RESEARCH

Association of microalbuminuria with left ventricular dysfunction in type 2 diabetes mellitus

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Abstract

Background: The prevalence of diabetes mellitus is on rising trend in developing countries like India. In type 2 diabetes patients, albuminuria has been shown to predict development of dysfunction in other organ systems such as kidneys, nervous system, and retina and increase risk of cardiovascular (CV) morbidity and mortality. In this study, we plan to assess association of microalbuminuria with left ventricular dysfunction in type 2 diabetes mellitus.

Results: This cross-sectional study was conducted among 100 type 2 diabetes mellitus patients attending a tertiary care hospital in Gujarat, Western India. Based on urine albumin excretion status, they were divided in two groups of 50 each—normoalbuminuric and microalbuminuric patients. The mean FBS, PPBS, and HbA1c level was significantly lower in normoalbuminuric group compared to microalbuminuric group. There was an increase in cholesterol, triglyceride, VLDL, and LDL levels and decrease in HDL levels in microalbuminuric group as compared to normoalbuminuric group. Multivariate logistic regression analysis revealed that increase in age and a decrease in E/ A ratio in patients with microalbuminuria was significantly associated with left ventricular diastolic dysfunction (LVDD).

Conclusion: The presence of microalbuminuria is associated with increased likelihood of LVDD in type 2 diabetes patients. Increase in age and decrease in E/A ratio show direct and independent association with LVDD in normotensive diabetic patients with microalbuminuria. Therefore, diabetes patients who have microalbuminuria should be regularly (or more frequently) evaluated for development of LVDD using Echocardiography. This can allow early identification of myocardial diastolic dysfunction.

Keywords: Diabetes, IHD, CAD, CHD, Microalbuminuria

Background

The prevalence of diabetes is increasing rapidly all over the globe at an alarming rate. Since last 30 years, the status of diabetes has changed from being considered as a mild disorder of the elder people to one of the major causes of morbidity and mortality affecting the young and middle-aged people [1].

Scientific studies from various parts of India have reported the rising prevalence of lifestyle-related diseases such as type 2 diabetes mellitus (T2DM), the metabolic syndrome, hypertension, and ischemic heart disease (IHD), frequently in association with increased body weight or obesity [2].

Patients with diabetes who are at increased risk of Diabetic Kidney Disease (DKD) include those with poor glycemic control, longer duration of diabetes, hypertension, retinopathy, raised proteinuria levels, non-White race, family history of hypertension, and cardiovascular diseases (CVDs) [3]. The prevalence of microalbuminuria in hypertensive and diabetic populations varies from 10 to 40%. However, microalbuminuria may also be found in seemingly healthy individuals (5 to 7%) [4]. In the

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study by Adler AI et al., the prevalence of microalbuminuria in patients with diabetes and without known kidney disease was 40% [5]. The transition from normoalbuminuria to microalbuminuria is frequent despite adequate treatment which is about 2 to 2.5% per year [6].

Albuminuria has been shown to predict cardiovascular (CV) morbidity and mortality in individuals with both type 1 and type 2 diabetes mellitus (DM) independent of conventional CV risk factors including age, arterial hypertension, and hypercholesterolemia [7]. The mechanism of the association of albuminuria with cardiac events is not clear, it is possible that the vascular changes that lead to renal dysfunction, may be present in the vasculature of the heart and thus contribute to cardiac dysfunction. One of the earliest markers of vascular changes, also known as endothelial dysfunction, is the occurrence of microalbuminuria [8]. The presence of microalbuminuria in itself is associated with increased incidence of coronary heart disease (CHD) mortality in diabetic patients [9].

In addition, the existence of diabetic cardiomyopathy, characterized by systolic and diastolic dysfunction, may also contribute to the increased CV mortality seen in diabetic patients [5]. However, whether albuminuria is also associated with abnormal intrinsic left ventricular (LV) myocardial function independent of other confounding factors remains unclear.

Moreover, recent investigations have found that LV longitudinal myocardial systolic dysfunction, rather than LV diastolic dysfunction, should be considered the first marker of a preclinical form of diabetic cardiomyopathy in DM patients with preserved left ventricular ejection fraction without overt heart failure [10]. However, what factors contribute to impairment of LV systolic longitudinal myocardial function in type 2 diabetes patients is not fully understood.

Therefore, in this study, we assess the association of microabuminuria with LV dysfunction in type 2 diabetes mellitus and the other factors which may increase the likelihood of development of LVD in type2 diabetic patients.

