Original scientific paper

# LEFT ATRIAL VOLUME INDEXATION IN PREDIABETES AND TYPE 2 DIABETES: WHY HEIGHT MATTERS

## Lavdim IBRAIMI<sup>1</sup>, Nikola JANEV<sup>1</sup>, Marija BAJDEVSKA<sup>1</sup>, Lejla SHABANI-MISINI<sup>1</sup>, Emilija ANTOVA<sup>2</sup>, Ljubica GEORGIEVSKA-ISMAIL<sup>2</sup>

Department of Internal Medicine, General Hospital of Kumanovo, North Macedonia
 Department of Cardiology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia
 \*Corresponding Author: dr.lavdim\_i@hotmail.com

#### **Abstract**

**Introduction**: Overweight and obesity are major risk factors for left atrial volume (LAV) enlargement. Echocardiographic assessment of indexed LAV is essential for accurate evaluation diastolic function and risk stratification.

**Objectives:** To assess whether indexing LAV by height and height square offers better discrimination of LAV enlargement in pts with prediabetes (PDM) and type 2 diabetes mellitus (T2DM).

**Methods:** In 52 asymptomatic patients with T2DM and PDM, we performed conventional 2D echocardiography in addition to physical examination and laboratory analysis. LAV was measured using the area/length method and indexed by body surface area (BSA; LAVi), height (LAVh), and height squared (LAVh2).

**Results:** Among patients with T2DM, 48.8% were overweight and 43.9% were obese; among those with PDM, 27.3% were overweight and 45.5% were obese. There was a significant difference in the proportion of patients classified with dilated LAV depending on the indexing method used (BSA vs. height and height squared). Linear regression analysis showed that body mass index (BMI) was independent predictor of increased LAVi in T2DM patients and of increased LAVh and LAVh2 in those with PDM.

**Conclusion**: Indexing LAV by height or height squared results in significant reclassification of LAV from normal to dilated. This suggests that the current standard indexation method (BSA) may underestimate LAV dilation and potentially overlook patients at risk of diastolic dysfunction or future adverse cardiovascular events.

Keywords: left atrial volume, echocardiography, indexing methods, prediabetes, diabetes mellitus.

## Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common endocrine disorders worldwide (*Mukhtar Y et al, 2020*). According to the International Diabetes Federation (IDF), it was estimated that in 2021, 537 million adults aged 20–79 years had diabetes, accounting for 10.5% of the global population within this age group. In contrast, in developed countries such as the United States and the United Kingdom, more than one-third of the adult population is affected by prediabetes (PDM) (*Bullard KM et al, 2013*). Overweight and/or obesity are the main risk factors for the development of T2DM. Numerous clinical studies indicate an increased relative risk of developing T2DM by approximately 4.6 times in women and 3.5 times in men with a body mass index (BMI) greater than 29.9 kg/m² compared to those with a BMI less than 24.9 kg/m² (*Field AE et al, 2001*).

The detrimental effects of T2DM on the left ventricular (LV) myocardium, specifically the presence of systolic and diastolic dysfunction detected at rest and/or during exertion, have been demonstrated in multiple clinical studies (*Kosmala W et al, 2004*). Left atrial volume (LAV) is a surrogate marker for the severity and chronicity of LV diastolic dysfunction (*Thomas L et al, 2020*). Transthoracic 2D echocardiography is the most commonly used non-invasive technique for assessing left atrial (LA) size. Current guidelines recommend indexing LAV to body surface area (BSA) (*Lang RM et al, 2015*). Furthermore, LAV indexed to BSA is considered superior

to LA area and/or LA dimension in predicting future cardiovascular (CV) events (*Tsang TS et al, 2006*).

Due to the disproportionate redistribution of adipose tissue in individuals with overweight and obesity, indexing LAV by BSA may underestimate both the presence and the extent of LA enlargement in such populations (Singh M et al, 2020; Marwick TH et al, 2025). Recent hypertension guidelines have proposed indexing LAV based on body height (Williams B et al, 2018), although this method has not yet been endorsed by echocardiographic societies (Lang RM et al, 2015; Harkness A et al, 2020). Considering that a significant portion of the population with PDM and T2DM consists of individuals who are overweight or obese, our aim is to apply the method of LAV indexing by height and height squared, in order to achieve a better discrimination of LA enlargement in patients with PDM and T2DM.

