

## Original Research Article

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# Microalbuminuria as an early marker of left ventricular hypertrophy in type 2 diabetes mellitus

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## ABSTRACT

**Background:** Microalbuminuria and left ventricular hypertrophy (LVH) have both been shown independently to be associated with increased cardiovascular (CVS) mortality in type 2 diabetes mellitus (DM) patients. This cross-sectional study was conducted to examine whether microalbuminuria is associated with LVH in non-hypertensive type 2 DM patients with early or no diabetic nephropathy.

**Methods:** 100 patients of type 2 DM were studied. Patients with Hypertension (BP >140/90 mm hg or on anti-hypertensive medication), history of coronary artery disease or valvular heart disease, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m<sup>2</sup>, known thyroid disease or active urinary tract infection (UTI) were excluded from the study. All patients were subjected to spot urine test for microalbuminuria by urinary albumin creatinine ratio (UACR), 12 lead ECG to detect LVH, 2D echocardiography to calculate LV mass index (LVMI), anthropometry, urine routine examination, kidney function test, fasting lipid profile and HbA1c.

**Results:** Of the 100 enrolled patients, 39 were found to have normoalbuminuria, 39 had microalbuminuria & 22 patients had macroalbuminuria. The correlation between increased albuminuria and LVMI was found to be statistically significant (P value < 0.001) and the LV mass significantly increased as albuminuria increased along the continuum of normoalbuminuria to macroalbuminuria. UACR showed a statistically significant correlation with age, eGFR, duration of diabetes (P value < 0.01) and HbA1c (P value < 0.05).

**Conclusions:** Microalbuminuria is associated with LVH in non-hypertensive type 2 DM patients and thus may serve as an early marker of LVH and help identify patients at high CVS risk.

**Keywords:** Microalbuminuria, LVH, Type 2 diabetes mellitus, LV mass index, UACR

## INTRODUCTION

Type 2 DM has reached epidemic proportions in India and is a major risk factor for adverse CVS events. In fact, CVS complications are known to account for approximately 75% of mortality in patients with type 2 DM.<sup>1</sup> However, the association between diabetes and adverse CVS outcome cannot be merely explained by several risk factors such as hypertension, dyslipidemia and obesity being common to both and is believed to be at least partially due to the strong independent association

of type 2 DM with CVS target organ damage, such as LVH.<sup>2,3</sup> LVH is typically a response to increased afterload and is an independent risk factor for coronary heart disease, sudden cardiac death, and heart failure.<sup>4,5</sup> Increased cardiac mortality in such patients is in fact associated with the degree of increased myocardial muscle mass. Hence, type 2 DM has independent adverse cardiac effects, including increased LV mass and wall thickness, reduced myocardial function, and increased arterial stiffness. Type 2 DM patients thus are at increased risk of CVS complications due to adverse CVS

effects of DM in addition to the traditional risk factors of associated increases in Body mass index (BMI), arterial pressure and dyslipidemia.<sup>6</sup> Therefore, the early identification of such patients at greatest risk of increased CVS complications is of utmost importance so that potentially lifesaving treatment can be initiated at the earliest.

In this regard, urinary albumin excretion (UAE) may have a role as an early indicator for the future development of diabetic vascular complications and LVH. UAE has conventionally been divided into microalbuminuria and macroalbuminuria/ overt albuminuria. It is postulated that by being a marker of systemic endothelial dysfunction in type 2 DM patients, microalbuminuria may have a role as an early indicator of LVH.<sup>7</sup> Based on this, it appears that microalbuminuria is associated with LVH and consequent increased CVS mortality in type 2 DM patients. Hence this cross-sectional study was conducted to examine whether microalbuminuria is associated with LVH in non-hypertensive type 2 DM patients with early or no diabetic nephropathy.

## METHODS

This was a cross sectional study carried out at Chhatrapati Shivaji Subharti Hospital (CSSH), Meerut, Uttar Pradesh, India with a sample size of 100 patients. Diagnosed patients of type 2 DM satisfying ADA criteria for diagnosis of DM, whether currently on medication or not and with age above 18 years were enlisted in the study after informed consent. Patients with any of the following conditions were excluded: hypertension i.e. BP >140/90 mm hg or patients on anti-hypertensive medication, history of coronary artery disease (CAD) or valvular heart disease, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m<sup>2</sup>, any type of other renal disease, known thyroid disease, active UTI and current febrile illness. All cases were subjected to spot urine test for microalbuminuria by urinary albumin creatinine ratio (UACR), 12 lead ECG, 2D echocardiography, anthropometry and blood investigations.