Methods

This cross-sectional study was conducted in the medicine department of a tertiary level hospital over a period of 2 years. All adults >= 18 years old diagnosed with type 2 diabetes mellitus were included in the study. Patients with hypertension, type 1 diabetes mellitus, ischemic heart disease, heart failure secondary to valvular heart disease, steroids treatment, pregnant women, and cirrhosis of liver were excluded from the study.

Based on formula, $n = [z^2 p(1 - p)]/d^2$; Z = table value of alpha error from standard normal distribution table (0.95), power (p) = 80%, precision error of estimation (d) = 5.5% the calculated sample size was 100 (50 patients per group). All patients attending the diabetes OPD were included till required sample size of 100 was achieved including 50 type 2 DM patients with normoalbuminuria and 50 type 2 DM patients with microalbuminuria.

The study was done after due permission from the Institutional Ethics Committee and Scientific Review Board. Patients were enrolled in study after obtaining written informed consent including consent of publication. Once the patients were enrolled for the study, a thorough history and physical examination was done as per proforma.

Detail such as age, sex, weight, age of diagnosis, duration of treatment for type 2 diabetes mellitus, and detail history of clinical features were recorded on pre designed proforma. All investigations related to study were done as per the diagnostic workup followed in a hospital.

Weight was determined in kilograms (kg) using a weighing scale, height using a stadiometer, and waist and hip circumferences (WC and HC) were measured in centimeters (cm) using a tape measure. Body mass index (BMI), body surface area (BSA), and waist:hip ratio (WHR) were calculated.

A two-step microalbuminuria screening process was conducted. Combur 10 test strip (Roche Diagnostics, Mannheim, Germany), a visual colorimetric semi-quantitative urine test strip, was used to test for protein, blood, nitrite, and leucocyte levels. If all were absent then detection of microalbuminuria was performed on the same urine sample. Microalbuminuria was determined using Micral test strips, an optically read semi-quantitative immunoassay method (Roche Diagnostics, Australia) with a sensitivity and specificity of 80 and 88%, respectively. Microalbuminuria was considered to be present when the two urine samples collected one month apart, produced a reaction color corresponding to 20 mg/l or more. Based on this result the normoalbuminuria/microalbuminuria status of the subject was determined.

Echocardiographic examination was performed with the patient in the left lateral decubitus position using a Hewlett-Packard Sonos 4500 echocardiography machine with a 3.5-MHztransducer. Measurements were taken under two-dimensional guided M-mode, as recommended by the American Society of Echocardiography (ASE).

Data management

Data was entered in Microsoft Excel worksheet and then analyzed using SPSS software version 20.0. Continuous variables were presented as mean ± SD or median (IQR)

for non-normally distributed data. Categorical variables were expressed as frequencies and percentages.

The comparison of normally distributed continuous variables between the groups was performed using Student's *t* test. Nominal categorical data between the groups was compared using chi-squared test and Fisher's exact test. Multivariate analysis was done to determine the independent predictors of left ventricular diastolic dysfunction (LVDD) using logistic regression method. For all statistical tests, a *p* value less than 0.05 was taken to indicate a significant difference.

Results

Majority of the patients in normoalbuminuric group (44%) and microalbuminuric group (36%) were from the age group of 51–60 years. The mean age of the patients between two groups was comparable and the difference was statistically not significant ($p > 0.05$). The number of males in both the groups was (54% and 58%) respectively while female patients constituted 46% and 42% respectively of the study population. Only 6% of patients were obese in both groups. The mean duration of diabetes in normoalbuminuric group was 4.98 ± 3.61 years while it was 7.08 ± 2.88 years in microalbuminuric group, and this difference was found to be statistically significant (Table 1).

The mean fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and HbA1c levels were significantly lower in normoalbuminuric group compared to microalbuminuric group. The mean creatinine level was comparable between normoalbuminuric group and microalbuminuric group while mean eGFR was significantly higher and mean urine albumin-to-creatinine ratio (UACR) was significantly lower in normoalbuminuric group compared to microalbuminuric group. There was an increase in cholesterol, triglyceride, VLDL, and LDL levels and decrease in HDL levels in microalbuminuric group as compared to normoalbuminuric group but the difference was not statistically significant.

Left ventricular internal dimension in diastole (LVIDd), left ventricular end-diastolic volume (LVEDV), early (E) wave, and E/A ratio were significantly higher in normoalbuminuric patients compared to microalbuminuric patients. Whereas, atrial (A) wave and isovolumic relaxation time (IVRT) were significantly lower in normoalbuminuric patients compared to microalbuminuric patients. Other echocardiography parameters were comparable between the groups (Table 2).