## Materials and methods

This study is designed as an analytical, observational cross-sectional study, in which 52 asymptomatic patients of both sexes diagnosed with prediabetes (PDM) or type 2 diabetes mellitus (T2DM) were recruited from the Diabetes Center at the Public Health Institution General Hospital Kumanovo.

Participants were recruited using purposive sampling based on availability. Exclusion criteria included patients with diabetes types other than T2DM, significant valvular heart disease, permanent atrial fibrillation, renal insufficiency defined as eGFR <45 ml/min/1.73 m², life-threatening comorbidities (i.e., a history of active malignancy treated with chemotherapy or radiotherapy, end-stage heart failure, severe pulmonary disease, liver cirrhosis), as well as pregnant or breastfeeding women.

Baseline assessments included clinical examinations, laboratory testing, electrocardiography, and 2D echocardiography.

Echocardiographic assessments were conducted in the echocardiography laboratory of PHI "General Hospital – Kumanovo," using a GE-Vivid 7 ultrasound machine. Following the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), internal cavity dimensions, wall thicknesses, and end-systolic and end-diastolic volumes of the left ventricle (LV) were measured. Both systolic and diastolic LV functions were evaluated. Left atrial volume (LAV), expressed in milliliters, was calculated using the area-length method, derived from apical four-chamber and two-chamber views at the end of ventricular systole, according to ASE guidelines (*Lang RM et al, 2015*). LAV was indexed to body surface area (LAVi), to body height (LAVh), and to height squared (LAVh²).

LAV enlargement was defined using the following parameters:

- 1. LAV indexed to BSA (LAVi) >34 ml/m<sup>2</sup> according to current ASE/EACVI recommendations (*Lang RM et al, 2015*);
- 2. LAV indexed to height (LAVh) >35.7 ml/m in men and >33.7 ml/m in women, based on published reference values (*Poulsen MK et al, 2010*);
- 3. LAV indexed to height squared (LAVh²) >18.5 ml/m² in men and >16.5 ml/m² in women, based on ESC/ESH hypertension guidelines and their published reference values (*Poulsen MK et al*, 2010).

Statistical analysis was performed using the SPSS software package, version 25.0 (IBM SPSS, Inc., Chicago, IL, USA). Comparisons between the two groups (PDM and T2DM) for continuous variables were conducted using the Student's t-test and/or the non-parametric Wilcoxon Signed Rank Test. For categorical variables, the Pearson Chi-square test was applied. To identify significant predictors of alternatively indexed LAV enlargement within the T2DM and PDM subgroups, linear regression analysis was performed, including independent variables

that could potentially influence LAV. For all statistical tests, a p-value  $\leq 0.05$  was considered statistically significant.

#### **Results**

The study included 52 patients of both sexes, with a mean age of  $53.42 \pm 9.00$  years and an average body mass index (BMI) of  $30.36 \pm 6.47$  kg/m², categorizing them as overweight. Of these, 41 patients (78.8%) were diagnosed with T2DM and 11 (21.2%) with PDM. The baseline characteristics of the patients are presented in Table 1. Patients with T2DM were significantly older (p=0.001) and predominantly male (p=0.006). Overweight was more common, though not significantly, in the T2DM group, while obesity was more prevalent in the PDM group. The waist-to-hip ratio was significantly higher in the T2DM group, which also showed a greater prevalence of all monitored risk factors, with dyslipidemia being statistically significant (p=0.019). Hypertension was absent in the PDM group, while both systolic and diastolic blood pressure values measured in the ambulatory setting were significantly higher among T2DM patients (p=0.0001 and p=0.017, respectively).

