MICROALBUMINURIA: ASSOCIATION WITH ISCHAEMIC HEART DISEASE IN NON-DIABETICS

Rizwan Hashim, Shazia Nisar*, Khalil ur Rehman, Naeem Naqi*****

Departmetn of Pathology, Combined Military Hospital, Lahore. *Department of Medicine Combined Military Hospital, Lahore. **Department of Pathology, King Edward Medical College, Lahore., *, Classified Physician Combined Military Hospital, Lahore.**

Background: In view of the high morbidity and mortality associated with ischemic heart disease (IHD), the estimation of individual cardiovascular risk over and above the assessment of classic risk factors, such as age, hypercholesterolemia and hypertension, is an important prerequisite for focusing preventive measures and therapeutic measures. Microalbuminuria (MA) as a marker of IHD in nondiabetics is currently under international debate. The present descriptive study undertaken at Combined Military Hospital, Lahore was aimed to determine the frequency of MA in nondiabetic IHD patients. **Methods:** One hundred consecutive non diabetic patients with IHD (73 males, 27 females). Patients showing clinical albumiuria and with other causes of proteinuria were excluded. Urinary albumin in first morning sample was estimated by immunoturbidimetry method. Albumin to creatinine ratio (ACR) was calculated as mg/g. **Results:** The frequency of MA (ACR > 30 mg/g) was 37% in patients. Frequency was highest in older age bracket for both genders. The mean ACR was 131.8±66.2 mg/g. Significant difference was observed in mean MA level among different age groups. **Conclusion:** MA is common in nondiabetics patients with IHD. The mean level of MA was higher in older patients.

Key Words: Ischemic heart disease, nondiabetics, microalbuminuria, cardiovascular risk.

INTRODUCTION

Ischemic heart disease (IHD) is among the most frequent causes of morbidity and mortality worldwide.[1] In the presence of this alarming epidemic, the case for identifying and targeting patients with IHD for aggressive treatment to reduce cardiovascular risk is well established.[2] Risk factors for the development of IHD include age, gender, smoking, blood pressure, body mass index, and abnormalities of serum lipids. [3,4,5] However, these conventional risk factors do not account for all cases of IHD. The interest in improving cardiovascular risk assessment, resulting from a better understanding of the pathogenesis of atherosclerosis and identification of new targets for anti-atherosclerotic drug therapy, has always stimulated the search for novel risk factors. Currently, there is an intense debate whether they should be introduced into routine risk assessment. This especially concerns Lipoprotein (a)[6], C-Reactive Protein[7,8], fibrinogen[9], homocysteine[10] and microalbuminuria (MA)[11].

MA, ie, slightly elevated urinary albumin excretion, was initially demonstrated in patients with diabetes mellitus, where it was shown to be associated with atherogenic changes in the cardiovascular risk profile,[12] and to predict increased mortality and cardiovascular disease.[13,14] It has been used for many years as a predictor of incipient nephropathy in diabetic patients.[13] Recently, it has been suggested that MA may be a risk factor for the development of cardiovascular disease in non-diabetics as well and may therefore have a role in screening programmes. It has been reported in international literature that MA is an independent predictor of IHD and also substantially increases the risk associated with other risk factors. The Prevention of Renal and Vascular End Stage Disease (PREVEND) study concluded that urinary albumin measurement may be useful in early risk profiling and prevention of cardiovascular disease as it is independently associated with increased cardiovascular risk factors and cardiovascular morbidity.[15]

It has been hypothesized that MA is an indicator of wide spread endothelial cell dysfunction leading to increased penetration of atherogenic protein in the arterial wall. In the 1st MONICA (*Moni*toring Trends and Determinants of *Ca*rdiovascular Diseases) study in Copenhagen County, individuals with persistent MA had increased transvascular albumin leakage to a level similar to that seen among individuals with severe clinical atherosclerosis.[16] Though the underlying mechanism remains undetermined, it has been hypothesized that the magnitude of albumin excretion in urine reflects the degree of atherosclerosis. If this is so, the urinary albumin excretion should be high in patients with IHD even in non diabetics. Hence, a study was carried out with the aim to find out frequency and level of MA in non diabetic patients with IHD.

