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Original Research Article

Prevalence of microalbuminuria in patients with essential hypertension and its correlation with retinopathy and carotid artery intimal-medial wall thickness

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ABSTRACT

Background: Hypertension affects wide range of organs, eventually resulting in events like heart failure, chronic kidney disease, stroke and blindness. However, there are only subtle changes present initially, like microalbuminuria (MA), elevated CCIMT and retinopathy, in patients with uncontrolled hypertension. Patients with microalbuminuria are postulated to have significantly high risk of TOD and this study aims to explore this association. The primary objective of this study was to explore prevalence of MA in patients of essential hypertension and ascertain its correlation with elevated CCIMT and retinopathy.
Methods: A cross-sectional study was done on 250 patients of essential hypertension, designated as per JNC8 guidelines. Patients of diabetes (Type I/II), thyroid disorders, CKD, UTI, obesity (BMI>30 kg/m^2), cataract and those with history of stroke, were excluded from this study. A statistical analysis was performed and relationship between microalbuminuria and TOD evaluated.
Results: Significant prevalence of TOD was seen, namely, microalbuminuria in 44.8%, retinopathy in 56.8% and elevated CCIMT in 35.6% patients. Significant association could also be appreciated in hypertensive patients with microalbuminuria when compared to those without, with respect to the presence of other TOD, specifically, retinopathy (OR 6.21, 95% CI, p-value<0.001) and elevated CCIMT (OR 26.5 95% CI, p value<0.001).
Conclusions: Given the high prevalence and significant association, it was concluded that microalbuminuria could function as a great tool to identify possibility of other on-going target organ damage and initiate timely treatment, to prevent the occurrence of catastrophic events in the future.

Keywords: Common carotid intima-media thickness, Microalbuminuria, Retinopathy, Target organ damage

INTRODUCTION

Hypertension is the most common cardiovascular ailment plaguing the world. A disease that was usually rare in the Indian subcontinent and mostly confined to the western world in the early 1900s, is now diagnosed in more than 25% of the population throughout the world. As cited in the study undertaken by Kearney et al the estimated global burden of hypertensives in 2025 is around 29.2% of the global population.[1] This rise in the number of cases is mostly attributed to the poor lifestyle, that is usually sedentary, with simultaneous lack of any physical activity or minimal physical activity. Also, with substandard food habits, including rise in consumption of junk food, soft drinks and high salt containing diet, it has only added to the already existing problem. Social determinants play a significant role in hypertension, with Indian states exhibiting higher levels of urbanization, human development and social progress also showing increased prevalence of the condition, as explicitly observed by

Gupta et al in their study on trends of hypertension epidemiology in India.[2] What is more worrying is the fact that hypertension often goes undiagnosed in majority of population, following the "Rule of halves", a concept coined by Wilber and Barrow in 1972, that is around 50% of the population is afflicted with hypertension; of those 50% only half are symptomatic; of those symptomatic only half of them seek treatment and of those seeking treatment only half of them get adequate treatment resulting in blood pressure control.[3] Often, by the time patient is diagnosed, hypertension has already resulted in significant damage to the target organs, involving the heart, kidneys, retina, central nervous system and blood vessels, thereby rightly earning the sobriquet "the silent killer".

Though, hypertension is often asymptomatic, the disease is associated with subtle target organ changes such as retinopathy, vascular damage (gauged by increase in carotid artery intimal medial wall thickness), microalbuminuria, left ventricular hypertrophy (LVH) and cognitive dysfunction, that occurs early in the course of hypertensive disease. If detected, in time, robust control of blood pressure through medication and lifestyle modifications can help to prevent the occurrence of catastrophic events in future like myocardial infarction and cardiac failure, blindness, stroke (ischemic or haemorrhagic), renal failure and dementia, that usually occurs as a result of long periods of uncontrolled blood pressure.

Persistent microalbuminuria (30-300 mg/gm) is the earliest pointer towards evolving nephropathy in patients of hypertension. Patients with microalbuminuria have been postulated to have significantly high risk of other target organ damage as well. Therefore, early screening of patients of essential hypertension for microalbuminuria could prove to be a viable strategy to predict the presence of ongoing vascular damage in other organs and future risk of adverse vascular events. Early screening and prompt intervention in positive cases could very well serve to reduce the burden of future catastrophe like stroke, blindness, coronary artery disease, cardiac failure and chronic kidney disease.

