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Review Article

Microalbuminuria as Risk Indicator in Rheumatoid Arthritis: An Updated Review

*Nidavani RB[1], Mahalakshmi AM[1], Patil JS[2]

[1]*Department of Pharmacology, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwar Nagar, Mysore-570 015, India.*
[2]*Department of Pharmaceutics, SVERI College of Pharmacy, Pandharpur- 413 304, Maharashtra, India.*

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ABSTRACT
Rheumatoid arthritis (RA) is an autoimmune, symmetrical polyarticular disease that affects primarily the diarthrodial joints, which is characterized by chronic inflammation of the synovial joints. Microalbuminuria occur leakage of small amounts of albumin into the urine, when there is an abnormal high permeability for albumin in the renal glomerulus of kidney. Microalbuminuria is generally associated with elevated levels of several inflammatory factors in the presence or absence of hypertension or diabetes. It is clear that kidney is involved in RA with both glomerular and tubular damage. Renal disease in RA however is usually asymptomatic and is detected only on laboratory investigations. It is often difficult to differentiate between damage due to disease activity and that due to drugs used to treat RA. Microalbuminuria is one of the important biomarker involved in various disorders in related to RA. The present review work bounces limelight on role of microalbuminuria in RA as well as in relation with other disorders.

Key words: Microalbuminuria, rheumatoid arthritis, diabetes mellitus, atherosclerosis, inflammation, hypertension.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune, symmetrical polyarticular disease that affects primarily the diarthrodial joints, which is characterized by chronic inflammation of the synovial joints. The pathogenic characteristic features of RA includes synovial hyperplasia and inflammation accompanied by cartilage loss and joint destruction which results in extremely painful, impaired functional status, and produces substantial morbidity as well as an increase in mortality[1]. The cause of RA is remains unclear and also the various diagnostic parameters gives idea about severity of RA, the microalbuminuria is considered as one of the chemical diagnostic indicator for the RA.

Microalbuminuria occur leakage of small amounts of albumin into the urine, when there is an abnormal high permeability for albumin in the renal glomerulus of kidney. An albumin level above the upper limit values is called microalbuminuria. A microalbumin urine test determines the presence of the albumin in urine. In a properly functioning body, albumin is not normally present in urine because it is retained in the bloodstream by the kidneys. Microalbuminuria is perhaps a misnomer. It is not a small albumin molecule found in the urine, but it can be express as albumin present in low amounts, below the level of detection of the standard office multi-test urine dipstick method[2]. In general, blood contains cells and proteins that we need, as well as waste products that our body needs to get rid of. Blood is filtered by the kidneys and waste products are removed from the body via the urine whilst cells and proteins stay in the blood, but sometimes a small amount of protein is lost into the urine along with other waste products. Microalbuminuria is when the level of the protein albumin in urine is always slightly raised. Microalbuminuria is defined as 30 to 300mg of albumin being lost in the urine per day. This is different from proteinuria, which is when the levels of protein in urine are higher than 300mg a day.

To compensate for variations in urine concentration in spot-check samples, it is helpful to compare the amount of albumin in the sample against its concentration of creatinine. This is termed the albumin/creatinine ratio (ACR) and it is expressed as ACR ≥3.5 mg/mmol (female) or ≥2.5 mg/mmol (male). A repeat test should be done 3 to 6 months after the first positive test for microalbuminuria. Sometimes the test is inaccurate in a person with too much or too little muscle mass. This is due to the variation in creatinine level which is produced by the muscle[2,3].

Microalbuminuria in Various Disorders: A slightly microalbuminuria, predicts mortality in patients with diabetes mellitus. According to the American Diabetes Association (ADA), it is urinary albumin excretion of 30–299 mg/ 24 h or albumin/creatinine ratio of 30-299 lg/mg creatinine[2]. So microalbuminuria is regarded as a significant marker of mortality in many diseases including diabetes[4].