MATERIAL AND METHODS

This descriptive study spanning over three months from Sep to Nov 2004 was conducted in the Departments of Medicine and Pathology of Combined Military hospital, Lahore. The study

population included one hundred non diabetic IHD patients (73 were men, 27 were women), consecutively reporting to the hospital. The majority of patients belonged to middle socioeconomic group. The diagnosis of IHD was based on finding of characteristic electrocardiographic changes, cardiac enzyme elevation, positive coronary arteriogram or hospital discharge diagnosis of IHD. Patients with diabetes, macroalbuminuria, renal disease, urinary tract infection and cardiac failure were excluded.

After obtaining informed verbal consent, recording of demographic data, brief clinical history and physical examination of patients were carried out. A 12- lead electrocardiography was recorded. Fasting blood and first morning urine samples were collected. Two more urine samples were taken on the following days. Blood was tested for urea, creatinine and glucose. Routine urine examination was performed. Urinary albumin and creatinine were estimated and albumin to creatinine ratio (ACR) was calculated. Urinary albumin was measured by immunoturbimetric method using a commercial kit (Randox Laboratories, UK).[17] All the chemical analyses were carried out on Auto Analyzer Selectra E (Vital Scientific, The Netherlands). Patients were considered microalbumiuric if ACR was between 30-300 mg/g in 2 out of 3 urine samples. Below this level they were regarded as nomoalbuminuric. All the data was recorded on a Performa. Then data was entered and processed on SPSS software V. 11. It was presented as percentages, means and standard deviation. Analysis of variance F- test was applied to observe the mean difference.

RESULTS

Out of a total 100 selected non diabetic patients with IHD, 73 were men and 27 women. The mean ages were 59.1±13.7 (range 31-90), 60.3 ±9.9 (range 42-80) and 59.4±12.8 (range 31-90) years in men, women and all patients respectively. Frequency of MA in different age groups of study population is described in Table 1. The relative frequency was same in both sexes. However, it was higher in older patients. In patients over 70 years the frequency was highest (45.5%). Table 2. shows a comparison of level of albuminuria in microalbuminuric patients in relation to age. The level of albuminuria increased with increasing age (Fig. 1). The average level of MA was 131.8±66.2 mg/g in the study population. Significant difference was observed in mean MA levels among different age groups.

Table-1. Frequency of microalbumiuria in different age groups

Age Group (years)	Number	Positive	Relative Frequency
31-40	9	3	33.3%
41-50	18	6	33.3%
51-60	24	8	33.3%
61-70	27	10	37.0%
>70	22	10	45.5%
Total	100	37	37.0%

Table-2: Comparison of level of albuminuria in different age groups

Age Group (years)	Mean±SD (mg/g)	Minimum (mg/g)	Maximum (mg/g)
31-40	55.0±15.6	44.4	72.9
41-50	79.7±41.0	42.5	136.9
51-60	133.5±42.2	75.4	198.9
61-70	153.3±85.2	40.8	290.8
>70	163.2±50.2	85.9	225.9
Total	131.8±66.2	40.8	290.8

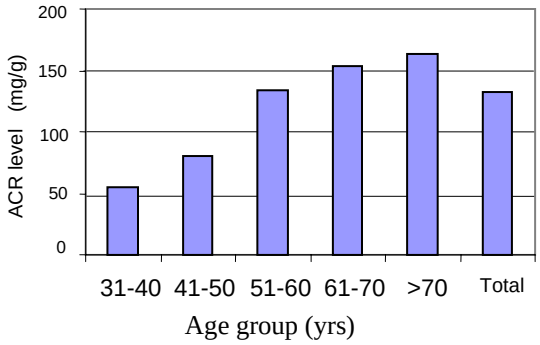

Fig.1 Level of albuminuria in relation to age in

DISCUSSION

Worldwide, ischemic heart disease is assuming an increasing role as a major cause of morbidity and mortality. From 1990 to 2020, the proportion of worldwide deaths due to cardiovascular disease including IHD is expected to increase from 28·4% to 33·7%. In terms of years of life lost, cardiovascular disease will jump from fourth to first place. For premature death and disability, cardiovascular disease will move from fifth to first place. [1] However,

despite the rising tide of this tragic disease, the physicians' ability to predict the development of a cardiovascular event is limited by the low prognostic specificity of the traditional risk factors for atherosclerosis. This justifies the ongoing search for new bio markers of atherosclerosis.

