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RESEARCH ARTICLE

Microalbuminuria as a predictor of cardiovascular disease in patients with essential hypertension

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Abstract

Hypertension is a major risk factor for cardio-vascular diseases that killed 2.7 million people in 2004 and will result in the death of over 4 million people by 2030. Microalbuminuria is a marker of hypertensive and atherosclerotic organ damage in essential hypertension and has powerful prognostic value for cardiovascular morbidity and mortality .For a sensitive assessment of global risk thorough evaluation of target organ damage needs to be undertaken while cost effectiveness of the same should also be kept in mind. Microalbuminuria seems to be a cost effective, widely available and predictive marker for identifying the hypertensive patients who are at higher risk of cardiovascular events.

INTRODUCTION

Microalbuminuria (MA) is a marker of hypertensive and atherosclerotic organ damage in essential hypertension and has powerful prognostic value for cerebral and cardiovascular morbidity and mortality. Despite overwhelming evidence that effective treatment of hypertension is associated with a significant reduction of cardiovascular events, the number of patients who are aware of their condition and who achieve adequate blood pressure (BP) control remains unacceptably low. This issue has now become a major public health problem that needs to be faced with more aggressive treatment strategies to contain the incumbent epidemic of cardiovascular complications. The key issue when dealing with such a large number of patients is the ability to identify and target the subgroup at higher risk for future events. In the last decade there has been lot of advancement in management of hypertension and resultant target organ damage. Accurate risk evaluation for target organ damage is a prerequisite for devising cost-effective therapeutic strategies in patients with essential hypertension. Thorough evaluation of target organ damage is the key to sensitive assessment of global risk, but cost-effectiveness of the same should also be taken into consideration. Hence the need for a cost effective and widely available marker for identifying the hypertensive patients who are at higher risk of cardiovascular events as well as other target organ damage.MA as an indicator seems to be promising.

Prevalence of HTN

As per the World Health Statistics 2012, of the estimated 57million global deaths in 2008, 36 million (63%) were due to non communicable diseases (NCDs). The largest proportion of NCD deaths were caused by cardiovascular diseases (48%). In terms of attributable deaths, raised blood pressure is one of the leading behavioural and physiological risk factor to which 13% of global deaths are attributed (WHO report 2003).

Worldwide, raised blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths. This account for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS. In a worldwide scenario estimated total number of adult with hypertension in year 2000 was 972 million. In the same year in economically developed countries it was 333 million and in economically developing countries it was 639 million. It is projected that by the year 2025 this figure will reach1.56 billion worldwide (Kearney PM, 2005).Globally cardiovascular disease accounts for approximately 17 million deaths a year, nearly one third of the total of these are complications of hypertension and account for 9.4 million deaths worldwide. Every year over 140 million people are believed to be suffering from high blood pressure in the country and the number is expected to cross the 214 million mark in 2030 The prevalence of hypertension in India is reported as ranging from 10 to 30.9 %.The average prevalence of hypertension in India is 25% in urban and 10% in rural inhabitants. A WHO estimate in 2008 suggested 33 % men and 32 % women older than 25 years had hypertension in India. There is a strong correlation between changing lifestyle factors and increase in hypertension. The prevalence of hypertension in populations like Lepchas of Sikkim Himalayas varies between 15 to 42 % (Mukhopadhyay B et al, 1996). Hypertension has serious economic implications too.

HTN and cardiovascular disease

Hypertension is the commonest cardiovascular disorder affecting about 20% adult population worldwide. It is an important risk factor for cardiovascular mortality. Hypertension is a major risk factor for cardio-vascular diseases that killed 2.7 million people in 2004 and will result in the death of over 4 million people by 2030. Blood pressure levels have been shown to be positively and continuously related to the risk for stroke and coronary heart disease. In some age groups, the risk of cardiovascular disease doubles for each increment of 20/10 mmHg of blood pressure, starting as low as 115/75 mmHg. Treating systolic blood pressure and diastolic blood pressure until they are less than 140/90 mmHg is associated with a reduction in cardiovascular complications. Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, diastolic dysfunction, congestive heart failure (CHF), abnormalities of blood flow and cardiac arrhythmias.CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia.