Aims and objectives

Prevalence of microalbuminuria, increase in carotid artery intimal medial wall thickness and retinopathy in patients of essential hypertension. Correlation between microalbuminuria and increase in carotid artery intimal medial wall thickness and retinopathy in the study participants.

METHODS

This research was carried out in Kanpur, Uttar Pradesh, India, at the Ganesh Shankar Vidyarthi Memorial Medical College. The study was conducted from February 2023 to July 2024 for a total of one and half year. Both patients who were admitted to the hospital and those from the Outpatient Department (OPD) were recruited. The purpose of this approach was to evaluate the correlations and prevalence in a specific population at one particular moment in time.

A cross-sectional study was done on 250 adult consenting patients of essential hypertension, designated as per JNC8 guidelines. Patients of type I/II diabetes (fasting glucose >126 mg/dl, post prandial sugar >200 mg/dl or HbA1c >6.5%), impaired glucose tolerance (fasting glucose 100-126 mg/dl, post prandial sugar 140-200 mg/dl or HbA1c 5.7-6.5%), thyroid disorder (hypothyroidism or hyperthyroidism), CKD (chronic kidney disease), UTI (Urinary tract infections), obesity (BMI>30 kg/m^2), any ocular disorder (Ex. cataract, glaucoma) and those with history of stroke (haemorrhagic or ischemic), were excluded from this study.

The patients were categorized as hypertensive if blood pressure came out to be more than 140/90 mm Hg (measured thrice at 5 minutes interval, with average of last two readings). Patient's early morning mid-stream spot urine sample was sent for urine ACR (albumin-creatinine ratio). Urine ACR values between 30-300 mg/gm was labelled as microalbuminuria.

Hypertensive retinopathy was assessed by fundus examination through direct ophthalmoscope and it was described as per Keith, Wagner and Barker's (KWB) classification which classified changes into grade 1 (mild narrowing or sclerosis of retinal arterioles), grade 2 (moderate to severe retinal arteriolar narrowing with venous compressions at A-V crossing), grade 3 marked by retinal haemorrhages, exudates and cotton wool spots and grade 4 marked by papilledema. The common carotid artery wall dimension was measured at a position 15 mm proximal to its bifurcation (manual measurement) by carotid doppler study. Three readings were taken on either side of the common carotid artery. The average reading from both sides was calculated and the final average value was used as the CCIMT value. In this study, CCIMT greater than 0.08 cm was categorized as elevated.

A statistical analysis was performed and the relationship between microalbuminuria and target organ damage (TOD) evaluated.

RESULTS

In this study, 250 hypertensive patients were included from OPD and IPD. The patients were categorized as hypertensive if blood pressure came out to be more than 140/90 mm Hg (measured thrice at 5 minutes interval, with average of last two readings). The age distribution of patients with essential hypertension reveals a broad range of ages, with the highest prevalence observed in the middle-aged group. Among the patients included in our study, maximum number of them fell in the age group 40-50 years (91 patients out of 250), with overall mean age of 49.81±11.05 years. The prevalence of microalbuminuria

among patients with essential hypertension is notable. Out of the total patients, 138 (55.2%) do not exhibit microalbuminuria, while 112 (44.8%) do. The prevalence of microalbuminuria, with a 95% confidence interval, is 44.8% (38.6%-51.0%). Also, the prevalence of retinopathy among patients with essential hypertension is significant. Of the total patients, 108 (43.2%) do not have retinopathy, while 142 (56.8%) do. The prevalence of retinopathy, with a 95% confidence interval, is 56.8% (50.7%-62.9%).

