<0.001*	1.6 (0.2)	<0.001*	0.3 (0.2)	0.07	−0.7 (0.1)	<0.001*
Relative wall thickness	0.05 (0.02)	0.01*	0.03 (0.01)	0.04*	0.03 (0.01)	0.002*	−0.01 (0.01)	0.27
Sphericity index (per 0.01 increase)	−0.24 (0.55)	0.66	−0.58 (0.38)	0.13	0.46 (0.27)	0.08	−0.08 (0.23)	0.72
Left atrial end-systolic volume index, mL/m^2	4.4 (1.7)	0.01*	−1.0 (1.2)	0.38	−1.7 (0.8)	0.04*	0.2 (0.7)	0.78
Diastolic measures								
Peak E velocity (cm/s)	0.18 (0.04)	<0.001*	0.11 (0.03)	0.0001*	0.00 (0.02)	0.99	0.001 (0.02)	0.97
Peak A velocity, cm/s	0.29 (0.04)	<0.001*	0.07 (0.03)	0.009*	0.03 (0.02)	0.12	0.03 (0.02)	0.08
E/A ratio	−0.10 (0.06)	0.09	0.05 (0.04)	0.25	−0.03 (0.03)	0.32	−0.03 (0.02)	0.19
E deceleration time, ms	4.0 (15.5)	0.80	10.2 (10.5)	0.33	16.0 (7.3)	0.03*	3.4 (6.5)	0.60
Lateral e′, cm/s	−2.4 (0.5)	<0.001*	−0.7 (0.4)	0.04*	−0.5 (0.3)	0.03*	0.15 (0.2)	0.52
Septal e′, cm/s	−1.1 (0.4)	0.004*	−0.2 (0.3)	0.40	−0.4 (0.2)	0.05	0.1 (0.2)	0.40
$E/e'_{lateral}$	6.0 (0.9)	<0.001*	2.1 (0.6)	0.002*	0.6 (0.5)	0.22	−0.3 (0.4)	0.46
E/e'_{septal}	5.4 (1.1)	<0.001*	2.1 (0.7)	0.003*	1.0 (0.5)	0.05*	−0.2 (0.5)	0.68
Systolic measures								
Ejection fraction, %	−0.8 (1.7)	0.65	−2.9 (1.2)	0.02*	−0.8 (0.9)	0.35	3.1 (0.7)	<0.001*
Global longitudinal systolic strain, %	1.2 (0.6)	0.05*	1.8 (0.4)	<0.001*	0.6 (0.3)	0.03*	−1.0 (0.2)	<0.001*
Global longitudinal systolic strain rate (per second)	0.11 (0.04)	0.003*	0.05 (0.03)	0.04*	0.02 (0.02)	0.37	−0.03 (0.02)	0.09
Global circumferential systolic strain, %	1.3 (1.2)	0.28	2.6 (0.9)	0.003*	0.3 (0.6)	0.61	−0.7 (0.5)	0.19
Global circumferential systolic strain rate (s^{-1})	0.2 (0.08)	0.01*	−0.01 (0.05)	0.79	−0.01 (0.04)	0.75	0.01 (0.03)	0.82

A indicates atrial diastolic mitral inflow velocity; BMI, body mass index; E, early diastolic mitral inflow velocity; e′, early diastolic myocardial velocity at the level of the mitral annulus; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; SE, standard error; T2D, type 2 diabetes mellitus.
*$P<0.05$.

men this was seen with LV hypertrophy and systolic dysfunction.[30] Surprisingly, there was no association of left atrial size and increasing burden of uncontrolled metabolic risk factors. This is contradictory to what we would expect because of the strong association of the burden of uncontrolled metabolic risk factors and diastolic dysfunction. Our results suggest that left atrial size was influenced by other unmeasured confounding factors in this population.

Table 5. Multivariable Association of Systolic Blood Pressure, Body Mass Index, HbA1c, HDL-Cholesterol, and Echocardiographic Findings in Patients With T2D

