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REVIEW ARTICLE

MICROALBUMINURIA: A NOVEL MARKER OF SYSTEMIC DISEASE ACTIVITY

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ABSTRACT

Microalbuminuria is associated with increased risk for renal and cardiovascular mortality and morbidity in diabetes mellitus, hypertension and patients with acute myocardial infarction but the significance of microalbuminuria in other chronic diseases has been very rarely explored. This article highlights the pathogenesis, implications and methodology of testing for microalbuminuria in various systemic disorders.

INTRODUCTION

Microalbuminuria or dipstick negative albuminuria is conventionally defined as urinary albumin excretion between 30-300 mg/24 hour for timed 24 hours urine collections and between 20-200 mg/L for untimed samples (Bangstad *et al.,* 1991). High normal albuminuria is defined as morning urinary albumin concentration of 10-20 mg/l. Low normal albuminuria is morning urinary albumin concentration of less than 10 mg/l.

Mechanism

The intimate relationship between low-level albumin excretion and vascular permeability makes urinary albumin excretion highly sensitive to the presence of any inflammatory process. The kidney is ideally placed to amplify any small changes in the systemic vascular permeability. The glomeruli receive 25% of the cardiac output. Of the 70 kg of albumin that pass through the kidneys every 24 hours, less than 0.01% reaches the glomerular ultra filtrate (i.e., less than 7g/24 hour) and hence enters the renal tubules. Almost all the filtered albumin is absorbed by the proximal tubule via a high affinity, low capacity endocytotic mechanism, with only 10-30 mg/24 hr appearing in the urine. Assuming that 7 gm of albumin is filtered every 24 hour, 1% increase in systemic vascular permeability in response to an inflammatory stimulus would result in an additional 70 mg of albumin passing into the filtrate. Since tubular mechanisms for albumin reabsorption are near saturation, urinary albumin excretion would increase from a maximum of 30 to approximately 100 mg/24 hour (Andrew Hartland and Peter Gostling, 1999). Glomerular permeability to albumin is dependent on endothelial charge selectivity as well as size selectivity. The negative charge conferred on the glomerular memrane by its consistent glycoprotein plays a role in restricting the permeability of anionic proteins. Loss of glomerular charge selectivity has been found in both diabetic and non-diabetic population with microalbuminuria (Gosling and Beevers, 1989).

Other possible mechanisms of microalbuminuria include the following:

- **Systemic transvascular albumin leakage**: Transcapillary escape rate of albumin (TERalb) is defined as the fraction of the intravascular mass of albumin (IVMA) going through the vascular bed per unit time. The transcapillary escape rate of albumin is an overall measure of macromolecular permeability of the vascular bed in vivo. As microalbuminuria reflects systemic transvascular leakiness for albumin, which may also allow for a higher degree of lipid insudation into the large vessel wall, this may link microalbuminuria to atherogenesis (Stender and Hjelms1987).
- **Role of sialic acid**: Sialic acid has been reported to affect several haematological factors, transvascular permeability and accumulation of lipid in the arterial wall. Studies showed that in subjects without diabetes mellitus, an elevated serum concentration of sialic acid is predictive of atherosclerotic vascular disease in presence of concomitant elevation of urinary albumin excretion (UAE) (Lindberg *et al., 1*991).

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- **Impaired arterial dilatory capacity**: Slightly elevated urinary albumin excretion is associated with impaired conduit arterial dilatory capacity in clinically healthy subjects, and this impairment may be explained by a reduced dilatory response to nitric oxide of both endogenous and exogenous origin. Impaired arterial dilatory capacity may contribute to the increased cardiovascular risk in subjects with elevated UAE (Clausen *et al.,* 1869).
- **Elevated VWF concentrations and other prothrombotic factors**: Studies showed that prothrombotic factors like fibrinogen and factor VII C, Von Willebrand Factor antigen (VWF) are elevated in patients with type 1 diabetes complicated by microalbuminuria, so also in hypertensive patients. These were considered a potential markers of endothelial dysfunction (Lee *et a.,* 1993; Bhattacharya, 2004).
- **Hyperinsulinaemia**: In vitro, insulin has been shown to cause smooth muscle cell proliferation; stimulate LDL binding to smooth muscle cells, fibroblasts and monocytes; and stimulate cholesterol synthesis in monocytes (Kuusisto *et al.,* 1995). Hyperinsulinaemia and microalbuminuria are components of metabolic syndrome and are associated with a highly abnormal cardiovascular risk factor pattern.
- **Hyperhomocysteinaemia**: The enhanced risk of cardio and cerebrovascular disease with microalbuminuria may also be due in part to an association with hyperhomocysteinaemia, a risk factor for atherosclerosis (American Diabetes Association, 2004).

