

Cardiovascular and renal prognosis in patients with arterial hypertension, type 2 diabetes mellitus and microalbuminuria

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Abstract. Diabetes Mellitus is a metabolic disease defined by hyperglycemia, secondary to insulin deficiency both in secretion and activity, which alters the metabolism of carbohydrates, lipids and proteins. Diabetic nephropathy is a microvascular complication of diabetes mellitus defined by an increased excretion of proteins in urine. The early stage is characterized by a mild albumin excretion, named as microalbuminuria or incipient diabetic nephropathy. The screening for diabetic nephropathy should be performed when the diagnosis of diabetes mellitus type 2 is confirmed, because approximately 7% of the patients already have microalbuminuria. Microalbuminuria is a known risk factor for cardiovascular morbidity and mortality and for end-stage renal disease in general population and also in patients with type 2 diabetes mellitus and arterial hypertension. Microalbuminuria is an independent predictor of cardiovascular mortality (cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease) in diabetes mellitus or hypertensive patients in the general population. The microalbuminuria test is recommended as a strategy in stratifying the risk of diabetic and hypertensive patients. Albuminuria is associated with a poor renal and cardiovascular outcome. By reducing the microalbuminuria and the blood pressure values using angiotensin-converting-enzyme inhibitors or angiotensin renin blockers, we can improve the prognostic. The physicians should routinely measure urinary albumin excretion in patients with type 2 diabetes mellitus and hypertension and aggressively treat the modifiable risk factors, such as high glycemic values, cholesterol and blood pressure, in order to suppress the microalbuminuria and thus to prevent the renal and cardiovascular adverse effects.

Key Words: diabetes mellitus, hypertension, cholesterol, microalbuminuria.

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Introduction

Diabetes Mellitus is a metabolic disease defined by hyperglycemia, secondary to insulin deficiency both in secretion and activity, which alters the metabolism of carbohydrates, lipids and proteins.

Type II Diabetes Mellitus (T2DM) represents a major health problem worldwide. A study published by Wilds et al in *Diabetes Care* in 2004 estimated that approximately six individuals die each minute because of this pathology (Amer et al 2012).

Long term complications of DM are classified into two categories:

1) Microvascular complications (nephropathy, neuropathy and retinopathy) and

2) Macrovascular complications due to atherosclerosis.

Diabetic nephropathy (DN) is defined by an increased excretion of proteins in urine. The early stage is characterized by a mild albumin excretion, named as microalbuminuria or incipient diabetic nephropathy. The screening for DN should be performed when the diagnosis of T2DM is confirmed, because approximately 7% of the patients already have microalbuminuria (ADA 2004).

It is known that the presence of microalbuminuria has a high predictive value for the proteinuria of patients with T2DM (Pollak & Sypniewska 2008) and is a negative predictive factor for renal and cardiovascular evolution in patients with T2DM and essential arterial hypertension.

Microalbuminuria is a known risk factor both for end-stage renal disease and for cardiovascular mortality and morbidity in general population and also in patients with T2DM and arterial hypertension (Anavekar et al 2004, Pinto-Sietsma et al 2000). Studies performed in Europe, US (United States) and Australia have found a prevalence of microalbuminuria of 5-15% in the general population, approximately 20-30% in diabetic patients and 11-17% in hypertensive patients (Pollak & Sypniewska 2008). A study published in Romania in 2011 reports that the prevalence of microalbuminuria in patients with arterial hypertension and T2DM is 29%, respectively 20% in patients with T2DM without arterial hypertension and 15% in hypertensive patients without T2DM (Bacanu et al 2011).

Klausen et al examined 2762 patients without known coronary heart disease pathology and concluded that microalbuminuria was a significant determinant of death and coronary heart

disease. An overnight urinary albumin excretion higher than 5 μg / minute was a strong predictor for coronary heart disease and death in general population (Klausen *et al* 2004).

Definition and microalbuminuria measurement

Albumin represents 20-70% of urinary protein excretion. Microalbuminuria means persistently high urinary albumin excretion and is defined as one of the following:

- 1) Urinary albumin excretion (UAE): 30-300 mg/24 hours in urine collected in the past 24 hours or
- 2) Urinary albumin excretion rate (AER): 20-200 $\mu\text{g}/\text{min}$ in timed urine sample or
- 3) Urinary albumin to creatinine ratio (ACR): 3.5-35 mg/mmol or 30-300 mg/g in females, 2.5-25mg/mmol or 20-200 mg/g in males in a spot urine collection or
- 4) Urinary albumin concentration (UAC): 20-200 mg/L in spontaneous morning urine (Pollak & Sypniewska 2008).