	Log_2 (Systolic Blood Pressure)		Log_2 (BMI)		Log_2 (Hemoglobin A_{1c})		Log_2 (HDL-Cholesterol)	
	β-Coefficient (SE)	*P* Value	β-Coefficient (SE)	*P* Value	β-Coefficient (SE)	*P* Value	β-Coefficient (SE)	*P* Value
Structural measures								
Left ventricular mass index, $g/m^{2.7}$	6.9 (2.2)	0.002*	15.2 (1.6)	<0.001*	−1.8 (1.1)	0.09	−2.6 (1.1)	0.02*
Interventricular septum diameter, mm	0.8 (0.3)	0.01*	1.5 (0.2)	<0.00*1	0.3 (0.2)	0.09	−0.1 (0.2)	0.50
End-diastolic internal diameter, mm	1.6 (1.3)	0.20	4.2 (0.9)	<0.001*	−1.8 (0.6)	0.004*	−1.2 (0.6)	0.06
Posterior wall diameter, mm	0.9 (0.3)	0.004*	1.6 (0.2)	<0.001*	0.03 (0.1)	0.84	−0.1 (0.1)	0.32
Relative wall thickness	0.02 (0.02)	0.29	0.03 (0.01)	0.03*	0.02 (0.01)	0.02*	0.01 (0.01)	0.46
Sphericity index (per 0.01 increase)	0.55 (1.09)	0.61	−0.79 (0.41)	0.05	0.42 (0.29)	0.15	0.31 (0.28)	0.26
Left atrial end-systolic volume index, mL/m^2	3.8 (1.7)	0.03*	0.4 (1.2)	0.77	−1.6 (0.8)	0.06	−0.5 (0.8)	0.56
Diastolic measures								
Peak E velocity, cm/s	0.15 (0.04)	<0.001*	0.10 (0.03)	<0.001*	−0.01 (0.02)	0.58	−0.02 (0.02)	0.38
Peak A velocity, cm/s	0.21 (0.04)	<0.001*	0.08 (0.03)	0.003*	0.03 (0.02)	0.09	−0.01 (0.02)	0.42
E/A ratio	−0.04 (0.06)	0.52	0.02 (0.04)	0.70	−0.04 (0.03)	0.12	0.00 (0.03)	0.98
E deceleration time, ms	−19.3 (15.6)	0.22	21.0 (11.0)	0.06	17.2 (7.4)	0.02*	2.8 (7.5)	0.71
Lateral e′, cm/s	−1.1 (0.5)	0.02*	−1.1 (0.3)	0.002*	−0.4 (0.2)	0.05	0.4 (0.2)	0.12
Septal e′, cm/s	−0.2 (0.4)	0.53	−0.5 (0.3)	0.05	−0.3 (0.2)	0.06	0.4 (0.2)	0.02*
$E/e'_{lateral}$	4.1 (0.9)	<0.001*	2.0 (0.6)	0.002*	0.2 (0.4)	0.60	−1.1 (0.4)	0.02*
E/e'_{septal}	3.3 (1.0)	0.001*	2.3 (0.7)	0.002*	0.4 (0.5)	0.13	−1.0 (0.5)	0.04*
Systolic measures								
Ejection fraction, %	−0.5 (1.8)	0.77	−2.2 (1.3)	0.09	−0.3 (0.9)	0.72	2.3 (0.9)	0.01*
Global longitudinal systolic strain, %	0.6 (0.6)	0.29	1.7 (0.4)	<0.001*	0.4 (0.3)	0.17	−0.6 (0.3)	0.05
Global longitudinal systolic strain rate, s^{-1}	0.08 (0.04)	0.03*	0.05 (0.03)	0.07	0.01 (0.02)	0.58	−0.04 (0.02)	0.04*
Global circumferential systolic strain, %	0.9 (1.3)	0.46	2.3 (0.9)	0.01*	0.07 (0.6)	0.91	0.1 (0.6)	0.82
Global circumferential systolic strain rate, s^{-1}	0.17 (0.08)	0.04*	−0.03 (0.06)	0.59	−0.02 (0.04)	0.63	−0.05 (0.04)	0.25

Multivariable model adjusted for age, sex, hemoglobin A_{1c}, body mass index, systolic blood pressure, HDL-cholesterol, triglyceride level, and albuminuria. A indicates atrial diastolic mitral inflow velocity; BMI, body mass index; E, early diastolic mitral inflow velocity; e′, early diastolic myocardial velocity at the level of the mitral annulus; HDL, high-density lipoprotein; SE, standard error.
*$P<0.05$.

Metabolic Syndrome and LV Mechanics

In this study we confirmed the association of systolic blood pressure, BMI, and HbA_{1c} with LV structure and function. Also, we found an undescribed but also rather inconsistent association of HDL-cholesterol and LV structure and function. Previous studies have established a close relation between hypertension, obesity, and HbA_{1c} and LV structure and function. The association of hypertension and LV hypertrophy is 1 of the earliest described in cardiology and is caused by pressure

overload of the LV.[9] When present, LV hypertrophy is closely related to prognosis whether detected by electrocardiography,[31] echocardiography,[32] or magnetic resonance imaging,[33] and regression of LV hypertrophy in serial ECGs has also been linked to improved prognosis.[34,35] In obesity, there is a strong association of both diastolic and systolic dysfunction that seems to be related to obesity severity,[36] and regarding dysglycemia, a close relationship of HbA_{1c} with LV mechanics exists even in elderly patients without overt diabetes mellitus.[29] The same is the case for low-grade states of albuminuria.[37] Thus, we have previously described a close association of LV structure and function with both microalbuminuria and increasing levels of triglycerides in this cohort,[23,24] and there is convincing evidence that all components of the metabolic syndrome have an impact on the myocardium.

Strengths and Limitations

The strength of this study is the size of the cohort, which enables stratification of patients in groups with increasing burden of uncontrolled metabolic risk factors present (except that only 12 patients had all metabolic risk factors uncontrolled). In addition, all patients and the control group underwent comprehensive echocardiography. Some limitations of this study must be acknowledged. A hallmark of the metabolic syndrome is increased waist circumference, which was not measured in this study, and thus, BMI was used as the only measure of obesity. Albuminuria was not assessed in the control group, and we were not able to exclude people with this metabolic risk factor from the control group. Another limitation is that only patients from specialized diabetes mellitus clinics were included in the study, thus limiting the interpretability to T2D patients followed in primary care. Although the presented diastolic measures are the most commonly used, other diastolic measurements, including strain rate during isovolumetric relaxation and ratio of early diastolic mitral inflow velocity and strain rate during isovolumetric relaxation,[38] may be more sensitive markers of diastolic dysfunction and were not measured in this cohort. In addition, we were not able to evaluate the association of biomarkers of cardiac function, in particular NT-pro–brain natriuretic peptide. Also, HDL functionality, eg, macrophage cholesterol efflux, which is considered to be the main determinant of the beneficial effect of HDL-cholesterol, was not measured.[39] Finally, because this is an observational study, no inferences on causality can be drawn from the data.

Conclusion

In this study we have shown that patients with T2D and well-controlled metabolic risk factors had impaired diastolic function but preserved LV structure and systolic function. This was in contrast to previous studies that had not excluded patients with present metabolic risk factors. Because the burden of uncontrolled metabolic risk factors increased, increasing LV structural and systolic changes emerged, further indicating that these changes are predominantly caused by an effect of concomitant metabolic risk factors.

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