Table 1. Baseline clinical characteristics of 52 patients by presence/absence of T2DM

Parameter	Diabetes mellitus	PDM	n
1 at affletet	(n=41)	(n=11)	p
Age (years)	$55,44 \pm 8,32$	$45,91 \pm 7,58$	0,001
Gender (m/f) (n/%)	23(56,1)18(43,9)	1 (9,1)/10(90,9)	0,006
BMI (kg/m2)	$30,53 \pm 6,15$	$29,70 \pm 7,84$	0,707
Weight distribution by			
BMI (n/%)			
Normal	3/7,3	2/18,2	0,705
Overweight	20/48,8	3/27,3	0,703
Obesity	18/43,9	5/45,5	
Underweight	0	1/9,1	
Waist circumference (cm)	$100,24 \pm 13,43$	$92,36 \pm 14,85$	0,097
Hip circumference (cm)	$107,17 \pm 11,82$	110,18± 14,14	0,475
Waist/hip circumference	$0.93 \pm 0.73$	$0.83 \pm 0.05$	0,0001
ratio(cm)			
Risk factors (n/%)			
HTN	8/19,5	0	0,127
Smoking	18/43,9	3/27,3	0,261
Dyslipidemia	24/58,5	2/18,2	0,019
Physical activity (n/%)			
None	18/43,9	5/45,5	
Irregular	15/36,6	5/45,5	0,695
Regularly	8/19,5	1/9,1	
SBP (mmHg)	124,63± 14,37	$107,73 \pm 5,64$	0,0001
DBP (mmHg)	$75,98 \pm 8,60$	69,09± 6,64	0,017
GFR (%)	$94,87 \pm 19,55$	96,71± 22,28	0,789

PDM=prediabetes; BMI=body mass index; HTN=hypertension; SBP=systolic blood pressure; DBP=diastolic blood pressure; GFR=glomerular filtration rate.

Laboratory test results are shown in Table 2. Patients with T2DM exhibited significantly higher glycemia and HbA1c values, not only exceeding reference values but also surpassing those of

PDM patients, as expected. All other parameters were within reference ranges. However, T2DM patients had significantly higher serum creatinine and calcium, significantly lower sodium, and slightly worse lipid profiles compared to PDM patients, consistent with the significantly higher prevalence of dyslipidemia. CRP and NT-proBNP levels were also higher, though not significantly, in the T2DM group, whereas troponin levels were higher in the PDM group. Estimated GFR and thyroid function markers were nearly identical in both groups.

The results of 2D echocardiography are presented in Table 3. All patients had preserved left ventricular systolic function; however, diastolic dysfunction was observed among T2DM patients. Patients with T2DM had interventricular septal hypertrophy, significantly differing from the PDM group. LV mass indexed to BSA was within normal range for both sexes (female/male:  $95 \text{ g/m}^2 / 115 \text{ g/m}^2$ ), but LV mass indexed to height showed elevated values in both sexes across both patient groups (female/male: 47 g/m / 50 g/m).

Table 2. Baseline laboratory characteristics in 52 patients stratified by presence/absence of T2DM.

Parameter	Diabetes mellitus	PDM	n	
1 at afficier	(n=41)	(n=11)	p	
Glucose (mmol/L)	$8,05 \pm 2,74$	$5,05 \pm 0,44$	0,001	
HbA1c (%)	$6,45 \pm 0,93$	$5,43 \pm 0,33$	0,001	
Insulin (µIU/mL)	$16,23 \pm 17,62$	$13,02 \pm 9,28$	0,581	
Urea (mmol/L)	$5,05 \pm 1,53$	$4,48 \pm 1,77$	0,290	
Creatinine (mmol/L)	$68,82 \pm 14,94$	$57,86 \pm 14,17$	0,034	
Sodium (mmol/L)	$138,41 \pm 1,76$	$139,82 \pm 2,78$	0,045	
Potassium (mmol/L)	$4,47 \pm 0,33$	$4,44 \pm 0,29$	0,788	
Calcium (mmol/L)	$2,46 \pm 0,09$	$2,39 \pm 0,07$	0,031	
AST (IU/L)	$24,35 \pm 11,70$	$20,07 \pm 9,14$	0,268	
ALT (IU/L)	$32,45 \pm 27,68$	$24,07 \pm 16,62$	0,345	
Total cholesterol	$4,74 \pm 1,10$	$5,02 \pm 1,10$	0,453	
(mmol/L)				
LDL-C (mmol/L)	$3,40 \pm 0,89$	$3,23 \pm 0,90$	0,573	
HDL-C (mmol/L)	$1,05 \pm 0,27$	$1,26 \pm 0,39$	0,047	
Triglycerides (mmol/L)	$2,43 \pm 1,53$	$1,67 \pm 1,10$	0,132	
CRP (mg/L)	$4,05 \pm 4,62$	$2,83 \pm 2,41$	0,405	
Troponin (ng/L)	$0,20 \pm 0$	$0,22 \pm 0,06$	0,053	
Nt-proBNP (pg/ml)	66,20± 81,98	$44,20 \pm 25,75$	0,410	
TSH (mmol/L)	$3,49 \pm 3,45$	3,07± 2,29	0,706	
FT4 (mmol/L)	1,28± 0,22	1,28± 0,29	0,946	
GFR (%)	$94,87 \pm 19,55$	96,71± 22,28	0,789	

