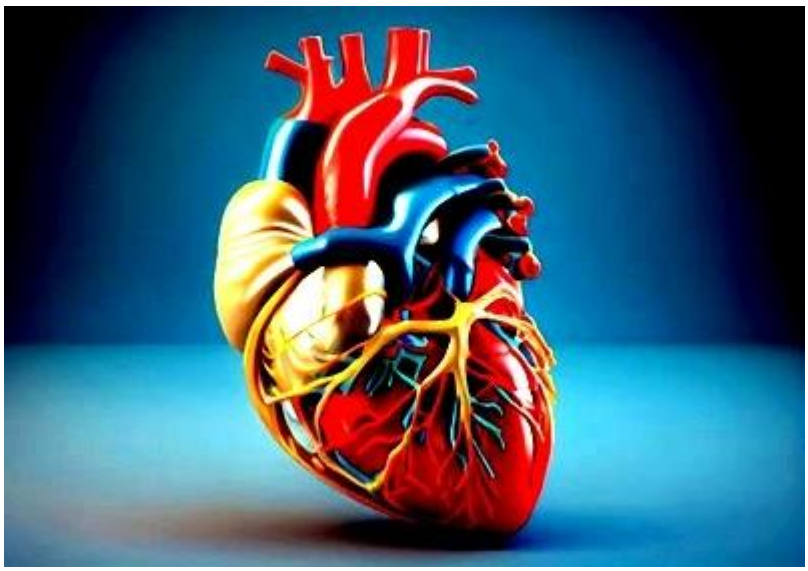
In a 7-year follow-up, 61% of patients diagnosed with type 2 diabetes who had no cardiovascular disease were found to have subclinical left ventricular dysfunction | 1

The prevalence of diabetes is increasing, and it is projected to reach 783 million people worldwide in 2045. There is a parallel rise in the prevalence of major complications of diabetes, including heart failure (HF), among others. HF is believed to be caused by diabetic cardiomyopathy (DCM), defined as the structural and functional myocardial disorder associated with the metabolic disorders of diabetes in the absence of other leading cardiac factors such as hypertension, coronary heart disease, and valvular disease. During a seven-year follow-up period, the Russian authors investigated long-term structural and functional abnormalities of the left ventricle (LV) myocardium, in particular, asymptomatic DCM, referred to as subclinical left ventricular dysfunction (LVD), in patients with type 2 diabetes who were asymptomatic or had no history of severe somatic and cardiovascular disease.

Specific diagnostic criteria for DCM have not yet been established. In studies, DCM prevalence in patients with type 2 diabetes varies from 5% to 58%. The initial DCM represents a transitional phenotype before the onset of symptomatic heart failure (HF). The main triggers for DCM development are hyperglycemia and insulin resistance, but, its full pathogenesis remains unclear. Since DCM is not manifested clinically for a long time in the early stages, asymptomatic DCM is referred to as subclinical left ventricular dysfunction (LVD). Previous studies have shown that subclinical left ventricular dysfunction in asymptomatic patients with type 2 diabetes is associated with negative outcomes during long-term follow-up.



The main echocardiographic signs of a diabetic heart are systolic and diastolic dysfunction, and abnormal geometry of the left ventricle. Regarding LV geometry, the early stage of DCM is characterized by concentric LV hypertrophy. Even if ejection fraction (EF) is normal in patients with type 2 diabetes, they often show evidence of subclinical systolic dysfunction, as indicated by a lower global longitudinal strain (GLS). GLS is considered the earliest ultrasonic sign of preclinical diabetic cardiomyopathy and the most robust and reproducible parameter of myocardial strain. It reflects the proportion of the change in myocardial length

during the cardiac cycle. Myocardial systolic shortening is indicated by a negative value, while improved LV systolic function is shown by a higher absolute value.

The same team of researchers found that the proportion of patients with a reduced GLS absolute level increased in patients with type 2 diabetes from 45% to 72% over a 7-year follow-up. GLS also has prognostic significance. GLS reduction was found to be independently associated with adverse long-term outcomes in asymptomatic diabetic patients.