In 1998, World Health Organization (WHO) recommended excess weight and impaired insulin sensitivity as well as type 2 diabetes, impaired fasting

*Author for correspondence: E-mail: rameshnidavani@jssuni.edu.in

glucose, impaired glucose tolerance, hypertension, elevated triglycerides, reduced high density lipoprotein (HDL) cholesterol, and microalbuminuria as clinical criteria for the metabolic syndrome[5]. Microalbuminuria shows a strong correlation with the classic risk factors, such as hypertension, dyslipidemia and obesity, but it is also an indicator for cardiovascular risk, independent of the classic risk factors. Some study investigated that, the corticosteroids induce effects similar to the insulin resistance syndrome namely, obesity, insulin resistance, dyslipidemia and hypertension. Microalbuminuria is associated to these factors and it is suggested that microalbuminuria condition is a feature of insulin resistance syndrome. Furthermore, a rise in blood pressure could lead to an elevated urinary albumin excretion directly. Blood pressure, body mass index (BMI), and cholesterol levels to be higher in corticosteroid users. However, the adjustment of the odds ratio for these factors did not have any effect on the point estimate. The use of corticosteroids can cause microalbuminuria[6,7]. Consequently, the National Cholesterol Education Program's Adult Treatment Panel (ATP III) no longer recommended assessing insulin sensitivity in the identification of subjects with the metabolic syndrome in 2002[8,9].

Microalbuminuria has been proposed as an atherogenic risk factor[10] and it is one of the most important single predictor for future development of overt diabetic nephropathy[11]. So it is recently recognized as risk factor for cardiovascular disease (CVD). Microalbuminuria is generally associated with elevated levels of several inflammatory factors in the presence or absence of hypertension or diabetes. Many of the same inflammatory factors associated with microalbuminuria also were associated with congenital heart disease (CHD). Together, these results suggest an association between microalbuminuria, inflammation, and CHD. Inflammation preceded the development of microalbuminuria. The levels of inflammation markers, age, and higher systolic blood pressure correlate with microalbuminuria in older individuals, either with or without hypertension or diabetes. Because these factors are risk factors for CHD, the investigations finds the association of microalbuminuria and CHD and the study also suggested that microalbuminuria is not related to CHD risk through endothelial dysfunction measured by flow-mediated vasodilation in response to ischemia[12,13]. Albuminuria reflects generalized vascular damage and it is closely associated with inflammation which underlies all stages of atherosclerotic lesion formation, including early atherogenesis[14]. Microalbuminuria has initially been demonstrated to be a predictor of cardiovascular morbidity and mortality in patients with diabetes mellitus. Later studies have shown that microalbuminuria predicts coronary heart disease and mortality even in nondiabetic populations. The mechanism linking microalbuminuria with increased cardiovascular morbidity and mortality has been explained by the Steno hypothesis. According to this hypothesis, microalbuminuria is a marker of generalized endothelial dysfunction, which enhances the penetration of atherogenic lipids into the arterial wall. If microalbuminuria is a sign of generalized vascular disease, it could be related to atherosclerotic changes in major vessels. The main result of the present study was that hypertension, smoking and male gender were more strongly associated with a high number of atherosclerotic plaques in major vessels than microalbuminuria[15].

Microalbuminuria in RA: Increased urinary albumin excretion is also been reported in patients with rheumatic diseases other than RA, such as systemic lupus erythematous us and systemic sclerosis. Systemic sclerosis patients with microalbuminuria have a worse prognosis than those with normal renal function[16,17].

Microalbuminuria in RA related to renal dysfunction: In RA, glomerular proteinuria has been considered as a complication of advanced disease caused by either direct effects of the disease on the kidney or action of nephrotoxic drugs or both. The elevated urinary albumin index in patients with RA, particularly receiving, disease modifying anti-rheumatic drugs (DMARDs) and estimation of microalbuminuria is useful for the finding of subclinical glomerular injury[18].