Factors known to influence the development of Microalbuminuria

- Body mass index
- Increased blood pressure (systolic, diastolic, mean)
- Altered lipid levels
- Insulin resistance (hyperinsulinemia)
- Smoking
- Salt sensitivity
- Elderly
- Endothelial dysfunction

Significance of Microalbuminuria

"Microalbuminuria signifies abnormal vascular permeability and its presencemay be considered as kidney's notice for markedly enhanced cardiovascular risk" (Rush University Hypertension Center, 2001). The importance of microalbuminuria was first appreciated in the early 1980s when two landmark studies in London and Denmark independently reported that it was predictive of development of overt diabetic nephropathy and progressive renal failure (Parving *et al.,* 1982; Viberti *et al.,* 1982). Since then, various studies have established the significance of microalbuminuria in several conditions:

- Several studies have shown that microalbuminuria in diabetic patients predicts diabetic nephropathy as well as increased cardiovascular and overall mortality (Mogensen, 1984). Persistent microalbuminuria in these patients also correlates with the presence of hypertension, obesity and dyslipidemia (Allawi and Jarrett, 1989). American Diabetes Association has adopted cut off values for diagnosis of diabetic nephropathy (Jorge *et al.,* 2005). In 1998 ADA included positive microalbuminuria as risk factor for coronary artery disease in diabetic subjects (Consensus development conference on the diagnosis of coronary heart disease in people with Diabetes, 1998).

ADA guidelines for Diabetic Nephropathy

Stages	Albuminuria cut-off values	Clinical characters
Microalbuminuria	* 20 - 199 mcg/min.	• Abnormal nocturnal fall in BP and rise in BP level.
	* 30 - 200 mcg/24 hours.	• Increased Triglyceride, total and LDL cholesterol. • Increased frequency of metabolic syndrome component.
	* 30 - 299 mg/gm.	
		• Endothelial dysfunction.
		• Association with diabetic retinopathy, amputation and CVD.
Macroalbuminuria	≥200 mcg/min.	• Hypertension.
	≥300 mg/24 hr.	• Increased triglycerides, total and LDL cholesterol.
	>300 mg/gm.	• Asymptomatic Myocardial ischemia.
		• Progressive GFR decline.

- Studies have shown that the prevalence of microalbuminuria is enhanced in hypertensive subjects, in particular in those with blood pressure characteristics that are associated with enhanced cardiovascular risk, such as salt sensitivity and an abnormal diurnal blood pressure rhythm. Microalbuminuria possibly identifies at an early stage, hypertensive patients with an enhanced risk of developing the well-known renal and cardio vascular hypertensive complications (Agarwal *et al.,* 1996).
- Studies have documented the relationship between the presence of microalbuminuria and other atherosclerotic risk factors such as hypertension, dyslipidaemia and smoking in the general population. Studies have revealed the significance of microalbuminuria as predictor of increased mortality in elderly persons (Dansgaard *et al.,* 1990).
- Microalbuminuria is detected early in the course of Acute Myocardial Infarction and is considered as an independent predictor of early mortality in this condition. Microalbuminuria has been found to be proportional to the size of the infarct. Gosling *et al* suggested that early rise in urinary albumin concentration is useful in distinguishing myocardial infarct from angina (Gosling *et al.,* 1991). Spyridon *et al* found that microalbuminuria is a strong independent predictor of 3 year adverse prognosis in patients who has sustained acute myocardial infarction (Shearman *et al.,* 1989).
- Roine *et al* demonstrated that microalbuminuria distinguished bacterial meningitis from aseptic meningitis with specificity of 94% (Pallister *et al.,* 1997).
- Shearman *et al* found that microalbuminuria peaked 36 hours after admission in patients with acute pancreatitis and that serious complications developed later, only in those

with the higher values of microalbuminuria (Mahmood *et al.,* 1993).

