Body Mass Index or Microalbuminuria, Which One is More Important for the Prediction and Prevention of Diastolic Dysfunction in Non-diabetic Hypertensive Patients?

Hasan Shemirani, Alireza Khosravi[1], Rohola Hemmati[2], Mojgan Gharipour[1]

Department of Cardiology, Faculty of Medicine, Isfahan University of Medical Sciences (IUMS), Isfahan, [1]Hypertension Research Center, Isfahan Cardiovascular Research Institute, IUMS, Isfahan, [2]Cardiology Department, Faculty of Medicine, Elam University of Medical Sciences, Elam, Iran

Correspondence to:
Asso. Prof. Alireza Khosravi,
Cardiology Department, Faculty of Medicine, and Hypertension Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
E-mail:alikh108@yahoo.com

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ABSTRACT

Background: Numerous studies have now demonstrated that heart failure with a normal ejection fraction (HFnlEF) is common. Hypertension is also the most commonly associated cardiac condition in patients with HFnlEF. Despite the observed link between microalbuminuria, obesity, and cardiovascular disorders, this question has remained — 'Which is more important for the prediction and prevention of diastolic dysfunction in non-diabetic hypertensive patients?'

Methods: The current study was a cross-section study conducted on a total of 126 non-diabetic hypertensive patients screened to identify those with hypertension. Urine creatinine was measured by the picric acid method and urine albumin content was measured by a sensitive, nephelometric technique. The urinary albumin/creatinine ratio (UACR) was determined as an indicator of microalbuminuria. Complete two-dimensional, doppler, and tissue-doppler echocardiography was performed and the recording of the diastolic function parameters was carried out.

Results: High body mass index and high systolic blood pressure were positively correlated with the appearance of left ventricular hypertrophy, whereas, the UACR index had no significant relationship with hypertrophy. Multivariable analysis also showed that advanced age and systolic blood pressure were significantly associated with the E/E annulus parameter.

Conclusion: According to our investigation obesity is more important than microalbuminuria for the prediction and prevention of diastolic dysfunction in non-diabetic hypertensive patients.

Keywords: Hypertension, microalbuminuria, heart failure, obesity

Original Article

INTRODUCTION

Hypertension can induce systolic and diastolic dysfunction, but until the last two decades, the possibility that a large number of patients with heart failure (HF) might have a normal ejection fraction (EF) was not considered. As numerous studies have

now demonstrated that heart failure with a normal ejection fraction (HFnlEF) is common; why it was not previously recognized is unclear. It may be that HFnlEF was always common, but the cardiology community failed to recognize it. It is also possible that the prevalence of HFnlEF has increased over time, leading to more widespread recognition. Support for this concept comes from a study which shows that the prevalence of HFnlEF among patients admitted for HF, at a single large institution, has increased dramatically during a 15-year period, from 1987 to 2001.

Hypertension is also the most commonly associated cardiac condition in patients with HFnlEF. Chronically increased blood pressure is an important stimulus for cardiac structural remodeling and functional changes. The resultant hypertensive heart disease is characterized by left ventricular hypertrophy (LVH), increasing vascular and ventricular systolic stiffness, impaired relaxation, and increased diastolic stiffness, all factors linked to the pathogenesis of HFnlEF.[1] In the presence of hypertensive heart disease, ischemia produces exaggerated increases in filling pressures, and hypertensive heart disease and ischemic heart disease are often present in combination in patients with HFnlEF. Elucidating which factors mediate transition to HFnlEF, in persons with hypertensive heart disease, is an area of active investigation.