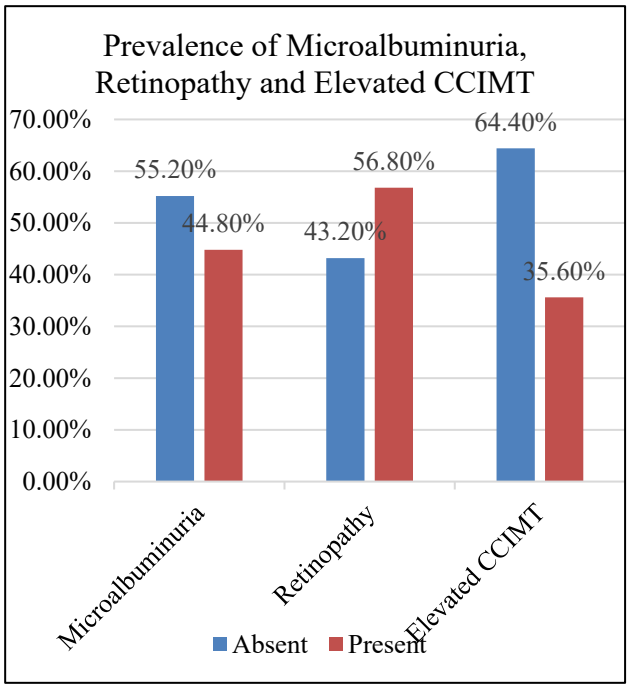

Figure 1: Prevalence of microalbuminuria, retinopathy and elevated CCIMT in patients of essential hypertension.

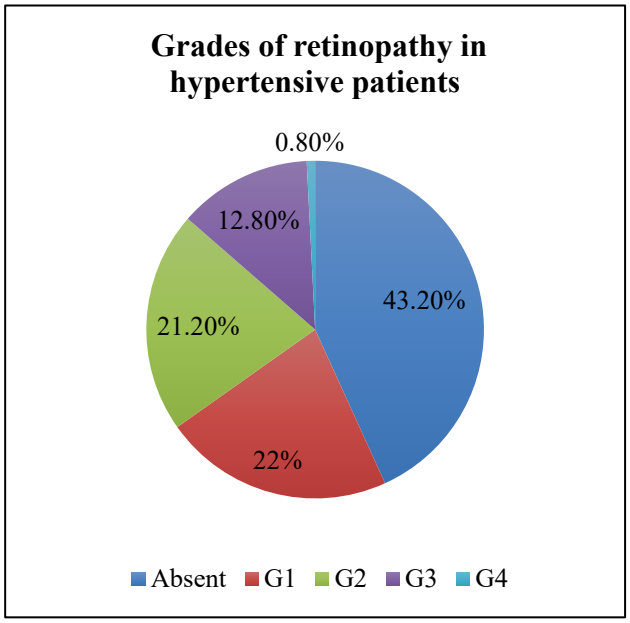

Figure 2: Varying grades of retinopathy in patients of essential hypertension.

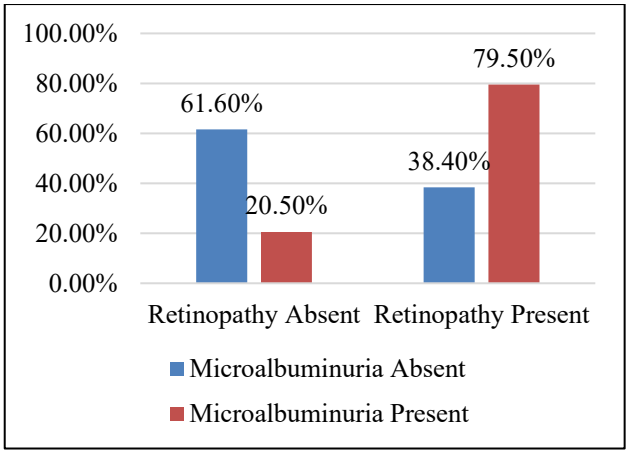

Figure 3: Depicting association of retinopathy with Microalbuminuria.