### Urinary albumin excretion

Albuminuria was detected and quantified by measuring UACR of a spot urine sample with the help of semi-automatic analyser and chemical assay in biochemistry lab in CSSH. Urine routine and microscopic examination was also done. Microalbuminuria was defined as levels of albumin ranging from 30 to 300 µg/mg of creatinine and overt albuminuria or macroalbuminuria was defined as a UAE of >300 µg/mg of creatinine in a spot urine sample.<sup>8</sup>

### Detection of left ventricular hypertrophy

12 lead ECG was used for detection of LVH by Sokolow Lyon criteria, Cornell criteria and Cornell voltage product as per the following criteria:

**Sokolow-Lyon criteria:** LVH was taken to be present if the sum of S wave in V1 and R wave in V5 or V6 was > 35 mm.<sup>9</sup>

**Cornell criteria:** LVH was taken to be present if the sum of R wave in aVL and S wave in V3 was > 28 mm in males or > 20 mm in females.<sup>9</sup>

The Cornell voltage product was calculated as the product of QRS duration and Cornell voltage. LVH was taken to be present if this product was  $\geq 244.0 \text{ mVms}$ .<sup>9</sup>

### LV chamber quantification

2D colour doppler echocardiography by Philips CX-50 was conducted in echocardiography lab in CSSH and certain relevant measurements such as LV mass, LV mass index (LVMI) and relative wall thickness (RWT) were recorded and calculated by Linear method using M-mode echocardiography. LV mass was calculated as per the geometric cube formula for chamber quantification as shown below:

$$\text{LV mass} = (0.8) \times (1.04) \times [(IVS + LVID + PWT)^3 - (LVID)^3] + 0.6 \text{ g}$$

Where IVS is interventricular septum, LVID is LV internal diameter and PWT is inferolateral wall thickness. M-mode measurements were obtained from a targeted short axis or a parasternal long axis view. All measurements were performed at end-diastole.<sup>10</sup> LVMI was calculated as the ratio of LV mass (in g) to body surface area (in m<sup>2</sup>). Further, LVMI was classified as per severity of abnormality as shown in Table 1.<sup>10</sup>

### Anthropometry

Anthropometry was used to measure weight, height, waist circumference (WC), hip circumference (HC), BMI and waist hip ratio (WHR) as specified in WHO technical reports.<sup>11,12</sup> Weight was measured with a manual weighing scale in Kg to the nearest 100 gm with the patient wearing light clothing and standing still in the center of the platform.<sup>11</sup>

Height was measured in cm to the nearest 0.1 cm with the help of a measuring tape, horizontal headboard and the patient standing barefoot on a flat surface with heels together and the head, back, buttocks and heels in contact with a vertical surface.<sup>11</sup> BMI was calculated as weight (kg)/ height (m)<sup>2</sup>.

WC was measured as per the WHO Stepwise approach to surveillance (STEPS) protocol with a non-stretchable measuring tape to the nearest 0.1 cm at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest.<sup>12</sup> HC was measured as per the WHO STEPS protocol with a measuring tape to the nearest 0.1 cm at the widest portion of the buttocks with the measuring tape just snug around the body and

the patient standing erect.<sup>12</sup> WHR was calculated as ratio of WC and HC.

### Blood investigations

Complete blood count (CBC), kidney function test (KFT), HbA1c, fasting blood glucose (FBG), random blood glucose (RBG) post prandial blood glucose (PPBG) and fasting lipid profile, were carried out via automatic analyzer in CSSH lab. eGFR was calculated as per the 4 variable MDRD equation.

### Statistical analysis

Data entry and statistical analysis was done by Microsoft Excel and SPSS 19. t-test and  $\chi^2$  test at 5% level of significance were carried out.

## RESULTS

### Sample characteristics

Table 2 shows the main clinical and biochemical characteristics of type 2 DM patients with normoalbuminuria or increased albuminuria.

### eGFR and UACR

Amongst the entire study population, 43 patients had  $eGFR > 90 \text{ ml/min}/1.73\text{m}^2$  while 57 patients had  $eGFR$  of  $60-90 \text{ ml/min}/1.73\text{m}^2$ .

As per urinary albumin excretion by UACR, 39 patients had normoalbuminuria, 39 patients had microalbuminuria and 22 patients had macroalbuminuria.