In patients with RA there is a high prevalence of renal impairment, with evidence of reduced glomerular filtration and tubular function[19,20,21]. Various morphological findings in the kidneys have been reported[19,22,23] and renal disease is presumed to be a frequent cause of death in RA[24,25]. It would be useful, therefore, to identify those at risk of developing clinical nephropathy, and sensitive measures of renal function should be available. In RA, glomerular proteinuria has been considered as a complication of advanced disease caused by the direct effects of the disease on the kidney, or the action of nephrotoxic drugs, or both. However, subclinical renal dysfunction is not uncommon in RA, and many of these RA patients with incipient nephropathy are not detected by routine laboratory tests such as assays for urine total protein or Albustix[26,27]. The advent of assays sensitive and specific for urinary albumin has enabled the detection of glomerular abnormalities at an earlier stage in patients without clinical renal involvement[28].

Renal dysfunction develops cause patient risk, earlier by the appearance of microalbuminuria. Increased urinary excretion of albumin may reflect not only glomerular disease, also the inflammatory state and disease activity. The occurrence of microalbuminuria in RA patients gives a reliable method for an accurate assessment of subclinical renal dysfunction. The RA patients are at risk of developing renal complications and proteinuria increases the mortality rate. It is therefore of crucial importance to have a sensitive method for reliable measurement of renal dysfunction in clinical practice[29,30,31].

Microalbuminuria in RA related to anti-rheumatoid drugs: The measure antirheumatic drugs used in in the treatment of RA are non-steroidal anti-inflamammtory drugs (NSAIDs) DMAD's, biological agents and others[32,33]. Renal function impairment resulting from treatment with antirheumatic drugs may be

underestimated, as it is often asymptomatic[34]. If adverse renal effects are to be reduced to a minimum, sensitive tests of renal function should be available. Testing for microalbuminuria is a simple screening procedure in patients treated with nephrotoxic drugs. The method could be used to detect early renal dysfunction and monitor patients at risk, especially those who require therapy with drugs which are nephrotoxic, providing an accurate clinical assessment of glomerular function and a rational therapeutic approach and most of the patients were treated with NSAIDs, often combined with DMARDs. Treatment with penicillamine and gold was associated significantly with microalbuminuria. These findings are reliable with other studies suggesting that these drugs are important contributors to proteinuria and microalbuminuria in patients with RA[35]. A research study shows that, because of the complexity of rheumatoid drug histories, it is difficult to correlate results with individual drug treatments and only a few of the patients did not receive anti-rheumatic drugs. Therefore, it concludes that if microalbuminuria is solely a drug induced side effect. The study also suggested that changes in renal permeability to plasma proteins reflect increased systemic vascular permeability in acute inflammatory conditions[36]. Thus the urinary excretion of albumin may reflect a systemic reaction in the acute phase response[37].

Various reports of Microalbuminuria in RA: Lars M et al., (1995) investigated that a highly significant correlation between C-reactive protein (CRP) and urinary excretion of albumin was demonstrated. Nevertheless, the correlation with erythrocyte sedimentation rate (ESR) was not significant. The ESR is partially explained by some patients with normoalbuminuria who had increased values of ESR for reasons other than RA; it may also reflect a low sensitivity of ESR as a marker of disease activity. Microalbuminuria was mainly related with the duration of disease. The possible correlation between urinary excretion of albumin, disease activity, and duration of RA may be explained in two ways. One way is severe and chronic RA tends to affect the kidneys and increases systemic vascular permeability, and another way is patients with more severe and long standing disease receive more nephrotoxic drug therapy. In this condition the urine analyses reflecting renal tubular function that correlate with disease activity in RA. Microalbuminuria and subclinical renal damage are frequent in RA, particularly in those with long standing disease. A subclinical renal involvement may not be revealed by routine laboratory tests such as serum creatinine. The study results and suggests that microalbuminuria is a more sensitive predictor of renal dysfunction in patients at risk. Its measurement may serve as a useful tool for the management of patients with RA but without clinical nephropathy. However, the long term renal prognosis in patients with microalbuminuria requires clarification in longitudinal studies. The research considers that in the majority of patients with microalbuminuria in RA, the problem is reversible and rarely develops to end stage renal failure. The effects of many anti-rheumatic drugs on glomerular and tubular function can be of clinical importance and should be monitored with sensitive methods. It has been recommend immunological methods measuring urinary excretion of albumin as a routine procedure to detect glomerular involvement in its initial phase in order to devise the most appropriate treatment in patients with RA. Further studies are recommended to clarify a possible association between urinary excretion of albumin and disease activity, and to evaluate microalbuminuria as an indicator of the long term prognosis in RA[38].