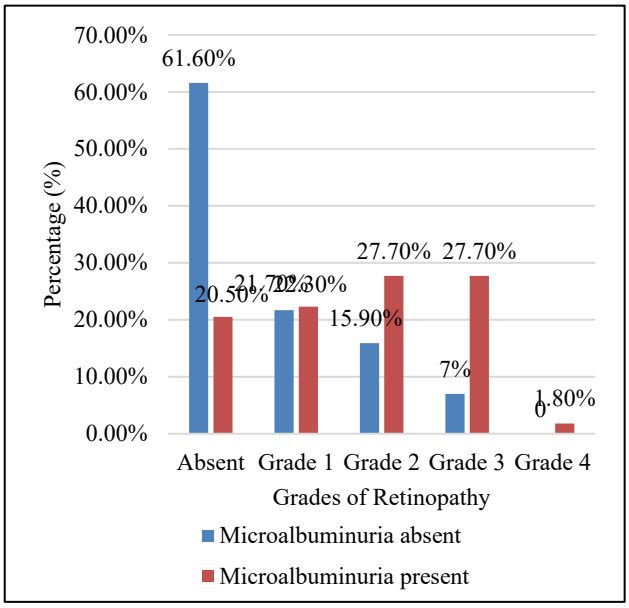

Figure 4: Association of grade of retinopathy with Microalbuminuria.

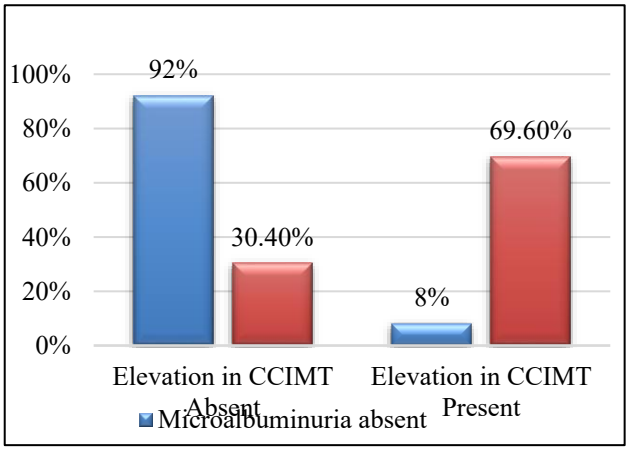

Figure 5: Association of elevated common carotid intima-media thickness (CCIMT) with microalbuminuria.

In the cohort of patients with essential hypertension, elevated carotid intimal-medial thickness (CCIMT) is present in 89 individuals, constituting 35.6% of the population. The prevalence of CCIMT, with a 95% confidence interval, is calculated to be 35.6%.

Distribution of retinopathy according to grade (Keith-Wagner-Barker classification)

The distribution of retinopathy grades indicates varying levels of severity. Of the total patients, 142 (56.8%) exhibit retinopathy, specifically, 55 patients (22.0%) are at grade 1, 53 patients (21.2%) are at grade 2, 32 patients (12.8%) are at grade 3 and 2 patients (0.8%) are at grade 4. The association between retinopathy and microalbuminuria among patients with essential hypertension reveals a significant relationship. Of those without microalbuminuria, 61.6% (85 out of 138) do not have retinopathy, whereas only 38.4% (53 out of 138) do. In contrast, among those with microalbuminuria, only 20.5% (23 out of 112) are without retinopathy, while a substantial 79.5% (89 out of 112) have retinopathy.

The chi-square test confirms a strong association (chi sq=42.48, p<0.001), indicating that the presence of microalbuminuria increases the likelihood of retinopathy. The odds ratio (OR) further supports this association, calculated at 6.21 (95% CI 3.50-11.00), suggesting a significantly elevated risk of retinopathy among hypertensive patients with microalbuminuria compared to those without. The association between retinopathy grades and microalbuminuria among patients with essential hypertension shows varying patterns across different severity levels. For those without microalbuminuria, the distribution across retinopathy grades is as follows: 61.6% (85 out of 138) have no retinopathy, 21.7% (30 out of 138) are in Grade 1 (G1), 15.9% (22 out of 138) are in Grade 2 (G2) and only 0.7% (1 out of 138) are in Grade 3 (G3). Notably, no patients in this group fall into Grade 4 (G4). In contrast, among patients with microalbuminuria, the distribution shifts significantly: 20.5% (23 out of 112) have no retinopathy, while 22.3% (25 out of 112), 27.7% (31 out of 112) and 27.7% (31 out of 112) are in Grades 1, 2 and 3, respectively. A small percentage, 1.8% (2 out of 112), are categorized under Grade 4.