Although 24 hour urine collection would avoid problems with daytime variation of albumin excretion, this method has its limits and may involve various errors due to inadequate collection. Because women excrete a lower level of creatinine compared to men and that the microalbuminuria levels are based on a set albumin urinary excretion per day, the definition of microalbuminuria differs in women and in men when ACR formula is used. UAC determination without concomitant determination of urinary creatinine value is subjected to errors due to variable urinary creatinine concentration depending on the state of hydration (Basi *et al* 2008).

The Kidney Outcomes Quality Initiative Guidelines established that ACR measurement from the spontaneous first morning urine is adequate without the need to collect it for 24 hours (K/DOQI clinical practice guidelines for chronic kidney disease 2002). Microalbuminuria was defined the first time in 1984 by Mogensen as the urinary excretion of albumin of 30-300mg/24 hours (Mogensen 1984), but at that time the inhibitors of the renin-angiotensin system (IRAS) drugs were not used as frequently as today. IRAS decrease the urinary excretion of albumin. In consequence, a patient with an urinary albumin excretion of 30-300 mg/24 hours treated with IRAS might have a higher AER values if such drugs are not administered (Basi *et al* 2008). Macroalbuminuria is defined as higher values as those described above.

Cardiovascular risk and endothelial dysfunction in diabetic patients

Microalbuminuria can be both a cause but also a consequence of vascular disease. Endothelial dysfunction may contribute directly to the albuminuria pathogenesis by increasing the basal glomerular pressure, which leads to transvascular extravasation and loss of albumin (Pollak & Sypniewska 2008). The relationship between microalbuminuria and the appearance of cardiovascular disease is not completely understood, but the endothelial dysfunction and chronic inflammation seem to explain the underlying mechanisms. Although there is a connection between low grade inflammation, endothelial dysfunction and microalbuminuria, they seem to be independent risk factors for

the appearance of cardiovascular death (Pollak & Sypniewska 2008; Nosadini *et al* 2005).

Multiple mechanisms were implied in the appearance and development of cardiovascular complications in T2DM patients with albuminuria such as the association between microalbuminuria and high levels of Vascular Endothelial Growth Factor (VEGF) and C reactive protein (CRP), an acute phase protein that acts as a marker of chronic inflammation (Bakker *et al* 2005).

Endothelial dysfunction in T2DM and T2DM with micro and macroalbuminuria is generalized and involves multiple aspects of the endothelial function. Recent data shows that microalbuminuria and coronary vasomotor anomalies are predictors of cardiac events in T2DM. These patients have an altered coronary vasodilatation, dependent on the endothelium when microalbuminuria is present. The connection between cardiovascular events and microalbuminuria is only partially explained by age, gender, presence of diabetes and dyslipidemia, obesity, arterial hypertension and smoking (Pollak & Sypniewska 2008; Weir 2007).

Endothelial dysfunction and hyperhomocysteinemia in patients with microalbuminuria

It has been demonstrated that the plasmatic levels of homocysteine were correlated with the rigidity of the arterial walls in hypertensive patients with an average age of 58 years. The high levels of homocysteine were associated with a low level of Glomerular Filtration Rate (GFR). Knowing that the plasma levels of homocystein are closely correlated to renal function, we should take it into account (Basi *et al* 2008).

The high levels of homocysteine were associated with the presence of microalbuminuria and diabetic retinopathy both in T1DM and T2DM patients. It has been found a direct and significant correlation between the high plasma levels of homocysteine and microalbuminuria levels. These data suggest that a high level of homocysteinemia in patients with T2DM might play a role in development of vascular complications (Pollak & Sypniewska 2008; Rudy *et al* 2005).

Metabolic syndrome and microalbuminuria

Both metabolic syndrome (MS) and microalbuminuria were associated with cardiovascular diseases. Large population studies indicated a strong connection between microalbuminuria and MS. Some conditions of the MS such as hyperglycemia and low insulin resistance, significant predictors of endothelial dysfunction seem to be particularly connected to the presence of microalbuminuria (Pollak & Sypniewska 2008).

In addition to the systolic blood pressure, conditions like obesity, insulin resistance and smoking were associated with high ACR levels (reported to systolic blood pressure values) (Basi *et al* 2008). The influence of obesity and insulin resistance suggest that albuminuria is influenced by the presence of MS. Studies shown that the prevalence of microalbuminuria grew once with the components of the MS (from 3% in patients with no MS to 9.8% in patients with 3 components and 22.1% in patients with 5 components) (Chen *et al* 2004).

The excessive amount of fats and the altered adipokine secretion and synthesis might contribute to T2DM, arterial hypertension and cardiovascular disease progress. In obesity, we have a diminished adiponectine secretion, which can contribute to the inflammatory response and endothelial dysfunction, causing atherosclerotic changes of the vessel walls (Goralski *et al* 2007). In patients with arterial hypertension, microalbuminuria negatively correlates with adiponectine levels, reflecting the progression of the atherosclerotic process (Basi *et al* 2008). It has been suggested that microalbuminuria is associated with proximal tube lesions and loss of the integrity of the glomerular filtration barrier when obesity and insulin resistance are present (Hazden *et al* 2006).