The multivariate logistic regression analysis showed that increase in age and decrease in E/A ratio in patients with microalbuminuria were independent predictors of left ventricular diastolic dysfunction (LVDD) (Table 3).

Discussion

Our patients in the study were predominantly from the age group of 51–60 years and the difference in gender distribution of patients between the two groups was insignificant. This patient profile in our study is similar to

Table 1 Demographic profile of study participants (*n* = 100)

Variables	Normoalbuminuric N = 50		Microalbuminuric N = 50		p value
	N	%	N	%	
Age (years)					
21–30 years	3	6%	4	8%	> 0.05
31–40 years	6	12%	7	14%	
41–50 years	11	22%	10	20%	
51–60 years	22	44%	18	36%	
> 60 years	8	16%	11	22%	
Gender					
Male	25	54%	29	58%	> 0.05
Female	23	46%	21	42%	
BMI					
Normal (18.5–24.9)	33	66%	32	64%	> 0.05
Overweight (25–29.9)	14	28%	15	30%	
Obese (≥ 30)	3	6%	3	6%	
Duration of DM					
0–2 years	17	34%	4	8%	< 0.05
3–5 years	9	18%	7	14%	
6–9 years	18	36%	30	60%	
≥ 10 years	6	12%	9	18%	

Table 2 Comparison of blood glucose levels, renal profile, lipid profile, and echocardiography parameters in study population ($n = 100$)

Parameter	Normoalbuminuric		Microalbuminuric		*p* value
	Mean	SD	Mean	SD	
FBS (mg/dl)	105.87	8.52	153.75	12.24	**< 0.05**
PPBS(mg/dl)	169.41	16.98	222.22	56.22	**< 0.05**
HbA1c (%)	7.02	0.55	9.38	0.89	**< 0.05**
Creatinine (mg/dl)	1.52	0.83	1.44	0.68	> 0.05
eGFR (ml/min/1.73 m^2)	140.98	39.06	83.01	14.18	**< 0.05**
UACR (μg/mg)	19.02	5.55	217.99	109.57	**< 0.05**
Cholesterol (mg/dl)	162.94	24.40	167.64	22.42	> 0.05
Triglyceride (mg/dl)	143.58	39.49	148.20	28.72	> 0.05
VLDL (mg/dl)	29.40	6.45	30.60	5.06	> 0.05
LDL (mg/dl)	100.29	26.25	101.89	21.33	> 0.05
HDL (mg/dl)	35.60	9.32	34.36	10.23	> 0.05
LVIDd (mm)	40.43	6.76	36.81	3.94	**< 0.05**
LVIDs (mm)	25.69	1.45	26.42	2.33	> 0.05
LVEDV (ml)	76.98	4.64	68.18	4.48	**< 0.05**
LVESV (ml)	26.28	2.13	25.83	2.02	> 0.05
Ejection fraction (%)	62.44	2.12	61.92	2.22	> 0.05
Early (E) wave (cm/s)	0.65	0.17	0.59	0.13	**< 0.05**
Atrial (A) wave (cm/s)	0.69	0.15	0.74	0.12	**< 0.05**
E/A ratio	0.99	0.33	0.81	0.20	**< 0.05**
DT (ms)	197.54	20.83	194.30	19.67	> 0.05
AT (ms)	85.96	8.56	83.72	10.04	> 0.05
IVRT (ms)	84.54	5.28	91.54	6.29	**< 0.05**

FBS fasting blood sugar, *PPBS* post-prandial blood sugar, *UACR* urine albumin-to-creatinine ratio, *LVIDd* left ventricular internal dimension in diastole, *LVIDs* left ventricular internal dimension in systole, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *DT* deceleration time, *AT* acceleration time, *IVRT* isovolumic relaxation time

Table 3 Multivariate analysis showing association of various parameters among microalbuminuria with LVDD ($n = 50$)

Parameters	OR	95% CI	*p* value
Age (years)	1.70	1.15–2.50	**< 0.05**
LVIDd (mm)	1.23	1.00–1.51	> 0.05
LVIDs (mm)	1.17	0.45–2.85	> 0.05
LVEDV (ml)	1.8	0.31–1.39	> 0.05
LVESV (ml)	0.81	0.61–1.09	> 0.05
Ejection fraction (%)	1.34	1.04–1.96	> 0.05
Early (E) wave (cm/s)	1.39	0.85–2.31	> 0.05
Atrial (A) wave (cm/s)	0.97	0.82–1.16	> 0.05
E/A ratio	1.45	1.21–1.75	**< 0.05**
DT (ms)	0.80	0.59–1.09	> 0.05
AT (ms)	0.75	0.54–1.03	> 0.05
IVRT (ms)	1.10	0.99–1.22	> 0.05

the studies of Kanwar BS et al., Shogade TT et al., and Mohamed GA et al, where they have studied myocardial structural and functional changes in Diabetic patients [11–14].