In the current study it was found that the frequency of microalbuminuria was elevated in the study population (37 %). This is significantly higher as compared to the general population which ranges from 2.2% to 10.2% in various studies[18,19,20] depending on variations in ethnic groups, specimen collection, the cut off value of albumin excretion and the analytical methods. This finding is similar to that found in studies in the west.[21] The frequency and level of MA in our study was found to be highest in the older age brackets for both genders. This positive correlation with age may be related to a degree of nephrosclerosis as found in an earlier study.[19]

Patients with renal or urinary tract disease or diabetes mellitus were excluded from this study, as urinary albumin excretion is elevated in these diseases for reasons other than atherosclerosis. The use of early morning urine sample was preferred to minimize the contribution of posture and exercise to urinary albumin excretion. By using the albumin creatinine ratio any variations in the urine volume were taken into account.

Despite the above-mentioned strengths of the study, it must be admitted that it has some limitations namely the small sample size and the fact that it is a hospital based study. However, these matters can be addressed by undertaking large population based and prospective studies.

The hypothesis of microalbuminuria as an atherosclerotic risk factor stems from diabetic research.[22] Several studies have now demonstrated that MA is an independent predictor of cardiovascular morbidity and mortality in non diabetic populations as well.[18,23,24] It has been postulated that MA is a marker of generalized endothelial dysfunction,[25] which is thought to be the first stage of atherosclerosis. According to the above hypothesis urine albumin should be elevated and MA occur more frequently in these patients. Therefore, the results of this study support the hypothesis and underline the clinical relevance of MA as a cardiovascular risk indicator even in the absence of diabetes mellitus.

In addition to scientific and academic speculation there is a very important practical aspect to the intriguing association between microalbuminuria and ischemic heart disease, which is of special significance for the clinician. The detection of microalbuminuria is straightforward, easy and inexpensive to perform and may be used to identify subjects at increased cardiovascular disease risk and to prompt screening for other risk factors.

Also, as it has been shown that an early increase of urinary albumin is a strong independent predictor of adverse clinical outcome in both men and women with acute myocardial infarction, [26] stratification of patients into low- and high-risk groups can be facilitated by ACR. So, it has been suggested that this measurement be included in the routine clinical work up of the patient with acute myocardial infarction. The aspect that makes it more attractive than some of the other emerging risk markers is that microalbuminuria is a modifiable risk factor whose correction, as in the case of hypercholesterolemia or arterial hypertension, would reduce, in its own right, the incidence of cardiovascular disease morbidity and mortality.

In short, our study highlights that MA is more frequent in non diabetic patients with IHD than the general population and thus may be an important emerging risk marker for it. Further large population based prospective studies are needed to assess the relationship between the occurrence of microalbuminuria and subsequent risk of IHD. Eventually the measurement of MA may prove to be useful in cardiovascular risk profiling and prevention of IHD and result in new therapeutic strategies in the prevention of this disease.

Though population wide screening is not recommended due to lack of definitive evidence, screening for microalbuminuria should be considered in high risk subjects e.g. those with a strong family history of IHD, smokers, those with hypertension and hypercholesterolemia to improve cardiovascular risk profiling.