Statistical analysis using chi-square tests reveals significant associations between microalbuminuria and retinopathy grades: Grade 1 (G1) shows an odds ratio (OR) of 3.08 (95% CI 1.53-6.22), Grade 2 (G2) shows an OR of 5.21 (95% CI 2.55-10.64) and Grade 3 (G3) exhibits the highest OR of 114.6 (95% CI 14.8-884.6), all indicating progressively elevated risks of various grades of retinopathy in the presence of microalbuminuria. The association between carotid intima-media thickness (CCIMT) and microalbuminuria among patients with essential hypertension reveals a striking relationship.

Among those without microalbuminuria, 92.0% (127 out of 138) exhibit normal CCIMT, while only 8.0% (11 out of 138) show abnormal CCIMT. In contrast, among patients with microalbuminuria, the distribution shows a notable increase in abnormal CCIMT, with 69.6% (78 out of 112) displaying thickened carotid intima-media.

Statistical analysis using chi-square tests indicates a highly significant association between microalbuminuria and abnormal CCIMT (p<0.001). The odds ratio (OR) of 26.5 (95% CI 12.7-55.3) underscores that individuals with microalbuminuria are significantly more likely to have abnormal CCIMT compared to those without microalbuminuria.

Table 1: Age distribution of patients of essential hypertension.

Age (in years)	No. of patients	%
30-40	48	19.2
40-50	91	36.4
50-60	59	23.6
60-70	36	14.4
>=70	16	6.4
Mean±SD	49.81±11.05 years	

Table 2: Prevalence of microalbuminuria, retinopathy and common carotid intimal medial thickness (CCIMT) in patients of essential hypertension.

Target organ damage	Microalbuminuria		Retinopathy		Elevated CCIMT	
	Present	Absent	Present	Absent	Present	Absent
Number of patients (Total patients=250)	112	138	142	108	89	161
Percentage	44.8	55.2	56.8	43.2	35.6	64.4
Prevalence (95% CI)	44.8 (38.6-51.0)		56.8 (50.7-62.9)		35.6 (29.7-41.5)	

Table 3: Association of retinopathy with microalbuminuria.

Retinopathy	Microalbuminuria				Significance	OR (95% CI)
	Absent		Present			
	N	%	N	%		
Absent	85	61.6	23	20.5	chi sq=42.48, p<0.001	6.21 (3.50-11.00)
Present	53	38.4	89	79.5		

Table 4: Association of grade of retinopathy with microalbuminuria.

Retinopathy grade	Microalbuminuria				Significance	OR (95% CI)
	Absent		Present			
	N	%	N	%		
Absent	85	61.6	23	20.5	Ref.	
G1	30	21.7	25	22.3	chi sq=10.24, p=0.001	3.08 (1.53-6.22)
G2	22	15.9	31	27.7	chi sq=22.07, p<0.001	5.21 (2.55-10.64)
G3	1	0.7	31	27.7	chi sq=59.51, p<0.001	114.6 (14.8-884.6)
G4	0	0.0	2	1.8	chi sq=6.93, p=0.009	NA

Table 5: Association of elevated common carotid intima-media thickness (CCIMT) with microalbuminuria.

Elevated CCIMT	Microalbuminuria				Significance	OR (95% CI)
	Absent		Present			
	N	%	N	%		
Absent	127	92.0	34	30.4	chi sq=102.6, p<0.001	26.5 (12.7-55.3)
Present	11	8.0	78	69.6		

DISCUSSION

The mean age of patients included in this study was 49.81 years with a standard deviation of 11.05 years, indicating that most patients fall within the middle-age bracket. There were 141 male and 109 female patients, representing 56.4% and 43.6% of the total, respectively, suggestive of slight male predominance. The prevalence of microalbuminuria in patients with essential hypertension, with a 95% confidence interval, is 44.8% (38.6%-51.0%), i.e., 112 out of 250 patients. A study by Parving HH et al, found microalbuminuria at 39% in a cohort of hypertensive patients, whereas Patel DK et al, reported 48% prevalence of microalbuminuria in essential hypertension.[4,5] The finding in our study was suggestive of the fact that almost half of the hypertensive patients in general had microalbuminuria, highlighting the need for careful monitoring and management of renal function in this population.