PDM=prediabetes; HbA1c=glycated hemoglobin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; CRP=C-reactive protein; GFR=glomerular filtration rate.

Measurements of left atrial (LA) dimensions and volumes are presented in Table 4. LA diameter was significantly greater in patients with T2DM compared with those with PDM (p=0.018), however, this difference was no longer significant when indexed to BSA. Both non-indexed LAV and LAV indexed to BSA and height (LAVh) were significantly higher in T2DM patients compared to those with PDM (p=0.028, p=0.052, and p=0.046, respectively). LAV indexed to height squared (LAVh²) was also higher in T2DM patients, though the difference was marginally significant (p=0.095).

*Table 3.* Echocardiographic assessment of systolic and diastolic function in 52 patients stratified by presence/absence of T2DM

Parameter	Diabetes mellitus	PDM	n
rarameter	(n=41)	(n=11)	p
LVIDd (mm)	$47,34 \pm 4,13$	$46,82 \pm 4,66$	0,740
LVIDs (mm)	$31,02 \pm 3,31$	$29,91 \pm 3,78$	0,388
IVSd (mm)	$11,00 \pm 1,39$	$9,64 \pm 0,80$	0,0001
LVPWd (mm)	$9,34 \pm 1,06$	$8,55 \pm 0,93$	0,026
LVEF (%)	$65,22 \pm 4,88$	$67,82 \pm 3,60$	0,064
SVi (ml/2)	$36,50 \pm 6,83$	$32,70 \pm 6,24$	0,097
COi (L/min/m2)	$2,86 \pm 0,66$	$2,54 \pm 0,43$	0,071
LVMi (g/m2)	$86,46 \pm 14,53$	$78,17 \pm 20,28$	0,227
LVMh (g/m)			
Female	$93,64 \pm 21,95$	$87,31 \pm 21,44$	0,467
Male	$108,44 \pm 15,68$	104,85	0,826
E/A	$0.95 \pm 0.29$	$1,10 \pm 0,25$	0,147
DT (ms)	$202,20 \pm 34,94$	$181,00 \pm 37,42$	0,111
IVRT (ms)	$95,12 \pm 17,02$	$89,55 \pm 11,03$	0,310
e's (cm/s)	$7,70 \pm 1,70$	$9,63 \pm 1,68$	0,004
e'l (cm/s)	$9,68 \pm 2,24$	$10,63 \pm 2,29$	0,237
E/e's	$8,80 \pm 2,10$	$7,45 \pm 1,42$	0,020
E/e'1	$7,06 \pm 1,91$	$6,80 \pm 1,24$	0,588
E/e' average	$7,76 \pm 1,79$	$7,09 \pm 1,28$	0,173

LVIDd= left ventricular internal diameter in diastole; LVIDs= left ventricular internal diameter in systole; LVEF=left ventricular ejection fraction; SVi= stroke volume indexed to body surface area; COi=cardiac output indexed to body surface area; E= early diastolic transmitral flow velocity; A= late diastolic transmitral flow velocity; DT=deceleration time; IVRT=isovolumic relaxation time; E0 diastolic tissue velocity measured at the mitral annulus using tissue Doppler imaging - E1 septal wall, E1 - E1 lateral wall.