Dyslipidemia and microalbuminuria

The relation between microalbuminuria and dyslipidemia is inconsistent. A high UAE in parallel with dyslipidemia was found in diabetic patients. In both types of DM, low HDL-cholesterol (high density lipoproteins) levels and dyslipidemia may affect the endothelial function. Some studies have shown that low HDL-cholesterol levels and hypertriglyceridemia were associated with microalbuminuria (Pollak & Sypniewska 2008; Wotherspoon *et al* 2006).

Microalbuminuria and arterial hypertension

Arterial hypertension, especially systolic values and pulse pressure are major factors in the pathophysiology of microalbuminuria. Microalbuminuria was associated with arterial hypertension. The prevalence of microalbuminuria in patients with arterial hypertension oscillates from 4 to 46% and these variations can be explained by the age difference, ethnicity, definition and dosing methods. UAE was associated with left ventricular dysfunction in patients with high blood pressure (Basi *et al* 2008; Wang *et al* 2005).

A study performed on 187 patients under the age of 57, with normoalbuminuria and with no hypertension medication prior to the inclusion, followed for a period of 2.7 years, treated with different hypertension drugs showed a progression from normoalbuminuria to microalbuminuria in 11% of the cases. Microalbuminuria was less frequent in patients treated with IRAS. Other determinant factors that influenced microalbuminuria were a high BMI score, inadequate control of the blood pressure, uncontrolled glycemic levels and high levels of the uric acid (Chambial *et al* 2013).

Glomerular endothelial dysfunction was considered as an early trait of essential arterial hypertension. It can lead to high blood pressure values and the albuminuria reflects the systemic dysfunction of the vascular endothelium. Microalbuminuria can be an early indicator for vascular complications due to hypertension. But it can be considered also as a prognostic factor for the cardiovascular diseases, independent of the blood pressure values in patients with hypertension and no vascular complications prior to the assessment.

Another study performed on 195 patients with normal blood pressure levels and 645 hypertensive patients with no treatment showed that the presence of arterial hypertension and left ventricular hypertrophy were associated with faster decline of GFR (glomerular filtration rate) (Wachtell *et al* 2002).

Renin-angiotensin-aldosterone system

The alteration of the endothelial function and altered vascular remodeling can be a result of the renin-angiotensin system (RAS) activation. Angiotensin II acts through type 1 angiotensin II receptors, which will increase the interleukin 6 (IL-6) expression, a proinflammatory agent, increase the reactive oxygen species, stimulate the induction of LDL-oxide (low density lipoproteins) receptors and the induction of adhesion molecules. Thus, it plays an essential role in the genesis of endothelial lesions and atherosclerosis (Pollak & Sypniewska 2008).

It has been demonstrated that by controlling the blood pressure values, the albuminuria levels are also reduced. Drugs that inhibit the renin-angiotensin system (IRAS) are capable of reducing the UAE more than it was originally expected, also due to the adequate control over the high blood pressure levels (Pollak & Sypniewska 2008; Van de Wal *et al* 2006).

In the TOMS (Treatment of Mild Hypertension Study) study, which included patients with mild hypertension (diastolic values between 85-99 mm Hg), the administration of enalapril over 12 months lead to a significant reduction of microalbuminuria compared to amlodipine, doxazosin, chlortalidone and acebutolol, even though these drugs properly controlled the blood pressure values (Neaton *et al* 1993; Pollak & Sypniewska 2008).

Albuminuria and renal function prognostic

In PREVEND (Prevention of Renal and Vascular End-Stage Disease) study, which included patients without DM, the GFR, estimated by creatinine clearance in 24 hours, had a tendency to increase in patients with high normal AER while the presence of macroalbuminuria was independently associated with the reduction of creatinine clearance levels under the expected values for the age and sex of the included subjects.

The multivariate analysis of the included subjects in the PREVEND study determined that the starting AER was a strong predictor for the renal dysfunction risk (Pinto-Sietsma *et al* 2000). Mogensen demonstrated that in patients with microalbuminuria, the GFR declined faster than in patients with normoalbuminuria (Mogensen 1984). A series of studies demonstrated that the reduction of albuminuria due to the administration of IRAS drugs associated with the safety of the renal function. The RENAAL (the Reduction of Endpoints in Non-Dependent Diabetes Mellitus with Angiotensin II Antagonist Losartan) study included 1513 patients with T2DM and nephropathy and compared the effect of losartan (50-100 mg/day) with placebo, together with conventional antihypertensive medication. In the lot of patients treated with losartan, the proteinuria was reduced by 32% when compared with placebo. A decrease of albuminuria levels by 50% in the first 6 months associated the reduction of the risk of end-stage renal disease with 45%. Decreasing the microalbuminuria levels with losartan was an important predictor concerning the preservation of renal function (Forman & Brenner 2006).