- Pallister *et al* found that microalbuminuria levels 8 hours after admission in trauma victims predicted the development of ARDS with a positive predictive value of 85% and a negative predictive value of 95% (Hickey *et al.,* 1990).
- Microalbuminuria has been found to be associated with wide variety of inflammatory conditions like rheumatoid arthritis, inflammatory bowel disorder, and surgery etc (Pederson *et al.,* 1995; Mahmood *et al.,* 1993; Hickey *et al.,* 1990).
- Highly significant association between microalbuminuria and carotid artery intima-media thickness has been reported - a finding which suggests that microalbuminuria may be a marker for early development of carotid artery atherosclerosis and points to a possible linkage between microalbuminuria and atherothrombotic stroke mechanism (Mykkanen *et al.,* 1997).
- Findings from several studies have suggested a relationship between microalbuminuria and disease activity in patients with rheumatoid arthritis.
- Pederson LM *et al*, found that 27.7% of patients with rheumatoid arthritis had microalbuminuria and it significantly correlated with CRP and is a sensitive indicator of disease activity (Pederson *et al.,* 1995).
- According to a study by Bhatt *et al*. microalbuminuria was present in 30% of rheumatoid arthritis patients, particularly in those with long standing disease and severe disease activity (Bhatt *et al.,* 2002).
- Saito *et al.* 1993 found that urinary albumin indices were elevated in patients with rheumatoid arthritis without macroalbuminuria and serial measurement of microalbuminuria especially in those receiving disease modifying anti rheumatic drugs are useful for detection of subclinical glomerular injury.