Table 4. Echocardiographic LA dimension and volumes in 52 patients stratified by presence/absence of T2DM

Parameter	Diabetes mellitus	PDM	n
1 at afficier	(n=41)	(n=11)	p
LA (mm)	$35,78 \pm 2,61$	$33,64\pm2,50$	0,018
LAi (mm/m2)	$18,15 \pm 1,53$	$18,03 \pm 2,20$	0,829
LAV (ml)	60,11±14,04	$51,37 \pm 9,89$	0,028
LAVi (ml/m2)	30,25±5,80	27,04±4,24	0,053
Female	29,11±4,99	27,05±4,47	0,289
Male	31,14±6,32	26,9	0,517
LAVi dilatation (n/%)	12/29,3	0	0,038
Female	4/22,2	0	0,149
Male	8/34,8	0	0,667
LAVh (ml/m)	35,83±7,99	31,32±5,72	0,046
Female	34,89±8,41	31,09±5,98	0,221
Male	37,57±7,5	33,56	0,707
LAVh dilatation (n/%)	24/58,5	4/36,4	0,166
Female	12,66,7	4/40,0	0,167

Male	12/52,2	0	0,500
LAVh2 (ml/m2)	21,45±4,94	19,14±3,55	0,095
Female	21,93±5,55	19,11±3,74	0,164
Male	21,06±4,49	19,47	0,723
LAVh2 dilatation (n/%)	33/80,5	9/81,8	0,647
Female	16/88,9	8/80,0	0,452
Male	17/73,9	1/100	0,750

 $\overline{LA}$ =left atrium;  $\overline{LA}$ i= left atrial diameter indexed to body surface area; LAVi = maximum left atrial volume indexed to body surface area; LAVh = maximum left atrial volume indexed to body height; LAVh2 = maximum left atrial volume indexed to height squared.

The percentage distribution of LAV dilation based to alternative indexing methods is visualized in Figure 1.

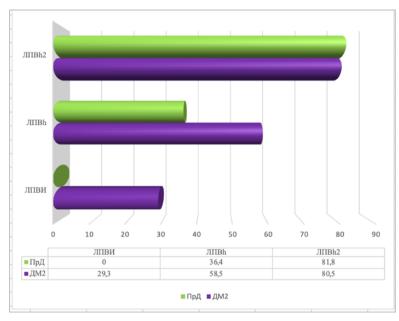


Figure 1. The percentage distribution of LAV dilatation based to alternative indexing methods.

Non-parametric comparisons of LAV dilation prevalence in T2DM versus PDM by sex (due to sex-specific cutoff values) are shown in Table 5. Analysis was not performed for males in the PDM group due to the presence of only one male subject. In both sexes and both groups, indexing by height and especially height squared more frequently identified the presence of LAV dilation, highlighting the clinical importance of alternative indexing in these populations.

*Table 5.* Non-parametric comparison of the prevalence of LAV dilatation based in different indexing methods in patients (n=52) stratified by sex.

	Diabetes mellit (n=41)	tus	Prediabetes (n=11)				
	Male (n=23)	Female (n=18)	Male (n=1)	Female (n=10)			
LAVi vs. LAVh	p=0,102	p=0,005	-	0,046			
LAVi vs.LAVh2	p=0,003	p=0,001	-	0,005			
LAVh vs.LAVh2	p=0,025	p=0,046	-	0,046			

 $LAVi = maximum\ left\ atrial\ volume\ indexed\ to\ body\ surface\ area;\ LAVh = maximum\ left\ atrial\ volume\ indexed\ to\ height;\ LAVh2 = maximum\ left\ atrial\ volume\ indexed\ to\ height\ squared.$ 

In order to identify significant predictors of increased left atrial volume (LAV) based on alternative indexing methods in the T2DM and PDM subgroups, we performed linear regression analysis, including the following independent variables: age, sex, BMI, presence of diabetes, dyslipidemia, and hypertension. The results of the analysis are presented in Tables 6–9. Among patients with T2DM, the analysis revealed no significant predictors for LAV indexed to body surface area (LAVi). In contrast, among patients with PDM, age emerged as the only independent predictor of LAVi, with each additional year of age associated with an increase in LAVi of  $0.432 \text{ ml/m}^2$  ( $\beta = 0.432, 95\%$  CI: 0.164-0.701, p = 0.005) (Table 6).