Most large contemporary studies have now suggested that the all-cause mortality for HFnlEF is similar to that of HF with a reduced EF.[2,3-5]

Hypertensive obese patients are at an increased risk for HF. In general, patients with HFnlEF are more often hypertensive obese than are patients with HF with a reduced EF, and the prevalence of diastolic dysfunction is increased in obese persons. Increased body mass index is a risk factor for hypertension, diabetes mellitus, coronary artery disease, and atrial fibrillation, all of which are associated with HFnlEF.[6]

Albuminuria has been identified as a life-threatening renal and cardiovascular risk profile.[7-9] This important diagnostic parameter can not only predict renal or concurrent renal and cardiovascular adverse events in high-risk patients, such as diabetics and hypertensive patients (ranging from 10 to 40%),[10,11] but can also be frequently found in seemingly healthy subjects, with an overall prevalence of 5 to 7% in normal individuals.[12,13] In spite of the observed link between microalbuminuria and cardiovascular disorders, its pathophysiological mechanisms responsible for progression of cardiac dysfunction or heart failure have been already unknown. However, some strong hypotheses for these processes have been put forward. First, it has been suggested that reduced glomerular filtration rate following renovascular damage can lead to activation of the renin–angiotensin–aldosterone system, which subsequently affect the cardiovascular system and result in ventricular dysfunction.[14] It has been also hypothesized that common cardiovascular risk factors such as systolic hypertension, hyperglycemia, and hyperlipidemia might have a triggering role for progressing atherosclerosis.[15] Of late, the appearance of microalbuminuria has been identified as a main indicator of left ventricular systolic and diastolic dysfunction, particularly in diabetic patients.[16,17] It seems that some patient's indices, such as raised night-to-day systolic blood pressure or high body mass index, which can be related to left ventricular hypertrophy may result in cardiac, systolic and diastolic dysfunction.[18] However, some other researchers could not confirm any significant differences in left ventricular systolic and diastolic functions between patients with and without microalbuminuria,[19] and therefore, its causative role has been already questioned.

Thus, the main aim of this study is comparing of microalbuminuria and body mass index for prediction and prevention of diastolic dysfunction in non-diabetic hypertensive patients.

METHODS

The current study is a cross-section study conducted on a total of 126 non-diabetic hypertensive patients. The data for this investigation were obtained from a large, cross-sectional study entitled "the Isfahan Healthy Heart Program" (IHHP) that was a population-based cohort survey of cardiovascular risk factors.[20]

A physician measured office BP thrice in each participant using a mercury sphygmomanometer, with an appropriate size cuff. During the measurements, the participant remained seated for 10 minutes with the arm comfortably placed at the level of the heart.

The participants were defined as hypertensive if resting systolic blood pressure was ≥140 mm Hg

and/or diastolic ≥90 mm Hg, or were treated with antihypertensive medications. Blood pressure was also stratified as stage 1 (systolic BP, 140 – 160 mmHg and/or diastolic BP 90 – 100) and stage 2 (systolic BP, >160 mmHg and/or diastolic BP >100 mmHg).

The exclusion criteria include the presence of diabetes mellitus, acute inflammatory disorders, ischemia, trauma, surgery, pancreatitis, febrile disorders, connective tissue disorder, documented coronary diseases, cerebrovascular accident, angina pectoris or myocardial infarction, cardiac arrhythmias, chronic pulmonary diseases, malignancies or heavy physical activities a day before the study begins. The study protocol, which complies with the principles of good clinical practice and the declaration of Helsinki, has been approved by the relevant ethics committee at the participating center. Written informed consent was required from each patient before enrolment in the trial.

After the final diagnosis of hypertension, all participants underwent a screening test with five plasma samples to measure the plasma levels of serum electrolytes and creatinine, fasting blood sugar and lipid profile, as well as five urine samples for measuring urine albumin and creatinine. Albuminuria was measured by collection of fasting random urine specimens on arrival to the clinic in the morning. Urine creatinine was measured by the picric acid method, and urine albumin content was measured by a sensitive, nephelometric technique (Pars Azmoon kits, Iran). The urinary albumin/creatinine ratio (UACR) and all other laboratory values were determined in a central laboratory within 24 hours after obtaining the urine and blood samples. Microalbuminuria was defined as UACR from 30 to 300 mg/g and macroalbuminuria as a UACR of more than 300 mg/g.