**Table 1: Reference limits and partition values of LVMI by linear method using M-mode 2D echocardiography for females and males.**

Females				Males				
Reference range	Mildly abnormal	Moderately abnormal	Severely abnormal	Reference range	Mildly abnormal	Moderately abnormal	Severely abnormal	
LVMI( $\text{g}/\text{m}^2$ )	43-95	96-108	109-121	$\geq 122$	49-115	116-131	132-148	$\geq 149$

**Table 2: Main clinical and biochemical characteristics of type 2 DM patients with normoalbuminuria or increased albuminuria.**

Characteristics	Normoalbuminuria (UACR $< 30 \mu\text{g}/\text{mg}$ ) (n = 39)	Increased albuminuria (UACR $> 30 \mu\text{g}/\text{mg}$ ) (n = 61)	p-value
Age (years)	47.05 (38-65)	58.21 (40-75)	< 0.01
Male (n,%)	20 (51.23%)	29 (47.54%)	> 0.05
Duration of diabetes (years)	4.87 (2-15)	11.66 (4-20)	< 0.01
HbA1c (%)	8.58 (6.8-11.2)	8.83 (6.9-14.3)	> 0.05
eGFR (ml/min/1.73m <sup>2</sup> )	137.17 (66.8-253.2)	80.35 (62.4-113.4)	< 0.01
UACR ( $\mu\text{g}/\text{mg}$ )	19.38 (9.4-28.5)	255.71 (31.8-896.2)	< 0.01

**Table 3: Association of albuminuria with LVMI.**

LVMI	Normoalbuminuria (UACR $< 30 \mu\text{g}/\text{mg}$ )	Increased Albuminuria (UACR $> 30 \mu\text{g}/\text{mg}$ )	p-value
Normal	38	13	
Mildly abnormal	1	23	
Moderately abnormal	0	14	
Severely abnormal	0	11	
Total	39	61	<0.001

### Detection and classification of LVH

With the help of ECG, 25 patients were detected to have LVH as per Sokolow Lyon criteria, 17 patients by Cornell voltage criteria and 17 patients by Cornell voltage product. With the help of 2D echocardiography,

51 patients were found to have normal LVMI, whilst 24 had mildly abnormal, 14 had moderately abnormal and 11 had severely abnormal LVMI respectively.

### Associations of LVMI and UACR with pertinent variables

LVMI and increased albuminuria showed a statistically significant association (p value <0.001) as shown in Table 3. LVMI showed a progressive increase as albuminuria progressed from normoalbuminuria to microalbuminuria and from microalbuminuria to macroalbuminuria (P value <0.001). Albuminuria and LVH showed a statistically significant association (p value <0.01) as shown in Table 4. A statistically significant association was also seen between

albuminuria and duration of type 2 DM (p value <0.0001), eGFR and albuminuria (p value <0.0001), eGFR and LVMI (p value <0.0001) and LVMI and duration of type 2 DM (p value <0.0001). Amongst the other pertinent variables in the study, neither UACR nor LVMI showed any statistically significant correlation with various anthropometric parameters (like Weight, Height, BSA, BMI, WC, HC, WHR), lipid profile or HbA1c (p value >0.05).

**Table 4: Association of albuminuria with LVH.**

Urinary albumin excretion	LVH by Lyon sokolow criteria (n)	LVH by Cornell voltage criteria (n)	LVH by Cornell voltage product (n)	p-value
Normoalbuminuria (UACR < 30 µg/mg)	1	2	2	
Increased albuminuria (UACR > 30 µg/mg)	24	15	15	< 0.01
Total	25	17	17	

## DISCUSSION

Diabetic Kidney disease (DKD) is a common microvascular complication of type 2 DM. It is the leading cause of chronic kidney disease (CKD) in patients starting renal replacement therapy and affects ~40% of type 1 and type 2 DM patients.<sup>13</sup> It increases the risk of death, mainly from CVS causes, and is defined by increased UAE in the absence of other renal diseases.<sup>14,15</sup>

DKD is associated with progressive decline in glomerular filtration rate (GFR) and diabetic retinopathy. Without intervention, diabetic patients with microalbuminuria typically progress to overt proteinuria/macroalbuminuria and overt diabetic nephropathy. Microalbuminuria is usually associated with stable kidney function, but a greater risk of macroalbuminuria and kidney failure whereas macroalbuminuria is associated with progressive decline in GFR, an increase in systolic blood pressure, and a high risk of kidney failure.<sup>15</sup>