*Table 6.* Linear regression analysis of predictors for LAVi in PDM patients **Coefficients**<sup>a,b</sup>

		Unstandardize	d Coefficients	Standardized Coefficients			95.0% Confider	nce Interval for 3
Model		В	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	7,201	5,518		1,305	,224	-5,281)	19,683
	Возраст	,432	,119	,772	3,640	.005	.164	.701

a. Dependent Variable: ЛПВИмакс

In the analysis aimed at identifying predictors of LAV indexed to body height (LAVh), the results showed that for every 1 kg/m<sup>2</sup> increase in BMI, LAVh increased by 0.640 ml/m<sup>2</sup> ( $\beta$ =0,640, 95%CI 0,274-1,006, p=0,001) (Table 7).

*Table 7.* Linear regression analysis of predictors of LAVh in patients with T2DM **Coefficients**<sup>a,b</sup>

		Unstandardize	Standardized Coefficients			95.0% Confide	nce Interval for 3	
Model		В	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	16,289	5,635		2,891	,006	4,891	27,688
	BMI	,640	,181	,493	3,537	,001	,274	1,006

a. Dependent Variable: ЛПВh

The analysis for patients with prediabetes showed that both age and BMI were significant predictors of LAVh. Specifically, for each additional year of age, LAVh increased by 0.533 ml/m ( $\beta$ =0.533, 95% CI: 0.249–0.818, p=0.003), and for each unit increase in BMI (kg/m²), LAVh increased by 0.452 ml/m ( $\beta$ =0.452, 95% CI: 0.177–0.727, p=0.005) (Table 8).

*Table 8.* Linear regression analysis of predictors of LAVh in patients with PDM. Coefficients<sup>a,b</sup>

		Unstandardize	Standardized Coefficients			95.0% Confide	nce Interval for B	
Model		В	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	9,121	8,986		1,015	,337	-11,207)	29,449
	Возраст	,484	,193	,640	2,501	,034	,046	,921
2	(Constant)	-6,591)	7,046		-,935)	,377	-22,840)	9,658
	Возраст	,533	,123	,706	4,325	,003	,249	,818
_	BMI	,452	,119	,619	3,791	,005	,177	,727

а. Dependent Variable: ЛПВh

The analysis limited to patients with T2DM showed that BMI was the only predictor of left atrial volume indexed to height squared (LAVh²). Specifically, for each 1 kg/m² increase in BMI, LAVh² increased by 0.471 ml/m² ( $\beta$ =0.471, 95% CI: 0.261–0.682, p=0.0001) (Table 9).

b. Selecting only cases for which ДМтип2 = Нема

b. Selecting only cases for which ДМтип2 = Има

b. Selecting only cases for which ДМтип2 = Нема

Table 9. Linear regression analysis of predictors of LAVh<sup>2</sup> in patients with T2DM **Coefficients**<sup>a,b</sup>

		Unstandardize	d Coefficients	Standardized Coefficients			95.0% Confidence Interval for B		
Model		В	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	
1	(Constant)	7,064	3,241		2,180	,035	,508	13,620	
	RMI	.471	.104	.587	4.526	.000	.261	.682	

a. Dependent Variable: ЛПВh2

The analysis limited to patients with prediabetes (PDM) showed that age and BMI were predictors of left atrial volume indexed to height squared (LAVh²). Specifically, for each additional year of age, LAVh² increased by 0.326 ml/m² ( $\beta$  = 0.326, 95% CI: 0.135–0.517, p = 0.004), and for each 1 kg/m² increase in BMI, LAVh² increased by 0.270 ml/m² ( $\beta$  = 0.270, 95% CI: 0.085–0.454, p = 0.010) (Table 10).

*Table 10.* Linear regression analysis of predictors of LAVh<sup>2</sup> in patients with PDM **Coefficients**<sup>a,b</sup>

		Unstandardize	d Coefficients	Standardized Coefficients			95.0% Confide	nce Interval for 3
Model		В	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	5,522	5,612		,984	,351	-7,172)	18,216
	Возраст	,297	,121	,634	2,457	,036	,024	,570
2	(Constant)	-3,850)	4,733		-,813)	,440	-14,766)	7,065
	Возраст	,326	,083	,697	3,940	,004	,135	,517
	BMI	,270	,080	,596	3,367	,010	,085	,454

a. Dependent Variable: ЛПВh2

### **Discussion**

In our study, increased LAVi was observed in 29.3% of patients with T2DM, which is consistent with findings by Poulsen et al, who reported moderate to severe LA enlargement (LAVi >32 ml/m²) in approximately one-third of their study population of 305 subjects with T2DM. The majority of studies published in the last decade investigating LA remodeling in T2DM patients have confirmed the presence of LA enlargement when using appropriate indexing methods (*Kadappu KK et al, 2012; Huang G et al, 2010; Zapolski T et al, 2013*). Individuals with PDM also show changes in LA volume and function, although these may be less pronounced compared to those with diabetes (*Eyyupkoca F et al, 2022*).