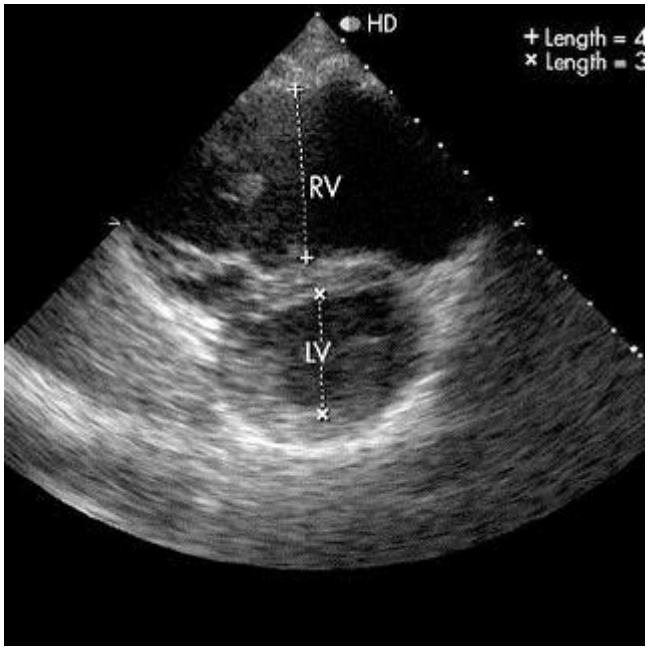
About the study

The study included patients with and without type 2 diabetes who had no symptoms and/or history of severe somatic diseases and cardiovascular disease, including hypertension, acute cerebrovascular accident, coronary heart disease, peripheral artery disease, heart failure, heart defects, or clinically significant disorders of the rhythm and conductivity of the heart.

In the first stage of the study, all patients underwent a complete physical examination, blood pressure measurement, and an electrocardiogram recording. Blood samples were taken to assess lipid profile, electrolytes, high-sensitive C-reactive protein (hsCRP), N-Terminal Pro-B Type Natriuretic Peptide (NT-proBNP), glucose, glycosylated hemoglobin (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR). Risk factors for cardiovascular complications, such as gender, age, dyslipidemia, arterial hypertension, obesity, and smoking, were also examined.

The BRUCE protocol and treadmill metabolic equivalents were used to assess silent ischemia and tolerance to physical activity. Transthoracic two-dimensional echocardiography was performed in all patients who met the inclusion and exclusion criteria, followed by an analysis of myocardial motion in different planes using speckle-tracking echocardiography.

In the second phase of the study, patients underwent the same examinations after a follow-up period of seven years. Recruitment of patients for the second phase of the study took place in 2020–2021, coinciding with the peak of the COVID-19 pandemic.



Results

120 patients of both genders, with a mean age of 57 years (ranging from 45 to 75 years), were recruited in this study. 55% of subjects were men.

The patients were categorized into two groups: patients diagnosed with type 2 diabetes and control individuals without this diagnosis. At study entry, the average duration of type 2 diabetes was 3.3 ± 2.4 years. Patients diagnosed with type 2 diabetes did not have diabetic complications. The presence and number of risk factors for coronary heart disease (arterial hypertension, dyslipidemia, obesity, smoking) did not differ between the two groups.

After a seven-year follow-up, 57 of 120 patients participated in the second phase (29 with type 2 diabetes and 28 controls). During follow-up, none of the patients developed cardiovascular complications. Also, there was no significant progression of hypertension, dyslipidemia, weight gain, obesity, smoking, or exercise capacity in either group.

At study entry, left ventricle dysfunction was detected by echocardiography in 53% of patients with type 2 diabetes and 32% of control subjects. During a 7-year follow-up, the prevalence of left ventricular dysfunction significantly increased to 61% in patients with type 2 diabetes regardless of age, dyslipidemia, and obesity. Additionally, the thickness of the interventricular septum and left ventricle posterior wall, a relative wall thickness, and the incidence of concentric hypertrophy increased significantly in patients with diabetes. In control subjects, these parameters altered insignificantly.

Patients with type 2 diabetes had significantly lower global longitudinal strain (GLS) values than the control group. During a 7-year follow-up, the proportion of patients with reduced

GLS absolute level (less than -18%) increased from 45% to 72% in this group.

These results showed that significant worsening of left ventricular dysfunction was represented by (1) first-degree diastolic dysfunction; (2) systolic dysfunction, with preserved LVEF in terms of lower global longitudinal strain (GLS); and (3) LV myocardial remodeling in the form of concentric hypertrophy.

Structural and functional echocardiographic parameters at baseline and after 7 years of follow-up according to diabetic status.