Microalbuminuria

Microalbuminuria (Paucialbuminuria) is the rate of albumin excretion. It is defined as urinary albumin excretion (UAE) in the range of 20-200 µg/min or 30 -300mg/24 hrs or 30 – 300mg/L in a spot sample. The urine samples which are currently acceptable are 24hrs urine collection, overnight (8-24hrs) collection, 1-2 hrs collection in laboratory /clinic or first morning sample for simultaneous albumin and creatinine measurement. Determination of UAE in the morning urine sample constitutes the ideal test for screening. MA is also defined as albumin creatinine ratio (ACR) $\geq$ 3.5 mg/mmol in women and $\geq$ 2.5 mg/mmol in men.

Mechanism of Microalbuminuria

There are several proposed mechanism for microalbuminuria.Increased UAE could be the consequence of an augmented intraglomerular capillary pressure and could reflect the existence of intrinsic glomerular damage that causes changes in glomerular barrier filtration. It could also be the consequence of a tubular alteration that impedes the normal reabsorption of filtered albumin. However, it has been suggested that MA may represent the renal manifestation of generalized, genetically-conditioned vascular endothelial dysfunction that may underlie the link between an increased UAE and an elevated risk for cardiovascular disease. MA is associated with a decreased size- and charge-selectivity of the glomerular vessel wall in clinically healthy subjects, and is an independent marker of systemic transvascular albumin leakiness.

Atherosclerotic vascular disease is associated with renal and systemic transvascular leakiness for albumin. A defective endothelial permeability could be the underlying mechanism of MA in the general population. A relationship between MA and endothelial dysfunction in hypertension that includes a positive correlation of UAE and circulating von Willebrand Factor antigen, Factor VII hyperactivity, fibrinogen and endothelial cell damage has also been documented. However, when endothelial function is directly assessed through acetylcholine vasodilatory action no correlation with UAE is observed. Other mechanisms such as renal hemodynamic changes due to the direct transmission of increased systemic pressure to the glomeruli, permselectivity changes of the glomerular filter

and/or insufficient tubular reabsorption of albumin, and structural damage to the glomeruli and arterioles could be implicated in the presence of MA in essential hypertension. The significant positive correlation found between office blood pressure levels and UAE by most groups favor a significant role of elevated systemic blood pressure facilitating the transglomerular passage of albumin. The correlation is more pronounced when UAE values are plotted against ambulatory blood pressure values and shows that systolic blood pressure is one of the most relevant determinants of MA in the early stages of hypertensive disease. On the other hand, higher levels of UAE have been described in those patients not exhibiting a nocturnal fall in blood pressure (non-dippers), indicating that a greater degree of target organ damage could be present in this particular group of patients.

Techniques of measurement

There are various techniques for measurement of urinary albumin concentration.Quantitative lab tests allow the precise measurement of low concentrations of albumin in the urine by the principles of Radio immunoassay, Enzyme linked immunosorbent assay (ELISA),Nephelometry and Immunoturbidimetry. These quantitative methods require sophisticated equipment and technical expertise. Screening requires methods that are simple, quick to apply, reliable and cost effective. Semi quantitative bedside tests based on immunoassay, latex agglutination, nigrosine assay and silver dot blot assay are simple, rapid, highly reproducible and have a high sensitivity and specificity (>90%) when used judiciously. Bedside testing has an important role in the screening of patients with MA but as reagent strips do not correct for creatinine, they are subject to error due to changes in urine concentration. Hence, positive test by reagent strips must be confirmed by quantitative tests. 24 hours collection of urine is a gold standard for estimation of MA but spot samples also show high sensitivity and specificity, is more convenient for the patient and so is most commonly used.