There was significant difference in mean duration of diabetes between microalbuminuric and normoalbuminuric groups in our study, which is comparable to the studies of Kanwar BS et al. and Shogade TT et al. [11, 12].

In the present study, the mean fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and HbA1c level was significantly lower in normoalbuminuric group compared to microalbuminuric group. This finding is concordant to the study by Kanwar BS et al. [11].

Proteinuria as an important risk marker of CVS mortality in general population is already well established by the Framingham study [14]. In recent times, several important studies like the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study, Prevention of Renal and Vascular End stage disease (PREVEND) study, and Nord-Trøndelag Health Study (HUNT) have showed that like diabetes,

Mehta *et al. The Egyptian Journal of Internal Medicine* (2021) 33:27

Page 5 of 6

presence of microalbuminuria is predictive of CVS events [15–17]. Indeed, some studies have suggested that the presence of microalbuminuria increases the relative risk of an adverse CVS event similar to the presence of hypercholesterolemia [15]. The presence of microalbuminuria in patients should therefore be considered a risk factor for CVD, on the same scale as high levels of blood pressure, cholesterol, and blood glucose [18].

It was observed in our study that there was an increase in cholesterol, triglyceride, VLDL, and LDL levels and decrease in HDL levels in microalbuminuric group as compared to normoalbuminuric group. Shogade TT et al. noted similar observations in their study [12].

Echocardiography parameters like left ventricular internal dimension in systole (LVIDs), left ventricular end-systolic volume (LVESV), ejection fraction, deceleration time (DT), and acceleration time (AT) were comparable between the groups in our study. This is in concordance to the studies of Kanwar BS et al., Shogade TT et al., and Swoboda PP et al. [11, 12, 19].

LVH too is an independent risk factor for CAD, sudden cardiac death, and heart failure. This is particularly significant as LVH is also associated with various signs and promoters of metabolic dysfunction, such as central obesity, dyslipidemia, insulin resistance, and type 2 DM, even in the absence of hypertension [20].

In our study, multivariate logistic regression analysis showed that increase in age and decrease in E/A ratio was significantly associated with left ventricular diastolic dysfunction (LVDD) in patients with microalbuminuria.

Conclusion
The association of microalbuminuria with LVDD and the direct and independent association of increase in age with LVDD in normotensive diabetic patients is conclusively established by this study. Therefore, periodic screening for microalbuminuria should be done in diabetic patients, along with other risk markers such as lipid profile and BP, to get a more comprehensive risk assessment, for the development of cardiovascular complications.

Further Type 2 diabetes patients with microalbuminuria should be annually screened with Echocardiography for early detection of LVDD. Assessment of cardiac function by means of echocardiography in patients with T2DM should be a part of mandatory early preventive strategies.

Abbreviations
T2DM: Type 2 diabetes mellitus; LVDD: Left ventricular diastolic dysfunction (LVDD); FBS: Fasting blood sugar; PPBS: Post-prandial blood sugar; DM: Diabetes mellitus; LV: Left ventricular; LDL: Low-density lipoprotein; HDL: High density lipoprotein; VLDL: Very low-density lipoprotein; HbA1c: Glycosylated hemoglobin; CV: Cardiovascular; CAD: Coronary artery disease; CHD: Coronary heart disease; IHD: Ischemic heart disease; WC: Waist circumference; HC: Hip circumference; BMI: Body mass index; BSA: Body surface area; WHR: Waist-hip ratio; SD: Standard deviation; IQR: Inter-quartile range; eGFR: Estimated glomerular filtration rate; UACR: Urine albumin-to-creatinine ratio; LVIDd: Left ventricular internal dimension in diastole; LVEDV: Left ventricular end-diastolic volume; E/A: Early to late ventricular filling velocities; IVRT: Isovolumic relaxation time

Declarations

Ethics approval and consent to participate
The study was done after due permission from the Institutional Ethics Committee and Scientific Review Board and after taking written informed consent from the patients. The study was approved by Institutional Human Ethics Committee, GMERS Medical Gotri Vadodara vide reference no. IHEC/ GMERSMCGV/190/2017 dated 4/11/2017.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests

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