Davies et al, noted that indexing LAV to body surface area (BSA) may underestimate both the presence and extent of LA enlargement in overweight and obese populations. For this reason, the 2018 ESC/ESH hypertension guidelines (*Williams B et al, 2018*), supported by numerous clinical studies (*Davies et al, 2022; Gulsin GS et al, 2019; Stritzke J et al, 2009*), recommended the use of alternative indexing methods based on height, and particularly height squared, as potentially more appropriate for LAV assessment.

Given that most of the participants in our study with T2DM (92.7%) and PDM (72.8%) were overweight or obese, we applied alternative indexing methods based on height and height squared to assess LA enlargement. These methods, especially height squared, most effectively identified LA enlargement, particularly among female patients (LAVh2: 88.9% vs. LAVi: 22.2%, p=0.001), which is of great relevance for this population.

Airale et al, evaluated 441 patients with essential hypertension, comparing LA enlargement prevalence using both BSA and height squared indexing methods. They reported nearly double the prevalence using height squared indexing compared to BSA (50.6% vs. 23.4%, p < 0.001), with significantly higher prevalence in women (p < 0.001), consistent with our findings.

b. Selecting only cases for which ДМтип2 = Има

b. Selecting only cases for which ДМтип2 = Нема

Similarly, the study by Volkanoska et al. which applied alternative indexing of LAV in 127 overweight and obese individuals, demonstrated significant reclassification from normal to dilated LA when height squared was used, with the greatest reclassification observed among women and those with severe obesity.

Our linear regression analysis of alternatively indexed LAV revealed that in T2DM patients, BMI was a significant independent predictor of increased LAVh and LAVh² ( $\beta$  = 0.640; 95% CI: 0.274–1.006; p = 0.001) and ( $\beta$  = 0.471; 95% CI: 0.261–0.682; p = 0.0001), respectively. Consistent with our findings, the MONICA registry identified LA size as a key measure in chronic LV diastolic dysfunction and found a strong association with BMI, but a weaker association with age, and no association with arterial hypertension (*Stritzke J et al, 2009*). Similarly, Takeda et al. identified BMI—not hypertension—as a significant predictor of heart failure with preserved LV ejection fraction among T2DM patients.

In a large cohort study of 17,454 individuals with varying body weights, which evaluated the effectiveness of different LAV indexing methods in predicting mortality and future cardiovascular (CV) events, Davies et al. concluded that: in a significant number of individuals, using height squared instead of BSA led to reclassification from normal to enlarged LA size; in patients with extreme obesity, BSA-indexed LAV failed to predict mortality and future CV events compared to other methods; LAVh² was the most effective predictor of mortality and CV outcomes; and reclassification exposed a high-risk group previously unrecognized using standard indexing.

These findings suggest that the conventional practice of indexing LA volume to BSA may underestimate LA enlargement and potentially fail to identify patients at elevated risk.

## **Study limitations**

Although the 2015 ASE guidelines for quantification of cardiac chambers (*Lang RM et al, 2015*), recommend the biplane method of disks (modified Simpson's rule) as the preferred technique for LAV assessment, our study used the area-length method as an alternative recommended method (*Kosmala W et al, 2004*). The primary limitation of our study is the relatively small sample size, particularly in the PDM group, which may impact the results of comparative analyses.

## Conclusion

Type 2 diabetes mellitus and PDM are associated with alterations in LA volume and function. Indexing LAV by body height and height squared leads to significant reclassification from normal to dilated in both T2DM and especially PDM patients. In our study, a higher prevalence of LA enlargement was identified using height squared indexing compared to BSA, suggesting that height squared may be a more sensitive method for detecting LA enlargement in overweight and obese populations with T2DM and PDM.

