# Microalbuminuria: present concepts

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**Abstract**

Microalbuminuria is defined as a urinary albumin excretion rate between 20 – 220 mg/minute. It is easily measured using the Micral–test II. The prevalence of microalbuminuria is high in some diseases, and several studies have demonstrated that Microalbuminuria is a morbidity and mortality predictive factor for essentially cardiovascular and renal complications, in various diseases, such as hypertension diabetes mellitus (type I and type II) and even in healthy individuals.

The role of therapy is still controversial, and more studies are needed in order to show that a reduction in microalbuminuria has favorable implications in the natural history of the disease. It seems that ACE inhibitors are the most efficient pharmacological agents available to decrease microalbuminuria.

Keywords: microalbuminuria, diabetes mellitus, hypertension.

## Introduction

Microalbuminuria was first described around thirty years ago, when Harry Keen observed that the excretion of albumin at levels lower than the proteinuria levels detected by testing strips was an important data in the natural history of initial nephropathy in diabetes.

Healthy individuals excrete extremely small amounts of albumin in urine daily when analyzed by testing strips or routine biochemical techniques, with values of between 1.5 and 20 mg/min,[1] which tend to increase with age.[2]

The concentration of albumin in the urine is usually expressed as the amount of albumin excreted over a determined period of time (mg/min). Microalbuminuria is defined as albumin excretion between 20-200 mg/min, i.e. 30-300 mg/24h,[3,4] in the presence of albumin excretion in urine within this range in at least two to three consecutive urine collections;[4,5] however, for some authors this definition extends positivity to a predictive factor of three out of four collections, thus increasing the specificity.[6]

## Determination

Several procedures for urine collection have been suggested, including 24h urine, occasional urine or urine collected during the night, the later having more advantages, since it can override variations that occur throughout the day, or as a result of exercise. [7]

It can be determined through several laboratory methods, such as the Micral-test II, a semi-quantitative method with 95% sensitivity and 93% specificity when compared to other quantitative radioimmunoassay methods.[8]

The test consists of dipping a testing strip in urine for a few seconds, then comparing the color of the strip, after 1 minute, with that of a reference strip. Besides being extremely practical and quick, the advantage of this method is that the color does not change until after a few minutes.[8]

There are factors that influence the onset of microalbuminuria, such as urinary infections, multiple acute or chronic diseases, obesity, orthostatic hypotension and even some drugs, such as NSAIDs,[4] which are frequently used.

Therefore, we should bear these factors in mind when determining the presence of microalbuminuria.

## Pathophysiology

Various mechanisms have been involved in the onset of microalbuminuria; however, this topic needs to be investigated further. One hypothesis that has been widely proposed in recent times is that the vascular endothelium would suffer a lesion followed by dysfunction; Deckert et al.[9] report that the onset of microalbuminuria, even in the initial stages of diabetes, reflects generalized vascular lesion.

The von Willebrand factor, glycoprotein synthe-

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sised by endothelial cells and megakaryocytes, plays an important role, resulting in this dysfunction,[10] its release possibly being induced by many other factors, such as glucose, cytokines or fibrin.

The von Willebrand factor is increased in many conditions, for example atherosclerosis and other vascular diseases,[10] suggesting that these high levels would reflect endothelial lesions.

In patients with diabetes type II or I, and particularly in those with microalbuminuria, the von Willebrand factor is high, and decreases with improved microalbuminuria.[10]

This association suggests that high levels of the von Willebrand factor may reflect endothelial lesion.[10]

Endothelial dysfunction, on the other hand, would leave the vessels more permeable to albumin which, reaching this level would cause more vascular damage due to a direct toxic effect or through cytokine-mediated mechanisms; the damaged endothelium would thus release additional von Willebrand factor.[11]

Alternatively, it could be a local cause in the kidneys, characterized by salt retention and microalbuminuria, resulting in endothelial dysfunction.[9]

The role of high blood pressure in the development of endothelial dysfunction needs to be clarified further in diabetes; nevertheless, several studies show that patients with high blood pressure and microalbuminuria have also higher levels of von Willebrand factor.[11-13]

Other mechanisms, such as renal hemodynamic changes, secondary to the transmission of blood pressure to the glomerular arterioles; changes due to permeability and selectivity of the exchanges in the glomerular filtration barrier; and changes to the tubular re-absorption of albumin, acting either individually or bundled, have also been pointed out.[14] Nevertheless, for some authors, there is no causal relationship between microalbuminuria and endothelial function.[15]

The cause of microalbuminuria therefore remains unknown; it is known, however, that it reflects initial renal disease or the existence of generalized endothelial disease.