Variable	Patients with T2D		*p* Value	Patients without T2D		*p* Value
	Visit 1	Visit 2		Visit 1	Visit 2	
LVD, *n* (%)	27 (53)	18 (61)	0.004 *	28 (39)	9 (32)	0.48
LV mass index, g/m2	95 [84.1–110]	90.5 [82.0–110.5]	0.49	84.8 [73–98.3]	88.0 [84.0–100.0]	0.84
LA volume index, mL/m2	27.0 [24.2–31.1]	26.5 [23.2–33.0]	0.63	26 [23.9–27.8]	25.0 [21.0–33.0]	0.66
IVS in diastole, cm	1.2 [1.1–1.2]	1.25 [1.15–1.4]	0.046	1.0 [1.0–1.2]	1.2 [1.0–1.2]	0.06
Posterior Wall thickness, cm	1.0 [1.0–1.0]	1.1 [1.0–1.15]	0.007	0.93 [0.9–1.0]	0.9 [0.9–1.0]	0.53
Relative Wall Thickness	0.44 [0.41–0.48]	0.49 [0.45–0.53]	0.06	0.43 [0.41–0.46]	0.45 [0.43–0.49]	0.58
Concentric Hypertrophy, *n* (%)	41 (22)	15 (53)	0.025	26 (12)	5 (16)	0.15
Concentric Remodeling, *n* (%)	28 (15)	12 (42)	0.063	33 (16)	6 (20)	0.65
Transmitral E/A ratio	0.8 [0.7–0.9]	0.7 [0.6–0.9]	0.03 *	1.1 [0.9–1.2]	1.2 [0.7–1.3]	0.15
Isovolumic relaxation time, ms	91 [87–96]	83 [72–99]	0.49	77 [70–88]	74 [67–95]	0.83
Deceleration time, ms	218 [187–232]	226 [191–277]	0.05 *	181 [169–203]	183 [169–229]	0.53
Average (med/lat) e', cm/s	8.7 [7.1–9.6]	6.7 [5.6–8.7]	0.034 *	10.2 [8.3–13.6]	9.0 [8.0–12.6]	0.059
E/e'	7.2 [6.4–8.5]	8.7 [7.9–11.1]	0.017 *	6.4 [5.4–7.6]	7.0 [5.6–8.8]	0.42
Ejection Fraction, %	60 [59–62]	65 [58–79]	0.088	64 [61–66]	67 [60–71]	0.48
GLS, %	−17.6 ± 1.4	−17.2 ± 1.24	0.008 *	−19.6 ± 1.8	−19.6 ± 1.8	0.26

* statistically significant *p*-value; LVD, left ventricular dysfunction; LV, left ventricle; LA, left atrium; IVS, interventricular septum; E, early diastolic transmitral flow velocity; A, late diastolic transmitral flow velocity; e', early diastolic tissue velocity; GLS, global longitudinal strain.

Also, over the 7-year follow-up, N-Terminal Pro-B Type Natriuretic Peptide (NT-proBNP) levels increased and hsCRP levels decreased only in the diabetic group, but both marker levels remained within normal limits. NT-proBNP increase correlated with decreased GLS and LV remodeling. According to the authors, low levels of NT-proBNP indicate an earlier subclinical stage of diabetic cardiomyopathy, characterized by initial signs of diastolic dysfunction (delayed LV relaxation), a slight decrease in GLP, and initial remodeling of the LV myocardium by type of concentric hypertrophy. There were no significant changes in

laboratory parameters in the control group.

Conclusion

The authors concluded that type 2 diabetes is an independent risk factor for subclinical left ventricular dysfunction in asymptomatic patients without cardiovascular diseases. They suggested that in the absence of obvious HF signs, the early diagnosis of diabetic cardiomyopathy should include both standard and speckle-tracking echocardiography. They also suggested that these findings and other issues related to diabetic heart failure development should be evaluated in further prospective multicenter studies with larger patient populations.

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Journal Reference

Akasheva, D.U.; Utina, T.G.; Dzhioeva, O.N.; Drapkina, O.M. Subclinical Left Ventricular Dysfunction over Seven-Year Follow-Up in Type 2 Diabetes Patients without Cardiovascular Diseases. Biomedicines 2024, *12*, 2031. https://doi.org/10.3390/biomedicines12092031