Body weight was measured with the patients in light clothing, without shoes.

Body mass index (BMI) was calculated as weight (kg)/height 2 (m^2). The patients were characterized as normal weight if their BMI was between 18.5 and 24.9, overweight if their BMI was between 25 and 29.9, and obese if their BMI was higher than 30.

All participants underwent standard two-dimensional M-mode, Doppler, and tissue-Doppler, echocardiograms within a week from the BP measurements. Left ventricle (LV) dimensions were measured, using the American Society of Echocardiography (ASE) and the European Society of Cardiology guidelines. [21] The numbers were randomly assigned to all echocardiograms, blinding all patient identifications. Two experts in echocardiography read the echocardiograms The ASE-recommended formula for estimation of left ventricular mass from left ventricular linear dimensions, validated with necropsy, was used. Left ventricular mass was indexed for height 2.7 (LVMI).[22] The kappa statistics between the two measurements suggested a high agreement between readers of echocardiograms, k was equal to 0.92 and intraobserver variability lower than 0.1. Left ventricular hypertrophy was defined as LVMI higher than 48 g/m 2.7 in men and higher than 44 g/m 2.7 in women, according to the guidelines.[21] Relative wall thickness (RWT) was also calculated.

Left ventricular diastolic function was assessed using pulsed-Doppler samples of mitral inflow and pulsed-tissue Doppler at the level of the septal wall of the mitral annulus. Standard diastolic indices were recorded, including early (E) and late (A) transmitral peak flow velocities, early deceleration time (DT), and LV isovolumic relaxation time (IVRT). IVRT as the time from aortic valve closure to mitral valve opening was measured by simultaneous Doppler and M-mode echocardiography, and its normal range was about 70 ± 12 ms.

Normal DT is also ranged between 160 to 240 ms.

Diastolic dysfunction can be graded according to the diastolic filling pattern.[23]

- Grade 1 (mild dysfunction): Impaired relaxation with normal filling pressure
- Grade 2 (moderate dysfunction): Pseudonormalized mitral inflow pattern
- Grade 3 (severe reversible dysfunction): Reversible restrictive (high filling pressure)
- Grade 4 (severe irreversible dysfunction): Irreversible restrictive (high filling pressure)

Results were reported as mean±standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's *t*-test or Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test, if required, for categorical variables. Predictors

exhibiting a statistically significant relationship with the appearance of left ventricular hypertrophy in the univariate analysis (P value <0.05) were taken for a multivariate logistic regression analysis, to investigate their independence. Odds ratios (OR) and 95% confidence intervals (CI) for OR were calculated. Model discrimination was measured using the c statistics, which was equal to the area under the ROC (Receiver Operating Characteristic) curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher P values imply that the model fits the observed data better). Multivariable linear analysis was also used to determine the main correlates of E/E annulus. P value of <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

The baseline data of study patients are summarized in Table 1. A total of 126 patients with the final diagnosis of primary hypertension were included in the study. The mean age of patients was 53.5 years (ranged 27 to 86 years) with a male to female ratio of 0.8. The mean body mass index (BMI) was 29.49 kg/m^2, and among them, 43.7% had obesity, with a BMI equal or more than 30 kg/m^2. Systolic and diastolic blood pressures on the first admission day were controlled in the normal ranges in 36.4 and 43.1% of the patients, respectively. Primary hypertension was newly diagnosed in 6.5%

Table 1: Baseline characteristics of study patients with hypertension with positive and negative urine albumin/creatinine ratio