MA and HTN

Prevalence of MA in essential hypertension varies between 5% & 37% (Donovan SJ, 2000). MA is common in the older population and in males. There is evidence showing correlation between systemic blood pressure and UAE rates, more in blacks even within the accepted non hypertensive range of blood pressure (Rodicio JL et al, 1998).MA & hypertensive patients with elevated UAE tend to have greater evidence of cardiovascular co morbidities including dyslipidaemia and glucose intolerance. These subset of patients have higher left ventricular mass, greater risk of hypertensive retinopathy and evidence of increased and more progressive atherosclerosis (Parving et al, 1974). Patients with elevated UAE have an increased thickness and presence of plaques in the carotid artery. Furthermore, the presence of MA in essential hypertensive patients has been interpreted as a marker of early intrarenal vascular dysfunction

MA and CVD in HTN

Microalbuminuria is associated with generalized endothelial dysfunction. The current consensus among researchers is that albumin passes through the vascular walls, and this increased permeability is a marker of endothelial dysfunction. Hypertensive patient having increased albumin leakage in glomerulus is linked to enhanced capillary permeability for albumin in systemic vasculature. Such leakage leads to hemodynamic strain and instability which could then start the atherosclerotic process, and eventually lead to adverse cardiovascular instability. It is interesting to note the data from the Losartan Intervention for Endpoint study which indicates that the relationship between urinary albumin excretion and cardiovascular risk holds true, well below the levels currently used to define MA .Furthermore, there is evidence that the regression of left ventricular hypertrophy parallels the reduction of albuminuria and is related to it to some degree regardless of BP changes. This opens the way to a broader use of MA assessment not only for its prognostic value but also for monitoring the efficacy of treatment.

MA is highly specific predictor of simultaneous occurrence of both cardiac and vascular abnormalities. MA is an independent predictor of cardiovascular morbidity and mortality in both men and women with essential hypertension. This could, in turn, be facilitated by the frequent association of an elevated urinary albumin excretion to a series of alterations, such as endothelial dysfunction, insulin resistance, altered lipid levels, higher body mass index, increased serum uric acid and salt-sensitivity. All these alterations could facilitate the accompanying risk for atherosclerosis, and it possibly explains such an association between UAE and the risk of coronary heart disease. Elevated albumin excretion rate (AER)is associated with a threefold excess mortality in elderly non diabetic individuals, mostly from cardiovascular disease (Damsgaard EM et al, 1990). After a large population survey it was concluded that proportion of persons free of ischemic events was significantly lower among those with MA (Jensen JS et al ,1995). Increase of UAE during acute myocardial infarction strongly predicts in-hospital mortality, and this prognostic information is greater and independent to other clinical markers. The rise in UAE was attributed to a

systemic increase in vascular permeability as part of the acute inflammatory process that accompanies the myocardial infarction(Berton G et al,1997). Clustering MA with other cardiovascular risk factors contributes to considering that MA in essential hypertension has a genetic origin.

In two studies which comprised of 870 subjects (628 men and 241 women) (Palatini P et al, 1996) and 121 subjects (Nancy B et al, 1999) respectively failed to show any correlation between albumin excretion rate and LVH. In another study it was observed that 30.5% subjects with hypertensive heart disease had MA and the remaining 23.43% with hypertensive heart disease did not have MA.Among the former group 17 subjects had LVH and 5 subjects had diastolic dysfunction. There was no significant correlation between MA and cardiovascular involvement (P=0.59) (Khandelwal B et al, 2014). On the other hand it has been observed that HTN with MA had 20 fold increase in both LVH and carotid wall abnormalities (Leoncini G et al,2002) and showed significant relationship between LVH and MA in patients with essential hypertension. Patients with LVH had significantly higher MA level compared with those without LVH.(Monfared A et al,2013). Left ventricular mass index is a predictor of new onset MA in hypertensive subjects which revealed that increase of LVMI leads to15% increased risk of MA. MA is also a marker for endothelial dysfunction and a predictor of cardiovascular events and the number of co morbidities is directly proportional to albuminuria.

Conclusion

The predictive capacity of MA for the development of cardiovascular events and mortality is as powerful as that of peripheral vascular disease especially amongst patients with hypertension. There is a definite relationship between mortality, cardiovascular events and LVH in patients with HTN but what needs further evaluation is whether left ventricular mass regression directly improves prognosis. With the available evidence, it is evident that early screening for MA of patients with essential HTN and aggressive management of those with MA may reduce the burden of cardiovascular events in HTN. Devising cost effective therapeutic strategies in patients with HTN requires accurate risk evaluation. Reduction of MA by various pharmacological agents has been effectively proved but whether this reduction of MA is beneficial in terms of morbidity and mortality needs to be assessed.

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