Chronic hypertension leads to nephrosclerosis. This is associated with progressive thickening of the afferent arterioles in an attempt to limit the increase in filtration pressure. However, this may also lead to ischemic damage to nephrons culminating in microalbuminuria. And, as more and more nephrons get involved, there is progressive rise in urine albumin loss corresponding to the extent of damage, eventually leading to chronic kidney disease. Thus, urine microalbuminuria (30-300 mg/gm) is an early indicator of ongoing hypertensive vasculopathic renal damage. And, according to finding in our study, untreated or inadequately treated hypertensives have high propensity to develop microalbuminuria (close to half in our case).

The prevalence of retinopathy in this study, with a 95% confidence interval, is 56.8% (50.7%-62.9%), i.e., 142 out of 250 patients. According to Besharati et al 39.9% of patients suffered from retinopathy from a cohort of 213 hypertensive patients in their study and the prevalence of hypertensive retinopathy increased with the severity of hypertension: 25.3% in mild, 34.5% in moderate and 84.6% in severe hypertension.[6] Similarly, Gudayneh et al showed that the prevalence of hypertensive retinopathy among adult hypertensive patients was 57.47%.[7]

These findings underscore the importance of regular eye examination and proactive management to prevent and address ocular ailments due to hypertension in this patient group. Chronic hypertension leads to damage of the retinal blood vessels. The retinal blood vessels lack sympathetic nerve supply. There is autoregulation of blood flow here. Thus, with rise in blood pressure, there is compensatory vasospasm to limit the transfer of this elevated pressure to fragile retinal vessels. However, with persistently elevated blood pressure, this compensatory tone is superseded and

damage to vessel wall ensues. There is thickening of the intimal wall, with muscle layer hyperplasia, visible as arteriolar narrowing on fundus examination (grade 1 and 2 retinopathy). If the blood pressure remains uncontrolled, there is disruption of vessel wall, leading to dot-blot and flame-shaped haemorrhages along with hard exudates and cotton wool spots formation (grade 3 retinopathy). Severe uncontrolled and late-stage hypertension leads to optic nerve ischemia and oedema (papilledema), i.e., grade 4 retinopathy. The successive stages of retinopathy underscore the extent of damage caused due to persistently elevated blood pressure.

The pathophysiological explanation of target organ damage (TOD), due to sustained hypertension, involving nephrosclerosis & microalbuminuria and vasculopathy of the retinal vessels, has been pertinently illustrated by Beevers et al and Wong et al in their study.[8,9]

The association between retinopathy and microalbuminuria among patients with essential hypertension reveals a significant relationship. Of those patients without microalbuminuria, 61.6% (85 out of 138) did not have retinopathy, whereas only 38.4% (53 out of 138) did. In contrast, among patients with microalbuminuria, only 20.5% (23 out of 112) did not have retinopathy, while a substantial 79.5% (89 out of 112) did. The chi-square test confirms a strong association (chi sq=42.48, $p<0.001$), suggestive of the fact that the presence of microalbuminuria increases the likelihood of retinopathy. The odds ratio (OR) calculated at 6.21 (95% CI 3.50-11.00), further corroborates this finding. Busari OA et al, conducted study in hypertensive Nigerian adults and it showed similar result.[10] In a cohort of 96 newly diagnosed non diabetic hypertensive adults in Nigeria, microalbuminuria was observed in 32.3% of participants. Those with MA were significantly more likely to exhibit hypertensive retinopathy (71% vs. 37%; P=0.001) and advanced retinopathy (Grades III–IV) occurred in 22.6% vs. 1.5% of MA negative individuals.

In this study, for those without microalbuminuria, the distribution across retinopathy grades is varied, as: 61.6% (85 out of 138) have no retinopathy, 21.7% (30 out of 138) are in Grade 1 (G1), 15.9% (22 out of 138) are in Grade 2 (G2) and only 0.7% (1 out of 138) are in Grade 3 (G3), whereas no patients in this group fall into Grade 4 (G4). Meanwhile, among patients with microalbuminuria, the distribution shifts significantly: only 20.5% (23 out of 112) have no retinopathy, while 22.3% (25 out of 112), 27.7% (31 out of 112) and 27.7% (31 out of 112) fall in Grades 1, 2 and 3 respectively. 1.8% (i.e., 2 out of 112), are categorized under Grade 4.