Characteristics	Total (n=126)	UACR (+) (N=10)	UACR (−) (N=116)	P value
Male gender	55 (43.7)	3 (30.0)	53 (44.8)	0.511
Age	53.56 ± 11.31	53.50 ± 10.02	53.57 ± 11.45	0.984
Body mass index	29.49 ± 4.59	29.44 ± 4.68	30.08 ± 3.54	0.601
Systolic blood pressure				
<140 mmHg	44 (36.4)	4 (40.0)	40 (36.0)	
140 – 160 mmHg	52 (43.0)	4 (40.0)	48 (43.2)	0.968
>160 mmHg	25 (20.7)	2 (20.0)	23 (20.7)	
Diastolic blood pressure				
<90 mmHg	50 (41.3)	5 (50.0)	45 (40.5)	
90 – 100 mmHg	49 (40.5)	2 (20.0)	47 (42.3)	0.338
>100 mmHg	22 (18.2)	3 (30.0)	19 (17.1)	
Duration of HTN				
New	8 (6.5)	0 (0.0)	8 (7.0)	
<5 years	84 (67.7)	6 (60.0)	78 (68.4)	0.507
5 – 10 years	19 (15.3)	3 (30.0)	16 (14.0)	
>10 years	13 (10.5)	1 (10.0)	12 (10.5)	
Abnormal ECG	11 (8.7)	1 (10.0)	10 (8.6)	0.999
Oral medications				
Calcium-blockers	11 (10.3)	0 (0.0)	11 (11.1)	0.266
Beta-blockers	59 (55.1)	5 (62.5)	54 (54.5)	0.626
ACE-inhibitors	27 (25.2)	3 (37.5)	24 (24.2)	0.353
Diuretics	10 (9.3)	0 (0.0)	10 (10.1)	0.291
Laboratory parameters				
Serum creatinine	1.08 ± 0.21	1.09 ± 0.28	1.08 ± 0.20	0.890
Potassium	4.00 ± 0.41	4.04 ± 0.32	4.00 ± 0.42	0.531
Fasting blood sugar	101.00 ± 6.74	111.50 ± 6.36	100.25 ± 17.05	0.257
Total cholesterol	202.96 ± 44.63	233.50 ± 20.51	200.42 ± 45.38	0.258
High density lipoprotein	46.64 ± 11.06	50.50 ± 6.36	46.25 ± 11.46	0.485
Low density lipoprotein	127.14 ± 39.28	138.50 ± 38.89	126.00 ± 40.13	0.554

of the subjects and 10.5% of the subjects had had hypertension for more than 10 years. No significant differences were found between the two groups, with and without microalbuminuria, in terms of demographics, blood pressure categories, duration of hypertension, electrocardiogram abnormalities, and oral medications administered, before the study began. There were also no significant differences in the baseline laboratory indices including total cholesterol, triglycerides, fasting blood sugar, high and low lipoprotein as well as serum creatinine level, across the two groups. Among all 126 study subjects, one of them was diagnosed with macroalbuminuria. He was a 49-year-old man with systolic and diastolic blood pressures of 160 and 100 mmHg, respectively. He had a serum creatinine concentration of 1 mg/dL, and appeared with a normal ECG.

Regarding left ventricular structure and diastolic function [Table 2], mild-to-moderate diastolic dysfunction (grade 1 – II) appeared in 33.3% of the patients with microalbuminuria and 21.6% of those without albuminuria (P=0.219). None of the patients had severe diastolic dysfunction (grade III – IV). Mitral E velocity and mitral A velocity were similar in the two groups with and without albuminuria. Consequently, the mitral E/A ratio was not different in the two groups. Left ventricular ejection fraction, left ventricular mass index, and mitral deceleration time were all similar in the patients with and without microalbuminuria. Left ventricular hypertrophy was found in 30.0% of the patients with microalbuminuria and in 25.9% of the group without microalbuminuria. No significant linear correlations were found between the UACR measurement and cardiac indices of the left ventricular mass index, declaration time, mitral A and E velocities, as well as E/E annulus index [Figures 1 and 2]. Positive microalbuminuria appeared in 9.1% of the patients with left ventricular hypertrophy, while among those without left ventricular hypertrophy; microalbuminuria was detected in 7.5% of them. Also, 11.1% of the patients with moderate left ventricular hypertrophy had microalbuminuria

Table 2: Cardiovascular parameters in patients with hypertension with positive and negative urine albumin/creatinine ratio