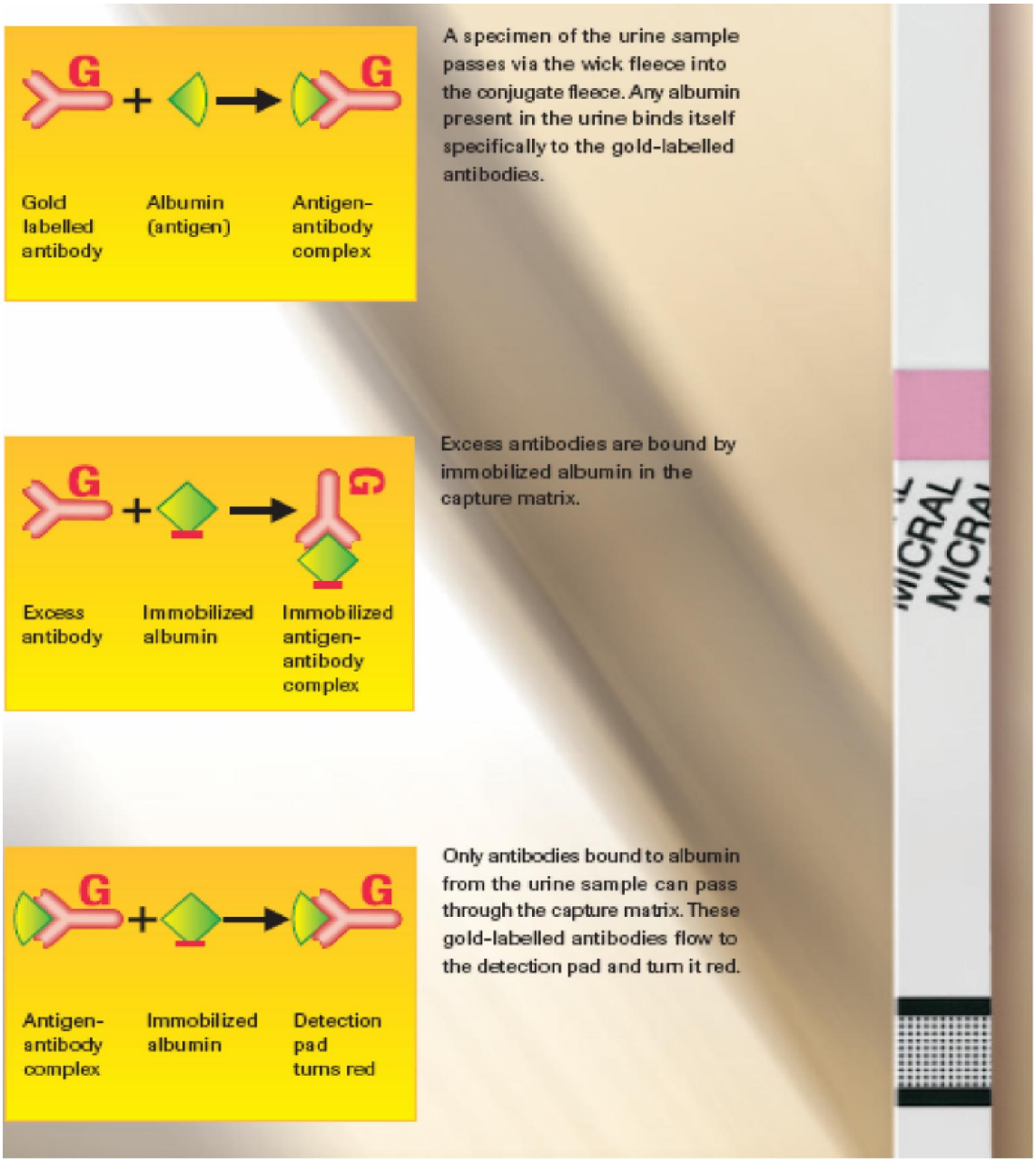


Fig. 5. Principle of Micral Test

- Nakamura *et al*. 2004 found that low grade inflammation as represented by CRP levels is significantly related to the presence of microalbuminuria.
- Tharwat *et al.* 1998 showed that microalbuminuria was present among 22.5% of the studied patients, more frequent among patients with extra-articular manifestations. It positively correlated with disease duration, treatment duration, morning stiffness articular index and ESR.
- Dimitrios Daoussis *et al.* 2011. Given the established association between MA and indices of inflammation in the general population (Dequeker and Rico, 1992), one would expect an increased prevalence of MA inpatients with increased inflammatory load, such as RA patients. In a study conducted more than a decade ago (The Nature and Treatment of Gout and Rheumatic Gout, 1859), MA prevalence in non-diabetic, non-hypertensive subjects was significantly higher in RA patients compared to controls (27.7% vs. 7.8%) (Dimitrios Daoussis *et al.,* 2011).

Tests for Microalbuminuria

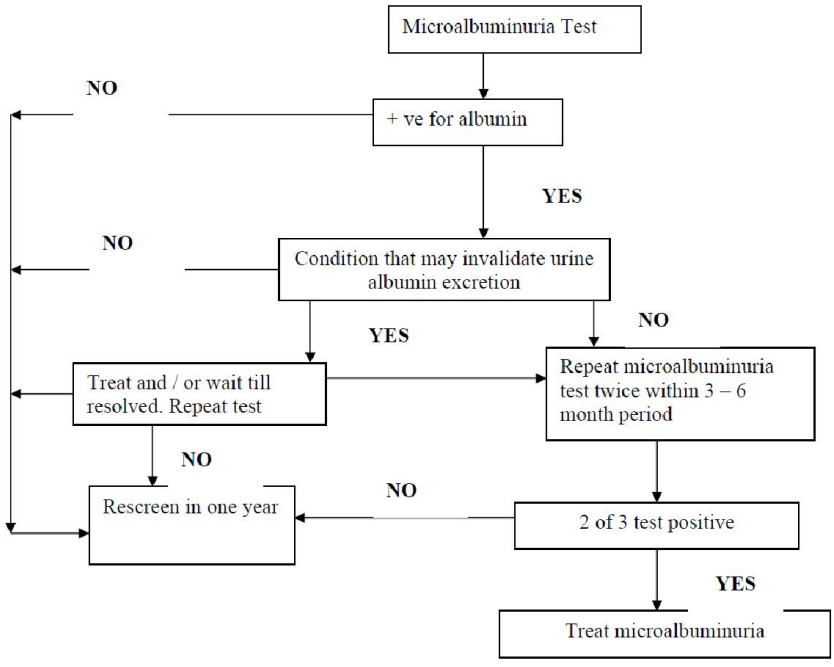
In 1963, Keen and Chlouveraskis described the first specific radioimmunoassay (RIA) for albumin in urine (Keen and Chloverakis, 1963). Since then several methods have been described for measurement of urinary albumin excretion with emphasis on unexpensive, easy to apply, rapid tests which can be used on a large scale population.

The various methods used are

1. Dipstick method.
2. Semi quantitative method.
   - Chemical precipitation (Sulphosalicyclic acid trichloroacetic acid)
   - Immuno precipitation (Micral Test).
3. Photometric method.
4. Nephelometric method.
5. Sensitive Quantitative methods
   - Radio immuno assay.
   - Cellulose acetate, agarose gel electrophoresis.