## References

- [1] Airale L, Paini A, Ianniello E, et al. Left atrial volume indexed for height2 is a new sensitive marker for subclinical cardiac organ damage in female hypertensive patients. *Hypertens Res.* 2021; 44: 1-8.
- [2] Bullard KM, Saydah SH, Imperatore G, et al. Secular changes in U.S. prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999-2010. *Diabetes Care*. 2013;36(8):2286-93.
- [3] Davis E, Crousillat DR, He W, et al. Indexing left atrial volumes. Alternative indexing methods better predict outcomes in overweight and obese populations. *J Am Coll CardiolImg*. 2022; 15:989-97.

- [4] Eyyupkoca F, Hidayet Ş, Özyalın F, et al. Evaluation of left atrial volume and functions by 3D echocardiography in patients with prediabetes and investigation of its correlation with NT-pro ANP levels. *Northwestern Med J.*2022;2(1):40-50.
- [5] Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch. Intern. Med.* 2001; 161:1581–86.
- [6] Gulsin GS, Athithan L, McCann GP. Diabetic cardiomyopathy: prevalence, determinants and potential treatments. *Ther Adv Endocrinol Metab*. 2019 Mar 27; 10:2042018819834869.
- [7] Harkness A, Ring L, Augustine DX, et al. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography. *Echo Research Practice*. 2020;7: G1–G18.
- [8] Huang G, Zhang L, Xie M, et al. Assessment of left atrial function in diabetes mellitus by left atrial volume tracking method. *J Huazhong Univ Sci Technolog Med Sci*. 2010; 30:819–23.
- [9] Kadappu KK, Boyd A, Eshoo S, et al. Changes in left atrial volume in diabetes mellitus: more than diastolic dysfunction? *Eur Heart J Cardiovasc Imaging*. 2012; 13:1016–23.
- [10] Kosmala W, Colonna P, Przewlocka-Kosmala M, et al. Right Ventricular Dysfunction in Asymptomatic Diabetic Patients. *Diabetes Care* 1 November 2004; 27: 2736–38.
- [11] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015; 28:1–39.
- [12] Marwick TH, Gillebert TC, Aurigemma G, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *Eur Heart J Cardiovasc Img*. 2015; 16:577–605.
- [13] Mukhtar Y, Galalain A.M, Yunusa U.M. A modern overview on diabetes mellitus: a chronic endocrine disorder. *Europian Journal of biology* 2020; 5:1-14.
- [14] Poulsen MK, Henriksen JE, Dahl J, Johansen A, Gerke O, Vach W et al. Left ventricular diastolic function in type 2 diabetes mellitus: prevalence and associationwith myocardial and vascular disease. *Circ Cardiovasc Imaging* 2010; 3:24–31.
- [15] Singh M, Sethi A, Mishra AK, et al. Echocardiographic imaging challenges in obesity: guideline recommendations and limitations of adjusting to body size. *J Am Heart Assoc*. 2020; 9: e014609.
- [16] Stritzke J, Markus MRP, Duderstadt S, et al. The aging process of the heart: Obesity Is the main risk factor for left atrial enlargement during aging. The MONICA/KORA (Monitoring of Trends and Determinations in Cardiovascular Disease/ Cooperative Research in the Region of Augsburg) Study. *J Am Coll Cardiol*. 2009; 54:1982-9
- [17] Takeda Y, Sakata Y, Mano T, et al. Competing risks of heart failure with preserved ejection fraction in diabetic patients. *Eur J Heart Fail* 2011; 13:664–69.
- [18] Thomas L, Muraru D, Popescu BA, et al. Evaluation of Left Atrial Size and Function: Relevance for Clinical Practice. *J Am Soc Echocardiogr*. 2020 Aug;33(8):934-52.
- [19] Tsang TS, Abhayaratna WP, Barnes ME, et al. prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol*. 2006;471018–23.
- [20] Volkanoska-Ilievska C, Andova V, Georgievska-Ismail Lj. Frequency of left atrial enlargement according to different modes of indexing in overweight and obese individuals. *April* 2023;44(1):97-103.
- [21] Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension. *Eur Heart J.* 2018; 39:3021–3104
- [22] Zapolski T, Wysokiński A. Left atrium volume index is influenced by aortic stiffness and central pulse pressure in type 2 diabetes mellitus patients: a hemodynamic and echocardiographic study. *Med Sci Monit*. 2013; 19:153–64.