## Prevalence

In recent years, several studies have shown that microalbuminuria can be considered as a predictive factor for the development of proteinuria, chronic renal insufficiency and cardiovascular mortality, not only in type I diabetes, but also in type II diabetes. The prevalence of coronary disease is also high, regardless of other risk factors.[16-19]

A correlation between the presence of microalbuminuria and cardiovascular and renal complications in hypertensive patients has also been widely reported.[11,16,20] The prevalence of microalbuminuria is around 25% in hypertensive patients, 13% in patients with type I diabetes, and 25% in patients with type II diabetes.[4]

## Microalbuminuria in diabetes

In relation to diabetic patients, several studies, both retrospective and prospective, show that microalbuminuria is a predictive factor of morbidity and cardiovascular mortality, correlating closely to blood pressure values, more precisely to systolic pressure values, but also to 24h blood pressure.[14] Brucks, in a study comparing diabetic and non-diabetic patients, observed that the so-called 'non-dippers' excreted more albumin and had more severe vascular complications;[21] however, Parving reports no difference in albumin excretion between dippers and non-dippers.[4]

Another currently accepted data is the increased incidence of microalbuminuria in Black diabetic patients when compared to White diabetic patients; the incidence is also associated with high blood pressure observed among Black patients.[22,23]

Insulin resistance is frequently associated with a series of clinical anomalies in diabetic patients type I and II when associated with microalbuminuria.[24,25]

Insulin resistance precedes the onset of microalbuminuria in patients with diabetes type II,[26] on the other hand, microalbuminuria precedes the development of this type of diabetes;[27] this close relationship between insulin resistance and microalbuminuria is extremely important, as both are risk factors, regardless of the ischemic disease affecting patients with diabetes type II.[26]

Some studies report that hyperinsulinism alone is not predictive of coronary diseases, and microalbuminuria has only a weak association; nevertheless, when they coexist, they are an excellent marker of the disease.[28]

For some authors, the association may have a genetic base, since changes observed in the lithium sodium channels[25,29] - genetic markers with a predisposition for high blood pressure - also occur when there is insulin resistance; for others, microalbuminuria reflects endothelial dysfunction which, in turn,

leads to insulin resistance. More precisely, insulin modulates the glucose uptake by the tissues after crossing the endothelial barrier. Transport through the micro vessels is dependent of their link to the endothelial receptors and hormone uptake by the endothelial cells and subsequent release in the interstitial space.[30] When endothelial lesion exists, this sequence would be impaired.

In patients with both type I and type II diabetes who can develop microalbuminuria, the glycemic control is poorer.[31] A study carried out by Bangstad shows that improved glycemia delays the progression to diabetic nephropathy in patients with type I diabetes.[32]

In relation to the HbA1C levels to be reached, DCCT has not yet concluded, from the various studies being carried out, which one best prevents renal changes; however, Krolewski et al.[33] observe and suggest that keeping HbA1C below 8.1% substantially decreases the incidence of microalbuminuria.

Neuropathy, which is often predictive of sudden death by vascular disease in diabetic patients, is also associated with microalbuminuria. Left ventricular hypertrophy, also more frequent in diabetic patients, also predisposes to ischemia, cardiac insufficiency, ventricular arrhythmia and sudden death.[19]

Peripheral polyneuropathy associated with an increase in the development of foot ulcer (diabetic ulcer) or retinopathy, which can frequently lead to blindness, tends to be more severe and significant in patients who have microalbuminuria.[34]

If we also consider the composition of lipoprotein, microalbuminuria may act as a predictive factor that aggravates its composition with reduced HDL, further aggravating vascular changes that are observed in diabetic patients.[35]