The procedures of various important methods include the following:

- **Dipstick method**: Chemically impregnated dipstick contains methyl red and bromophenol blue with buffering salts. The later dissolve on contact with urine and protein in the urine lowers the pH turning it green. It was traditionally known to detect albuminuria >300 mg/L and hence not advocated for screening for microalbuminuria. But, in a study by Alfredo Pegoraro *et al.* 1997 they found that the combination of sulfosalicylic acid testing and chemstrips was as good as and less expensive than Micral-Test in ruling out Microalbuminuria.
- **Chemical precipitation (Sulphosalicylic acid test)**: 5 drops of 20% Sulphosalicylic acid is added to 3 ml of urine in one test tube. This test tube is compared with test tube of untreated urine held against a dark background, immediately and turbidity is taken to indicate proteinuria (Magensen, 1997).
- **Immunoprecipitation (Micral test)**: It is based on color shift of monoclonal antibody to human albumin labelled with gold. Here Gold Labelled Optically Read Immuno Assay detects microalbuminuria. A specimen of the urine sample passes via the wick fleece into the conjugate fleece. Any albumin present in the urine binds itself specifically to the gold labelled antibodies. Excess antibodies are bound by immobilized albumin in the capture matrix. Only antibodies bound to albumin from the urine sample can pass through the capture matrix., These gold-labelled antibodies flow to the detection pad and turn it red. Test is performed on early morning random urine sample by immersing the strip for 5 sec and reading the result at 2 min, visually comparing with color blocks on vial (0 mg/l,20mg/l, 50 mg/l and 100 mg/l albumin) (Wachtell *et al.,* 2003).
- **4. Radioimmuno assay**: It is the "gold standard" for estimation of albuminuria. It is a double antibody technique where albumin in the sample has to compete with the fixed amount of 125I labelled albumin for the binding sites of the specific antibodies.



An algorithm for screening of microalbuminuria

- Bound and free albumin is separated by addition of a second antibody immuno absorbent followed by centrifugation and decanting. The radio activity in the pellet is measured with a C-counter, Albumin concentration in the sample is inversely proportional to the radioactivity. The sensitivity for RIA method was 0.3 mg/l.

Treatment of Microalbuminuria

- **Control of Blood pressure**: Systolic BP is one of the most relevant determinants of microalbuminuria. Studies of secondary prevention have shown that blood pressure reduction effectively reduces the albumin excretion rate. Among anti-hypertensives, ACE inhibitors and Angiotensin receptor blockers seem to be particularly effective.[37] The target BP should be < 140/90 mmHg in non-diabetics and < 130/80 mmHg in diabetic patients.
- **Glycemic control**: Intensive diabetic therapy can significantly reduce the risk of development of microalbuminuria and overt nephropathy in people withDiabetes (UKPDS, 1998).
- **Treatment of Dyslipidemia**: Statins modify endothelial dysfunction, inflammatory response, plaque vulnerability and thrombus formation. Their usage is known to slow progression of microalbuminuria and is associated with stabilization of UAE (Smulders *et al.,* 1997).
- **Smoking cessation**: Smoking should be strongly discouraged in patients with microalbuminuria not only to retard the progression of microalbuminuria but also to guard against cardiovascular disease.
- **Protein restriction**: Animal studies have shown that restriction of dietary proteins intake reduces hyper filtration and intraglomerular pressure hence retarding the progression of microalbuminuria. The general consensus is to prescribe a protein intake of 0.8 g/mg/day in patients with overt nephropathy.

Microalbuminuria: A Practical Perspective

Several pathways may link microalbuminuria and vascular disease. Several factors that cluster with microalbuminuria include insulin resistance, central obesity, low levels of high-density lipoprotein cholesterol, high triglyceride levels, systolic hypertension, lack of nocturnal dip in blood pressure on 24 hour monitoring, salt sensitivity, endothelial dysfunction, hypercoagulability, impaired fibrinolysis and renal dysfunction. This provides enough proof to support the role of microalbuminuria as a predictor or vascular events in high-risk population. Hence, screening for microalbuminuria on a regular basis may help to identify a subgroup of patients who are at high risk for cardiovascular disease and need more intensive therapy and closer follow-up because they could benefit from early intervention and treatment (Radrigo Tagle *et al.,* 2003).

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