Characteristics	UACR (−) (N=10)	UACR (+) (N=116)	P value
Diastolic function			
Normal function	0 (0.0)	29 (25.0)	
Grade I dysfunction	7 (66.7)	3 (33.4)	0.219
Grade II dysfunction	3 (33.3)	25 (21.6)	
Declaration time			
<160 ms	0 (0.0)	13 (12.8)	
160 – 240 ms	4 (44.4)	45 (44.6)	0.478
>240 ms	6 (55.6)	43 (42.6)	
Left ventricular ejection fraction	63.75 ± 9.26	64.52 ± 7.08	0.802
Left ventricular hyperthrophy	3 (30.0)	30 (25.9)	0.721
Severity of ventricular hypertrophy			
Normal	7 (70.0)	86 (74.1)	
Mild	2 (20.0)	19 (16.4)	0.924
Moderate	1 (10.0)	8 (6.9)	
Severe	0 (0.0)	3 (2.6)	
Left ventricular mass index	143.38 ± 53.18	154.34 ± 49.47	0.564
Left ventricular mass severity			
Normal	7 (77.8)	91 (78.4)	
Mild	1 (11.1)	12 (10.3)	0.783
Moderate	1 (11.1)	6 (5.2)	
Severe	0 (0.0)	7 (6.0)	
E/A ratio	6.90 ± 0.20	1.07 ± 0.36	0.134
A wave	81.70 ± 24.17	71.68 ± 18.69	0.230
E wave	70.70 ± 16.73	73.65 ± 16.49	0.603
E/E annulus	10.46 ± 2.60	10.30 ± 3.90	0.870

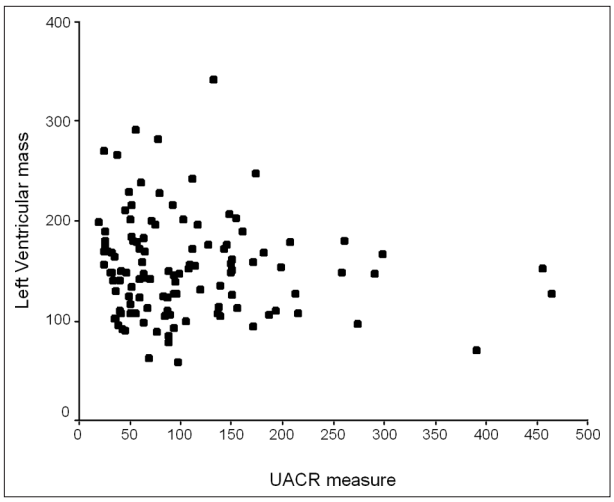

Figure 1: Association between urine albumin/creatinine ratio and left ventricular mass index in primary hypertensive patients

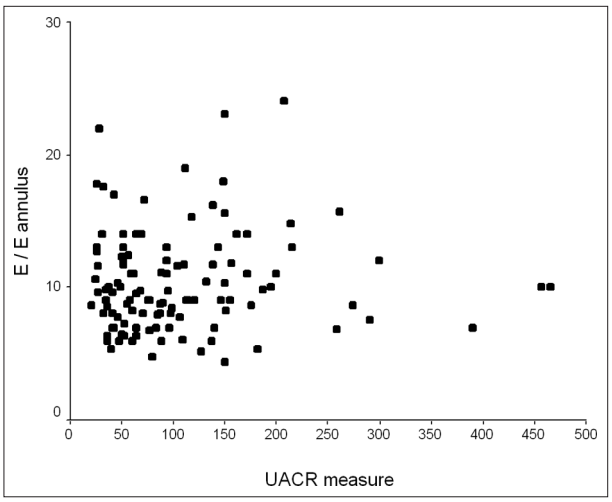

Figure 2: Association between urine albumin/creatinine ratio and E/E annulus in primary hypertensive patients