## Microalbuminuria in high blood pressure

In relation to hypertensive patients, Mimram[36] also observed a correlation between the level of excreted albumin and blood pressure, more specifically ambulatory pressure; however, more studies are needed to demonstrate that its existence is a marker for cardiovascular and renal risk. Berrut also observed that microalbuminuria occurs in "non-dippers", as occurs in diabetic patients.[37] Similarly, Redon proves that left ventricular hypertrophy is associated with higher levels of microalbuminuria, regardless of the importance of the degree of increased blood pressure levels, supporting the idea that microalbuminuria is a risk factor in patients with essential hypertension.[38]

Bakris, however, reports that microalbuminuria in hypertensive patients is not a predictive factor, but reflects the lesions caused by high blood pressure.[18] Nevertheless, macroalbuminuria is closely correlated with cardiovascular and renal complications caused by high blood pressure.[39]

Another problem is salt-dependent hypertensive patients, as microalbuminuria has found to be more prevalent in these patients than in salt-resistant patients. The sub-group of salt-dependent hypertensive patients is at higher cardiovascular and renal risk, and today, microalbuminuria is considered a good marker of disease in this sub-group of hypertensive patients, taking into account that it may lead to different therapies.[12]

Some studies that show the association of high blood pressure with the deterioration of renal function do not rule out the hypothesis that deterioration of renal function and high blood pressure are consequences of a pre-existent progressive renal disease. Indeed, there are hypertensive patients without proteinuria or altered renal function, and there are also hypertensive patients with macroalbuminuria and poor renal function exist.

Several authors suggest that these hypertensive patients with macroalbuminuria may have an underlying renal disease with microalbuminuria that was not previously detected.[12]

If microalbuminuria is a controversial topic in high blood pressure, it is even more controversial in healthy, normotensive patients, in whom its prevalence is estimated at around 4%.[12] Several studies have been carried out seeking to elucidate this. Yudkin et al. show that an association exists between microalbuminuria and coronary disease, particularly in the elderly[20] and peripheral vascular disease in patients aged over 40 years.[28]

Microalbuminuria also appears to be a little predictive of cardiovascular complications in obese patients who are neither diabetic nor hypertensive, and even in children of hypertensive patients.[40]

## Therapy

Several therapeutic measures have been the object of investigation in diabetic patients and in patients with essential hypertension; it was observed that within these various classes of anti-hypertensive drugs,

ACE inhibitors were superior to others in terms of reducing the albuminuria excretion rate, whether micro- or macroalbuminuria[12,49,40] in hypertensive diabetic patients.

Also in relation to essential hypertension, some studies have shown that anti-hypertensive therapy also reduces microalbuminuria. In a comparative study involving several anti-hypertensive drugs of different classes, all were shown to equally reduce microalbuminuria.[39] However, in another study that compared the effect of an ACE inhibitor with antagonist of Ca channels, b-blockers and diuretics, the ACE inhibitor was shown to further reduce microalbuminuria, but blood pressure regulation was similar for all of them.[12]

Regardless the differences are, it is evident that the treatment of high blood pressure reduces microalbuminuria, but studies have been carried out to better evaluate the beneficial effect of reducing microalbuminuria.[19]

Besides studies on anti-hypertensive therapy in hypertensive patients with microalbuminuria, no other studies have been published. It is also thought that dietary measures that include reduction of sodium transport and the possible use of nonsteroidal anti-inflammatory drugs may also lead to a reduction in microalbuminuria excretion.

Experiments involving lipid restriction therapy also reduced the microalbuminuria rate.[12]

A positive data relating to diabetic patients is that good glycemic control delays the development of microalbuminuria, but it is still unclear whether, after its onset, a direct association between these two factors exists.

It is also important to point out that one of the studies showed that the administration of heparin to these patients also reduced the microalbuminuria rate.[12]

## Conclusion

In conclusion, the cause of microalbuminuria remains unclear; however, knowing that its existence causes renal disease and increased morbidity and mortality, its detection in diabetic patients is extremely important, as recently confirmed in the action program St. Vincent Declaration,[41] but it is still controversial in hypertensive patients. Nevertheless, its screening and control may prevent complications in diabetic patients, and could also have an important role in other type of patients. Therefore, further studies are necessary to evaluate its usefulness. ■

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