Patients with diabetes at increased risk of DKD include those with poor glycemic control, longer duration of diabetes, hypertension, retinopathy, raised proteinuria levels, nonwhite race, and family history of hypertension, add cardiovascular diseases (CVDs), type 2 DM and DKD.<sup>16</sup> Microalbuminuria is highly prevalent; in hypertensive and diabetic populations, its prevalence varies from 10 to ~40%. However, microalbuminuria frequently is also found in seemingly healthy individuals (5 to 7%).<sup>17</sup> A recent study showed that 40% of the patients with diabetes and without known kidney disease had microalbuminuria. The transition from normoalbuminuria to microalbuminuria is frequent despite adequate treatment: ~2 to 2.5% per year.<sup>18</sup> Mogensen et al. described the importance of

microalbuminuria not only as a renal risk factor but also as a CVS risk factor in patients with diabetes. Many subsequent studies confirmed the importance of microalbuminuria in estimating CVS risk for patients with diabetes.<sup>19,20</sup>

The Framingham study also established in 1984 that proteinuria is an important risk marker of CVS mortality in the general population.<sup>21</sup> In recent times, several important studies have highlighted increased UAE as a CVS risk factor e.g. 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).<sup>22-24</sup> They all showed that, like in diabetes, microalbuminuria is predictive for CVS events.

The Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of Endpoints in non-insulin dependent diabetes mellitus (NIDDM) with the Angiotensin II Antagonist Losartan (RENAAL) study also demonstrated that the presence of albuminuria was associated with increased CVS events.<sup>25</sup>

Furthermore, Gimeno-Orna et al. showed that microalbuminuria was as potent a risk factor for CVS events as a previous history of actual CVS disease.<sup>26</sup>

The above studies found that microalbuminuria was associated and clustered with other widely known CVS risk factors (age, diabetes, hypertension, LVH, overweight, metabolic syndrome, etc.) that at least partially explains the increased CVS risk.

Evidence suggests that as the amount of UAE increases along the continuum from microalbuminuria to

macroalbuminuria/overt albuminuria, the risk of adverse CVS events increases. Although this has been primarily studied in the diabetic population, evidence supports the presence of albuminuria as a potent risk factor for adverse CVS events in the nondiabetic population as well. 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.<sup>24</sup> The presence of microalbuminuria may thus need to be viewed in the same light as other risk factors such as blood pressure, cholesterol, and blood glucose with respect to CVDs.<sup>27</sup>

Albuminuria is an independent risk factor of rapid progression of CKD and in type 2 DM, a warning sign for DKD. DKD itself is a known independent risk factor of CVDs. As the above mentioned studies show, the level of UAE has been associated with CVDs in diabetic patients with CKD. In this respect, 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 metabolic abnormalities, such as central obesity, dyslipidemia, insulin resistance, and type 2 DM, even in the absence of hypertension.<sup>6</sup>

Hence, LVH and albuminuria are both markers for CVDs in patients with type 2 DM. Studies in diabetics with microalbuminuria (which usually precedes macroalbuminuria by an interval of 5-10 years) have shown that increased albumin leakage in the glomerulus is linked to enhanced capillary permeability for albumin in the systemic vasculature as well.<sup>7</sup> This increased permeability is believed to be a marker of generalized or systemic endothelial dysfunction and it has been suggested that such leakage might lead to hemodynamic strain and instability, which could then start the atherosclerotic process, and eventually lead to adverse CVS outcomes such as LVH, congestive heart failure, acute coronary syndromes, myocardial infarction and stroke.

Based on these findings, this cross-sectional study was conducted to examine whether LVH is associated with albuminuria in non-hypertensive type 2 DM patients with eGFR > 60 mL/min/1.73 m<sup>2</sup>. The prevalence of microalbuminuria in the current study was 39% amongst the study population of 100 non-hypertensive type 2 diabetic patients with no or only mild renal impairment. At the same time 22% of cases had overt proteinuria or macroalbuminuria. This compared to a prevalence of 24.92% for microalbuminuria and 9.3% for macroalbuminuria in type 2 diabetics with no or early DKD in the study conducted by Nan Wu et al.<sup>28</sup> Whereas, in the study conducted by Gerstein HC et al. amongst the cohort from HOPE (Heart outcomes prevention evaluation) and MICRO-HOPE (microalbuminuria, cardiovascular and renal outcomes) sub-study, microalbuminuria was seen in 32.6% of cases with type 2 DM and 14.8% of those without DM.<sup>29</sup> Our study found a clear association between increased LVMI and

albuminuria status (normoalbuminuria vs. increased albuminuria) with P value < 0.001. This association was statistically significant overall for the entire study population as well as separately for males and females. In addition, the LVMI progressively increased as albuminuria status increased from normoalbuminuria to microalbuminuria and then to macroalbuminuria (P value <0.001).