Pedersen LM et al (1995) studied that, 65 patients with RA attending two rheumatology clinics were compared with 51 control subjects matched by age and sex. The controls consisted of 20 healthy subjects, 16 patients with osteoarthritis and 15 with non-articular rheumatism. Patients with hypertension, diabetes mellitus, or evidence of previous renal disease were not included. Urinary albumin was assayed by immune-turbidimetry in random urine samples on two occasions within seven months. The results were expressed as the ratio of urinary albumin to urinary creatinine ratio. Disease activity was assessed by the ESR and CRP. A drug history for the year before entry to the study was obtained for each patient. Urinary albumin to creatinine ratio in patients with RA was significantly greater than in controls. Microalbuminuria (urinary albumin to creatinine ratio 3-30 mg/mmol in either or both urine samples) was present in 27.7% of patients with RA and 7.8% of the control subjects. A significant relation was noted between urinary albumin to creatinine ratio and CRP, and the duration of disease. The number of patients treated with either gold or penicillamine was significantly greater in patients with microalbuminuria than in patients with normoalbuminuria. Microalbuminuria is frequently present in patients with RA. Treatment with gold and penicillamine seems to increase the risk of developing microalbuminuria. Urinary albumin measured by immunochemical methods is a simple and sensitive test to detect early subclinical renal dysfunction and drug induced renal damage in RA. Urinary albumin excretion was found to be significantly correlated with CRP and may be a sensitive indicator of disease activity in patients with RA[39].

In order to make an estimate of clinical significance of microalbuminuria in patients with RA, studied microalbuminuria in 138 patients with RA without macroalbuminuria. Microalbuminuria was assayed by double-antibody radio-immune assay (RIA) in the ambulatory urine. Moreover, urinary (U) beta 2-microglobulin (BMG) and N-acetyl-beta-D-glucosaminidase (NAG) were simultaneously measured. The values for microalbuminuria/U-creatinine (U-Alb index) in patients with RA, osteoarthropathy (OA) and normal controls were 25.7 +/- 38.2, 11.4 +/- 11.5 and 7.7 +/- 3.5, respectively, and U-Alb indices in patients with RA were significantly higher than U-Alb indices in patients with OA and normal controls. Especially, in patients with RA receiving lovenzarit disodium and gold sodium thiomalate (GST), U-Alb indices were elevated. U-Alb indices were not correlated with clinical findings

in RA. Also, U-Alb indices were not correlated with U-BMG indices and U-NAG indices in patients with RA. In serial measurements of U-Alb index, U-BMG index and U-NAG index in a patient with RA who developed massive macroalbuminuria during GST therapy, it was found that U-Alb index was elevated first, followed by U-NAG index and finally U-BMG index was elevated. These results indicate that U-Alb indices are elevated in patients with RA without macroalbuminuria, and serial measurements of microalbuminuria in patients with RA, especially receiving DMARDs, are useful for the detection of subclinical glomerular injury[40].

Another study expressed that, the assessment of the prevalence of microalbuminuria in patients with RA and its correlation with disease activity and drug treatment, the study includes 65 patients with RA and 51 sex and age matched control persons. Microalbuminuria was significantly increased in patients with RA (27.7%) as compared to 7.8% in the control group. Patients with microalbuminuria had a significantly greater median duration of disease (11.2 v 7.8 years. It was found that a significant correlation to CRP as a marker for disease activity. Also, a significant association to treatment with gold and penicillamine was found. The measurement of microalbuminuria by immunochemical methods represents a simple and sensitive test to detect subclinical renal damage and may be a sensitive indicator of disease activity in patients with RA. Study suggests its use in the monitoring of patients with RA to detect early subclinical renal dysfunction and drug induced renal damage[41]. A research study investigated that, all RA patients with microalbuminuria had a normal serum creatinine concentration and had no detectable macroalbuminuria and 24 hr urinary protein was also normal. A high prevalence of microalbuminuria found to correlation with disease activity. Thus microalbuminuria seems to reflect disease activity[42].