Albuminuria and the cardiovascular prognosis in T2DM

It has been discovered a strong connection between the microalbuminuria and the cardiovascular outcomes in T2DM patients.

The IDNT (Ibesartan Diabetic Nephropathy Trial) study reported that albuminuria represented an independent risk factor for the cardiovascular events. A cardiovascular event was defined as death of cardiovascular origin, non-fatal myocardial infarction, hospital admission due to heart failure, stroke, inferior limb amputation, coronary or peripheral revascularization procedures (Lewis *et al* 2001, Basi *et al* 2008).

The RENAAL (the Reduction of Endpoints in Non-Dependent Diabetes Mellitus with Angiotensin II Antagonist Losartan) study also demonstrated that the presence of microalbuminuria is associated with an increase of the cardiovascular events and correlates with severe and more advanced cardiovascular diseases (Forman & Brenner 2006, Sukhija *et al* 2006).

The data from the various studies we have presented shows that an increase in albuminuria (microalbuminuria, albuminuria and proteinuria) is associated with an increase in cardiovascular events. The data is applied also to non-diabetic patients, as demonstrated by the Framingham (Basi *et al* 2008) and PREVENT study. Therefore, microalbuminuria can be considered as a risk factor for the development of cardiovascular diseases, together with arterial hypertension, high cholesterol and diabetes mellitus.

Discussions

There is an agreement in which diabetic patients, even with normal blood pressure values should benefit from angiotensin-converting-enzyme (ACE) inhibitor treatment to reduce the risk of chronic kidney disease secondary to urinary albumin excretion (Pollak & Sypniewska 2008; Basi *et al* 2008).

Testing for microalbuminuria, generally once a year is recommended in diabetic patients and also in hypertensive patients, according to evidence-based guidelines. In hypertensive patients, the albuminuria should be determined after the first 6 months of treatment to evaluate the impact of the antihypertensive medication (Pollak & Sypniewska 2008; Basi *et al* 2008).

Observational prospective studies provided valuable information concerning the association of microalbuminuria with an increase of cardiovascular events and mortality rate. The screening for microalbuminuria seems to have a higher clinical significance that is comparable to the blood pressure values and serum lipids, thus we must consider introducing it in risk prevention strategies for diabetic patients. Older data reported in the US in 2004 revealed that diabetic patients are mainly tested for lipid profile (90%), HbA1c (glycated hemoglobin) levels (86%) and only 50% for microalbuminuria. In 2006, AHA (American Heart Association) published new guidelines for diabetic patients that include GFR and microalbuminuria testing (Pollak & Sypniewska 2008).

The ADA (American Diabetes Association) recommends that patients with T2DM get screened for microalbuminuria after the T2DM diagnosis is made and annually after that. In practice, we must consider ACE inhibitor or ARBs (angiotensin renin blockers) treatment in patients with microalbuminuria or proteinuria. Studies in the past years demonstrated the role that microalbuminuria plays as a predictor of cardiovascular morbidity and mortality rate (Basi *et al* 2008).

Conclusions

The presence of microalbuminuria is a strong predictor for kidney/renal disease and cardiovascular risk in patients with T2DM and arterial hypertension.

The primary pathophysiological mechanism is not fully clarified yet, but it is presumed that endothelial dysfunction, inflammation or possible anomalies of the renin-angiotensin-aldosterone system play a key role.

In summary, albuminuria is associated with a poor renal and cardiovascular outcome. By reducing the microalbuminuria and the blood pressure values using ACE inhibitors and ARBs, we can improve the prognosis. The physicians should routinely measure urinary albumin excretion in patients with T2DM and hypertension and aggressively treat the modifiable risk factors, such as high glycemic values, cholesterol and blood pressure, in order to suppress the microalbuminuria and thus to prevent the renal and cardiovascular adverse effects.

Acknowledgments

This paper was published through a project funded by internal research grants of the University of Medicine and Pharmacy Tîrgu Mureş, Romania, contract no. 10/23.12.2014.

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Citation Stoian A, Moțățăianu A, Bajko Z, Maier S, Bărcuțean L, Stoian M, Bălașa RI. Cardiovascular and renal prognosis in patients with arterial hypertension, type 2 diabetes mellitus and microalbuminuria. *HVM Bioflux* 2016;8(1):45-49.

Editor Ștefan C. Vesa

Received 30 December 2015

Accepted 10 January 2016

Published Online 12 January 2016

Funding Internal research grants of the University of Medicine and Pharmacy Tîrgu Mureș, Romania, contract no. 10/23.12.2014.

**Conflicts/
Competing
Interests** None reported