Over the past few years, the association between albuminuria and LVH in type 2 DM patients has been reported in various studies. Nguyen et al. reported an independent association of LVH with microalbuminuria.<sup>30</sup> Liu et al. showed a higher rate of LVH (49%) in type 2 DM patients with macroalbuminuria than that (31%) in patients with microalbuminuria and in those with no albuminuria (23%).<sup>31</sup> Nan Wu et al. showed that risks for LVH were significantly higher in patients with microalbuminuria and macroalbuminuria, when compared with that in patients with Non-DKD.<sup>28</sup> Niloofar N. et al. showed a positive correlation between log UAE and LV mass independent of BP.<sup>32</sup> They also evaluated the relationship of UAE and LV mass with mortality in type 2 DM patients and showed that during 5 years of follow up, survivors had significantly lower LV mass.<sup>32</sup> This relationship of increased mortality with microalbuminuria has also been suggested in the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study by Wachtell K et al.<sup>33</sup> The Study by Gerstein HC et al. also suggested that any degree of albuminuria is a risk factor for CVS events in individuals with diabetes and the consequent increased mortality.<sup>29</sup>

This association of LVH with microalbuminuria has also been demonstrated previously to be independent of BP (i.e. in absence of any hypertension or anti-hypertensive medications in the study population) in the studies conducted by Eguchi K et al. and Sato A et al.<sup>34,35</sup>

Our study also showed that both LVMI and UACR shared a statistically significant association with duration of diabetes (P value <0.0001). This may reflect the progressive increase in systemic endothelial damage and its ultimate sequelae i.e. increased LVMI and increased albuminuria with increasing duration of diabetes.

Both, UACR and LVMI, however failed to show a statistically significant association with the glycemic parameters of FBG, PPBG, RBG and HbA1c. This may be explained by the fact that the patient's glycemic parameters do not necessarily reflect the glycemic control during the entire course of type 2 DM.

The significant association between eGFR and UACR (p value <0.0001) found in the study showed that albuminuria increased with the decline in eGFR thus confirming that albuminuria is a risk factor for progression of CKD.

Besides this, we found that the relationship between LVMI and ECG criteria for diagnosis of LVH (Lyon sokolow criteria, Cornell voltage criteria, Cornell voltage duration product) was statistically significant (P value <0.01). This agreed with the study carried out by Niloofar N. et al.<sup>32</sup>

Taken together, these observations support the suggestion that albuminuria is a risk factor for CVDs by reflecting underlying diffuse endothelial dysfunction and its association with several other risk factors for CVDs like hyperglycemia, hypertension, renal dysfunction, dyslipidemia etc. Thus albuminuria is an easily measured marker of other CVD risk factors, as well as existing endothelial dysfunction, that likely reflects underlying macrovascular and microvascular disease. Albuminuria measured thrice over a period of 6 months as specified in ADA screening algorithm may thus overcome the various limitations associated with measurement of microalbuminuria and provide a relatively inexpensive and easily available test to identify diabetic individuals at highest risk of future CVS events and therefore most likely to benefit from adding a preventive intervention early in the course of the disease.

However, most previous studies focused on patients with predisposing factors for CVDs such as hypertension, obesity, high thyroid hormone status, and late chronic kidney disease (CKD stages 3-5). Our study was carried out on a highly-selected sub group of Indian population, that is, non-hypertensive type 2 DM patients with eGFR > 60 ml/min/1.73m<sup>2</sup> (i.e. patients with no or early nephropathy only). Our study thus found that UACR shows a statistically significant association with LVMI in non-hypertensive type 2 DM patients with no or early nephropathy. These findings suggest that albuminuria status could be used, even in the early stage of DKD, as a surrogate marker for subclinical damage and, particularly to assess the risk for CVS events. Our findings thus provide a possible link between the prognostic value of UACR and LVH in early DKD.

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