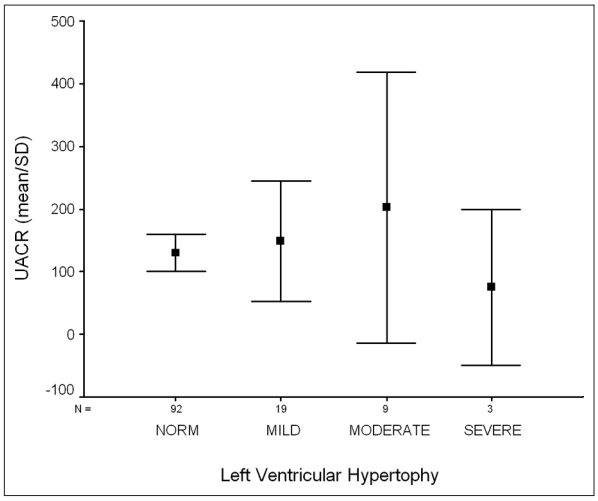

Figure 3: Relationship between urine albumin/creatinine ratio and severity of left ventricular hypertrophy in primary hypertensive patients

and none of the patients with severe hypertrophy had this urinary pathological abnormality.

No significant relationship existed between the severity of left ventricular hypertrophy and the UACR measurement [Figure 3].

With respect to the determinants, left ventricular hypertrophy, high body mass index, and high systolic blood pressure were positively correlated with the appearance of left ventricular hypertrophy, whereas, the UACR index had no significant relationship with hypertrophy [Table 3]. Multivariable linear analysis also showed that the variables of advanced age and systolic blood pressure were significantly associated with the E/E annulus parameter [Table 4].

Table 3: Multivariable logistic analysis of the determinants of left ventricular hypertrophy in patients with hypertension

Variable	Multivariate *P* value	Odds ratio	95% confidence intervals
Female gender	0.935	1.045	0.366 – 2.981
Advanced age	0.086	1.044	0.994 – 1.097
Body mass index	0.009	1.154	1.037 – 1.286
Systolic BP	0.006	1.053	1.015 – 1.092
Diastolic BP	0.031	0.922	0.856 – 0.992
Urine ACR	0.371	1.001	0.998 – 1.004

Hosmer-Lemeshow goodness of fit: Chi-square: 4.501; *P* =0.809

Table 4: Multivariable linear analysis of the determinants of E/E annulus in patients with hypertension

Variable	Multivariate *P* value	Beta	Standard error for beta
Female gender	0.126	1.132	0.733
Advanced age	0.026	0.074	0.033
Body mass index	0.132	0.114	0.075
Systolic BP	0.016	0.066	0.027
Diastolic BP	0.245	−0.062	0.053
Urine ACR	0.918	0.129	1.252

R-square: 0.157

DISCUSSION

In the present study, we found no association between microalbuminuria, LV mass, and wall thickness in hypertensive adults.

None of the measured indices of diastolic function was significantly associated with microalbuminuria. Although, the association of

baseline demographic and topographic variables such as female sex, smoking, higher waist circumference, and presence of the metabolic syndrome, insulin treatment, smoking, poor diabetes control, and even family history of cardiovascular disease with microalbuminuria, was demonstrated in some recent studies,[24,25] these observational associations might not have proved the causality.[26] Furthermore, the underlying predisposing factors for microalbuminuria have been mostly described among diabetic patients with multiple systemic defects and poor outcome, including renal dysfunction, and therefore, known causes of microalbuminuria might not have a causative role for appearing as microalbuminuria in the general population. Among our participants, none of the patients had uncontrolled fasting blood sugar (more than 126 mg/dL) and therefore our study was certainly focused on non-diabetic ones. Moreover, defects in both the glomerulus and the tubules have been implicated as the main pathophysiological etiologies of microalbuminuria. In acute inflammation, microalbuminuria is surmised to be a result of the endothelial glomerular leak in the kidneys, which is a manifestation of the systemic increases in capillary permeability, due to an intense inflammatory onslaught on the endothelium.[27,28] Each acute inflammatory condition may lead to endothelial glomerular defects and finally result in microalbuminuria. Thus, all subjects suspected as microalbuminuria should be screened with regard to acute or chronic inflammatory disorders. Also, with respect to the relationship between systolic blood pressure and the measurement of UACR, we did not demonstrate this association in the primary hypertensive population. It was better to compare the UACR measurement between hypertensive and normotensive ones, because numerous patients in our study population had a normal range of both systolic and diastolic blood pressure. In addition, more than half of the patients had a short-term experience of evidenced hypertension.