Statistical analysis using chi-square test reveals significant associations between microalbuminuria and retinopathy grades: Grade 1 (G1) shows an odds ratio (OR) of 3.08 (95% CI 1.53-6.22), Grade 2 (G2) shows an OR of 5.21 (95% CI 2.55-10.64) and Grade 3 (G3) exhibits the highest OR of 114.6 (95% CI 14.8-884.6), all indicating progressively elevated risks of retinopathy in patients with microalbuminuria. Multiple studies have demonstrated a strong, graded correlation between the severity of hypertensive retinopathy and microalbuminuria in essential hypertensive patients. For example, a Chinese cohort study carried out by Wu et al showed that higher Keith-Wagener-Barker retinopathy grades were associated with progressively higher mean urinary albumin-creatinine ratios.[11]

In this study, among the 250 patients with essential hypertension, elevated common carotid intima-media thickness (CCIMT) was identified in 89 individuals, representing 35.6% of the cohort. Thus, the prevalence of elevated CIMT was estimated at 35.6%, with a corresponding 95% confidence interval. Our findings were consistent with conclusions drawn from the studies carried out by Naseh et al and Mustafa et al.[12,13]

Among patients without microalbuminuria, only 8.0% (11 out of 138) show abnormal CCIMT. In contrast, among patients with microalbuminuria, the distribution shows a notable increase in abnormal CCIMT, with 69.6% (78 out of 112) displaying thickened carotid intima-media. Statistical analysis using chi-square tests indicates a highly significant association between microalbuminuria and abnormal CCIMT ($p<0.001$). The odds ratio (OR) of 26.5 (95% CI 12.7-55.3) underscores the potential role of microalbuminuria as a predictor for carotid artery structural changes in hypertensive patients. Sharma D et al, also investigated the association between microalbuminuria and carotid intimal medial thickness (CIMT) in patients with essential hypertension and found that microalbuminuria was significantly associated with increased CIMT values (suggesting a higher prevalence of subclinical atherosclerosis, as measured by CIMT).[14]

Authors observed that in all the patients exhibiting microalbuminuria, there is significantly high propensity to develop other target organ damage. Thus, it can be reliably used as a tool to predict ongoing target organ damage elsewhere, namely retinopathy and increase in common carotid intimal medial wall thickness. Agarwal et al proposed microalbuminuria as a cost-effective screening tool for target organ damage in hypertensives, resonating with our recommendation for routine ACR in hypertensives.[15]

Even though this study gave abundant information regarding prevalence of target organ damage in hypertensive population and their co-relation, however, the target population in this study was confined to one geographical area. In order to understand broader implications of hypertensive target organ damage and possibility of using microalbuminuria as a tool to ascertain other ongoing target organ involvement, a multicentric trial would have yielded a better perspective. Also, given the scale of hypertensive population in the country, a much larger sample size would have given a better outlook.

CONCLUSION

When evaluating microalbuminuria in context of other target organ damage significant inferences were drawn. In those hypertensive patients with microalbuminuria, a considerably higher prevalence of retinopathy and elevated CCIMT was appreciated. In the target population, the likelihood of microalbuminuric hypertensives developing retinopathy was almost six times and elevation of CCIMT nearly twenty-six times, when compared to those without microalbuminuria. When evaluating different grades of retinopathy, the patients with microalbuminuria had three-fold chances to develop grade 1, five-fold chances to develop grade 2 and almost 114 times the risk of developing grade 3 retinopathy when compared to hypertensive patients without microalbuminuria.

Therefore, it was concluded that microalbuminuria could function as a great tool to identify possibility of other target organ damage and initiate proper treatment in time, so as to prevent the occurrence of unfavourable vascular events in the future. This would not only reduce the possibility of prospective disease burden (like blindness, heart failure, cerebrovascular accidents, chronic kidney disease) and its associated economical strains, but also reduce morbidity and mortality associated with hypertension. Thus, it is being recommended to routinely send urine ACR of hypertensive patients and in case of presence of microalbuminuria, proactively look out for other target organ involvement to initiate their early treatment.

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