Several studies have revealed that high-grade systemic inflammation contributes to insulin resistance in RA. Suppression of inflammation with glucocorticoids and DMRDs results in a decrease in insulin resistance, at least in the short term[43,44,45]. Apart from systemic inflammation, continuous glucocorticoid use also independently predicts insulin resistance in RA[46]. In keeping with the latter, Wolfe and Michaud showed that prednisone use predicts the development of diabetes mellitus, a metabolic syndrome feature that was complicated by an increased risk for CV events in RA[47]. Overt or subclinical hypothyroidism was found to occur in 24% of RA patients and untreated subclinical hypothyroidism was independently associated with insulin resistance[48]. Taken together, apart from obesity, several other disease characteristics may contribute to insulin resistance in RA. In conclusion, insulin resistance is highly prevalent in RA and strongly implicated in RA atherogenesis. Apart from obesity, cytokines and/or consequent systemic inflammation, continued glucocorticoid use, and hypothyroidism are implicated in insulin resistance in RA. Insulin resistance and abdominal obesity are both independently associated with other metabolic syndrome features in RA. The use of ATP III criteria is inadequate to identify subjects with insulin resistance in RA who are at increased risk for CV disease and diabetes. These data confirm that the evaluation of insulin sensitivity may be important in delineating optimal preventative strategies for CV disease in RA.

Diabetic nephropathy is the leading cause of end-stage renal failure[49]. In diabetic nephropathy, damage to the glomerulus results in microalbuminuria, followed by progressive glomerular and interstitial fibrosis[50]. Increasingly, endothelial dysfunction is implicated in the process[51]. Microalbuminuria is a good predictor of future progression of renal damage, in addition to mortality, in diabetes[52].

Microalbuminuria in vascular disorders in relation to RA: Microalbuminuria arises from the increased passage of albumin through the glomerular filtration barrier. This requires ultrastructural changes rather than alterations in glomerular pressure or filtration rate alone. The loss of systemic endothelial glycocalyx protein-rich surface layer on the endothelium suggests that damage to this layer represents this missing link. The epidemiology of microalbuminuria reveals a close association with systemic endothelial dysfunction and with vascular disease, also implicating glomerular endothelial dysfunction in microalbuminuria[54]. Increased mortality was detected in RA patients with microalbuminuria with hazard ratio 2.77 when compared to those with normal clinical renal findings[55]. Its presence can be regarded as an index of increased cardiovascular vulnerability and a signal for vigorous efforts at correction of known risk factors and it is associated with high systolic and diastolic blood pressure. In hypertensive subjects, microalbuminuria tended to be independently associated with a high number of plaques[56]. Hypertension has been closely associated with microalbuminuria. The explanation for this finding could be that increased intra glomerular capillary pressure causes leakage of albumin, and microalbuminuria is an indicator of an early complication of hypertension[57].

Autoimmune disorders are characterized by the body's immune responses being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction. Recent research has shown that cardiovascular events are more frequent in patients who suffer from autoimmune disorders such as RA[58], systemic lupus erythematosus (SLE)[59] and systemic sclerosis[60], and have become the main cause of excessive mortality of certain auto- immune disorders. Endothelial dysfunction is one of the culprits in cardiovascular diseases, has been demonstrated in certain autoimmune disorders. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, is a newly identified risk factor for endothelial dysfunction associated with enhanced cardiovascular events[61]. Inflammation also plays an important role in atherosclerosis and certain autoimmune diseases. There is growing evidence that the more or less persistent high grade inflammation present in autoimmune disorders is the main driver of the development of premature atherosclerosis and its