REFERNCES

1. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, Mass: Harvard University Press; 1996.
2. McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn H, et al. The Minnesota Heart Survey Investigators. Recent trends in acute coronary heart disease: mortality, morbidity, medical care, and risk factors. N Engl J Med 1996; 334:884–90.
3. Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases. Part II: Variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001; 104:2855 - 64.
4. Abbas S, Abbas S, Riaz A, Malik N. Risk factors for coronary artery disease in Pakistan. Pak Armed Forces Med J 2003; 53(1):12-19.
5. Khan JA, Khan SP, Ahmed Z, Shah SH, Khaliq MA. Level of hypercholesterolemia in patients admitted for heart diseases: a pilot study. Pak J Med Res 2001; 40:18-9.
6. Nyuyen TT, Elleform RD, Hodge DO, Balles KR, Kolthe TE, Abu-Leddhl. Lp (a) as a risk factor for cardiovascular disease. Circulation 1997; 96: 1390-7.

7. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973–9.
8. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836–43.
9. MA J, Hennekens CH, Ridker PM, Stampfer MJ. A prospective study of fibrinogen and risk of myocardial infarction in the Physicians' Health Study. J Am Coll Cardiol 1999; 33:1347-52.
10. Christen WG, Ajani UA, Glynn RJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease: causal or casual? Arch Intern Med 2000; 160: 422–34.
11. Viberti GC, Thomas SM. Searching for new coronary heart disease risk factors. Eur Heart J 2000; 21:1905-6.
12. Ali I, Khan I, Baloch MK, Mustafa G. Comparative lipd profile studies in cardiac and diabetic patients. Pak J Pharmaceut Sci 2004; 17:25-30.
13. Parving HH, Osterby R, Ritz E. Diabetic nephropathy. In: Brenner BM, Levine S (edi). The Kidney. Philadelphia: WB Saunders; 2000:1731-73.
14. Garg JP, Bakris GL. Microalbuminuria: marker of cardiovascular dysfunction, risk factor for cardiovascular disease. Vasc Med 2002; 7:35-43.
15. Hillege HL, Janssen WMT, Bak AAA, Diercks GFH, Grobbee DE, Crijns HJGM et al. Microalbumniuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Inter Med 2001; 249:519-26.
16. Jensen JS. Microalbuminaria and the risk of atherosclerosis. Clinical, epidemiological and physiological investigations. Dan Med Bull 2000; 47(2):63-78.
17. Lloyd DR, Hindle EJ, Marples J, Gatt JA. Urinary albumin measurements by immunoturbidimetry. Ann Clin Biochem 1987; 24:(Pt2) 209-10.
18. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington Diabetes Survey. Lancet 1988; ii: 530–3.
19. Ritz E, Nowicki M, Fliser D, Horner D, Klin HP. Proteinuria and hypertension. Kidney Int 1994; 46 (Suppl 47):S76–80.
20. Cirillo M, Senigalliesi L, Laurenzi M, Alfieri R, Stamler J, Stamler R et al. Microalbuminuria in non-diabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. Arch Intern Med 1998; 158: 1933-9.
21. Taskiran M, Feldt-Rasmussen B, Jensen GB, Jensen JS. Urinary albumin Excretion in hospitalized patients with acute myocardial infarction. Scand Cardiovasc J 1998; 32:163-6.
22. Venkatt KK. Proteinuria and microalbuminuria in adults: significance, evaluation and treatment. South Med J 2004; 97(10):969-79.
23. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion. An independent predictor of ischemic heart disease. Arterioscler Thromb Vasc Biol 1999; 19:1992-7.
24. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. BMJ 1990; 300: 297–300.
25. Jensen JS. Renal and systemic transvascular albumin leakage in severe atherosclerosis. Arterioscler Thromb Vasc Biol 1995; 15: 1324-29.
26. Berton G, Cordiano R, Palmieri R, Cicchini F, DeToni R, Palitini P. Microalbuminuria during acute myocardial infarction. Eur Heart J 2001; 22:1466-1475

Address for Correspondence:
Dr. Khalil ur Rehman, 21/5 Birdwood Road, Lahore 54000. Phone Nos. 042-7576287, 0300-4237012
E-mail: khalilurrehman5@yahoo.com