Despite our non-significant association of microalbuminuria and parameters of left ventricular diastolic function, such as left ventricular mass, left ventricular hypertrophy pattern, and ejection fraction but direct relationship between these cardiac indices and UACR measurement has been documented. In a study by Djoussé *et al*., microalbuminuria was positively associated with left ventricular mass in normotensive subjects, as it was in hypertensive subjects, while this renal pathological defect was negatively related to ejection fraction only in hypertensive subjects.[29] In another study by Picca *et al*., microalbuminuria was associated with an increased left ventricular mass index, a higher prevalence of a concentric left ventricular hypertrophy pattern, a depressed midwall systolic performance, and thus, a markedly impaired diastolic function.[30] According to this fact that the appropriate cardiac diastolic function can be directly dependant on other important structural and functional indices such as impaired aortic elastic properties[31] and altered vascular dilatory capacity, these indices should also be considered for assessing the relationship between microalbuminuria and left ventricular diastolic dysfunction.

In this study, high body mass index and high systolic blood pressure were positively correlated with the appearance of left ventricular hypertrophy.

The heart of obese individuals is subjected to continued volume overload due to an elevated cardiac output (CO), which may stimulate the growth of cardiac walls, left ventricular dilatation, and subsequently induce left ventricular hypertrophy.[32-35]

In some other studies, left ventricular hypertrophy was 17.67 times more likely in obese patients as compared to normal-weight true normotensive individuals and it was concluded that high body mass index might represent a significant cardiovascular risk factor for left ventricular hypertrophy, even in normotensive individuals.[36] Some other authors showed that left ventricular hypertrophy was more common in patients with higher systolic blood pressure, pulse pressure, higher end-diastolic and systolic volumes, lower ejection fraction, and a calcium-phosphate product.[37,38] Therefore, systolic hypertension, especially in obese patients, could be independent predictors of left ventricular hypertrophy and its role was confirmed in the presence of other confounders. This relationship might be influenced by the duration of hypertension and its severity. According to the common association of hypertension and left ventricular mass index, as well as the predictive role of ventricular hypertrophy for mortality in cardiovascular disease patients,[39] minute assessment of the left

ventricular mass index in hypertensive patients, with suspected cardiovascular diseases, should be strongly recommended.

Hypertensive obese patients have more epicardial fat thickness that is metabolically active, which can induce coronary artery disease and heart failure.[40]

Also hypertension can induce premature coronary artery disease, like smoking, with respect to the number of vessel involvements and left main disease.[41]

For prevention of complication from obesity, weight loss has been shown to decrease left ventricular hypertrophy in obese patients. Diet has been documented to be at least as effective as antihypertensive medication in the normalization of an elevated left ventricular mass.[42] There is increasing evidence that obesity is associated with an increase in central arterial stiffness[43-46] and that weight loss reduces arterial stiffness.[46] There is increasing evidence that obesity is associated with an increase in central arterial stiffness[43-46] and that weight loss reduces arterial stiffness.[46] The mechanisms responsible for arterial stiffening in obese humans are unclear, but endothelial dysfunction, elevated advanced glycation end-products, collagen cross-linking, and activation of the vascular tissue renin–angiotensin–aldosterone system may play a role. A number of previous reports have suggested that the major determinant of left ventricular mass in obesity might be mediated by an increase in the metabolically active abdominal fat tissue.

According to our investigation obesity is more common and important than microalbuminuria for the prediction and prevention of diastolic dysfunction in non-diabetic hypertensive patients.

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