complications. Many of the cellular inflammatory processes ongoing during autoimmune disorders are similar to those involved in atherosclerosis. Macrophage, T cell, and mast cell activation, elevated levels of circulating acute phase reactants and adhesion molecules, and increased generation of pro-inflammatory media- tors are reported to be common mechanisms underlying both autoimmune disorders and atherosclerosis, which contribute to alterations in the function and structure of the arterial vessels, and are in line with increased cardiovascular morbidity and mortality in certain autoimmune disorders. Amazing, ADMA is not only a risk factor for endothelial dysfunction but also a novel proinflammatory mediator. Accumulating evidence documented that ADMA may induce vascular inflammation reaction to promote the development of cardiovascular diseases by activation of leukocyte adhesion and cytokines production[62,63]. Recently, there are a large body of evidence that plasma ADMA levels are elevated in certain auto- immune disorders including type I or II diabetes, RA[64], SLE[65], ankylosing spondylitis[66], systemic sclerosis[67], psoriatic arthritis[68], IgA nephropathy[69] and Graves' disease[70]. Thus, ADMA, as a novel linker between endothelial dysfunction and inflammation, might play a crucial role in the higher cardiovascular mobility and mortality associated with autoimmune dis- orders. However, to date, there are no reviews on the roles of ADMA in the excessive cardiovascular events linked with auto- immune diseases. This review will address this critical gap in the literature[71].

The traditional view of albuminuria is that it is the result of damage to an essentially impermeable glomerular barrier. However, over the years, critical evidence for this traditional model has been shown to be flawed. An alternative explanation has evolved in which the glomerular filter governs albumin permeability by size selectivity alone. This means that the filter offers a significant barrier to albumin, but it is imperfect, the barrier leaks albumin. The virtue of this leakage is that it endows the filter an inbuilt anticlogging mechanism. The filtered albumin, if not rescued, would be excreted at nephrotic levels in the urine. There is evidence that proximal tubular cells participate in retrieving most of this filtered albumin to return it back to the blood supply intact. A small amount of the filtered albumin is not retrieved but directed toward lysosomal degradation, and the peptide products are exocytosed into the tubular lumen and excreted. In conclusion, in acquired and chemically induced kidney disease, albuminuria is the result of dysfunction in proximal tubular cell processing of albumin rather than alterations in glomerular permeability[72].

Microalbuminuria and CRP in relation to RA: The CRP is considered a sensitive marker for low grade inflammation and an independent predictor of cardiovascular events[73]. Angiotensin II is a wellknown proinflammatory neurohormone, and several observational studies have suggested that therapy with inhibitors of the renin-angiotensin system is associated with significantly lower levels of serum levels of CRP[74]. Microalbuminuria may be a marker of diffuse systemic inflammation that results in systemic capillary leak in many vascular beds, including the glomerular endothelium of the kidneys, where it manifests as albuminuria[75]. Small increases in glomerular permeability are amplified by the renal concentrating mechanism to produce large changes in albumin excretion, especially as the tubular reabsorptive mechanisms for albumin are close to saturation[76]. As the kidneys receive a large part of the cardiac output, agents precipitating or contributing to the critical illness pass through the renal circulation in significant quantities potentially resulting in glomerular injury and, therefore, microalbuminuria[77].

Microalbuminuria and malignancy in relation to RA: Recent studies have suggested that urinary albumin excretion is influenced by malignancies[78]. Hypothetically, microalbuminuria may be a non-specific marker of malignancy reacting a microvascular response to tumor-related mediators[79,80]. Furthermore, microalbuminuria may have prognostic significance in malignancies, with presumed urinary albumin excretion reaecting the severity of the disease and response to treatment[81,82]. Salli *et al* studied microproteinuria as an index of initial renal lesion in patients with RA. Twenty patients of RA with a negative routine proteinuria test and 20 healthy controls were screened for microproteinuria using multifractional Cellogel RS electrophoresis of urinary proteins. 11 RA patients showed glomerular type proteinuria (five selective and six non-selective type) as against no microproteinuria in controls. The authors suggested that in view of the high sensitivity, easy handling and low cost of multifractionated electrophoresis, it should be introduced as a routine test for all RA patients[82].

CONCLUSION

Microalbuminuria has emerged as a very powerful clinical predictor for various disorders mainly including RA. Early detection of albuminuria allows early intervention with the goal of reducing inflammation development in RA, cardiovascular risk and delaying the onset of overt diabetic nephropathy. Thus, it is an indicator of the need for more intensive efforts to reduce cardiovascular risk factors.

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