# Diabetic nephropathy and cardiovascular diseases

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## Abstract

**Diabetic nephropathy is diagnosed either when persistent increase of urinary albumin excretion rate (UAER) above 30 mg/24h in a patient with diabetes was discovered (early or incipient nephropathy) or when UAER values are persistently elevated above 300 mg/24h (overt or clinical nephropathy). In both situations the additional criteria of presence of diabetic retinopathy and the absence of the evidence of other kidney or renal tract disease should be fulfilled. It was found that the excess of cardiovascular events and mortality occurs already in diabetic patients with persistent microalbuminuria, but is particularly evident in macroalbuminuric diabetic patients and results not only from end-stage renal failure (ESRF) but rather from cardiovascular disease (CVD), the latter mainly in type 2 diabetic patients. Several traditional risk factor for atherosclerosis has been identified in diabetic patients with micro- or macroalbuminuria including elevated blood pressure levels, dyslipidemia and procoagulatory state associated with endothelial dysfunction. Microalbuminuria is currently regarded as a marker of generalized endothelial damage, it reflects transvascular albumin leakage, now recognized as an early event in atherogenesis. Recently the association of microalbuminuria with the marker of chronic inflammation (C-reactive protein) and with increased production of vascular endothelial growth factor (VEGE) was described. Thus, multiple mechanisms are involved in the development and progression of cardiovascular complications both in micro- and macroalbuminuric diabetic patients and all these mechanisms should be regarded as the target for therapeutic intervention.**

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Received 22.02.2005 Accepted 03.03.2005

**Key words:** diabetic nephropathy, microalbuminuria, macroalbuminuria, cardiovascular diseases, mortality.

There are two different criteria of diabetic nephropathy in the medical literature. First one defines that persistent albuminuria (urinary albumin excretion rate, UAER >300 mg/24 hours or 200 μg/minute) is the hall-mark of diabetic nephropathy which can be diagnosed clinically if the following additional criteria are fulfilled: presence of diabetic retinopathy and the absence of clinical or laboratory evidence of other kidney or renal tract disease [1]. Another one defines that persistently raised UAER already above arbitrary established normal range, so-called microalbuminuria (UAER >30 mg/24 hours or 20 μg/min, and less than or equal to 300 mg/24 hours or 200 μg/min), associated with identical additional criteria as in the case of first definition, is sufficient for diagnosis of early (incipient) diabetic nephropathy [2]. According to this second criterion, persistently elevated UAER values >300 mg/24 hours or >200 μg/min, should be named macroalbuminuria, which is usually associated with proteinuria exceeding 0.5 g/24 hours and is indicative for more advanced stage of diabetic nephropathy: overt diabetic nephropathy.

Irrespective of differences in the criteria, diabetic nephropathy is a major cause of illness and death in diabetes. The excess of cardiovascular events and mortality occurs already in diabetic patients with persistent microalbuminuria, but is particularly evident in proteinuric diabetic patients and results not only from end-stage renal failure (ESRF) but rather from cardiovascular disease (CVD), the latter mainly in type 2 diabetic patients.

Until recently, microalbuminuria was said to confer a 60 to 85% risk of the development of overt proteinuria within 6 to 14 years in type 1 diabetic patients, suggesting an inexorable process leading to overt proteinuria [3,4]. The prospective study of patients with persistent microalbumiuria followed for six years revealed last year [5] that regression of microalbuminuria in type 1 diabetes was frequent, with a cumulative incidence of

58 percent. The determinants of the regression of microalbuminuria (defined as a 50 percent reduction in UAER from one two-year period to the next) were: short duration of microalbuminuria, glycosylated hemoglobin levels less than 8 percent, systolic blood pressure less than 115 mmHg, serum cholesterol level below 5.12 mmol/l (198 mg/dl) and serum trigliceride level below 1.64 mmol/l (145 mg/dl). The use of angiotensin-converting-enzyme inhibitors (ACEI) was not associated with the regression of microalbuminuria. These results indicated that elevated UAER does not imply inexorably progressive nephropathy and suggested that the definition of early diabetic nephropathy should be modified. It was hypothesized that very low systemic blood pressure attenuates shear stress and may permit the recovery of glomerular integrity and this and/or other mechanisms underlying the regression of microalbuminuria are most effective in the low range of glycosylated hemoglobin and low levels of cholesterol and trigliceride [5]. This hypothesis is based on the observations that microalbuminuria is associated with impairment of renal hemodynamic autoregulation [6,7]. Other factors, including genetic predisposition [8], should however-be considered as determinants of development and further evaluation of microalbuminuria in diabetic patients.

Although currently microalbuminuria should be considered as a marker of dynamic, rather than fixed renal injury in patients with type 1 diabetes [5], it was demonstrated that microalbuminuria is a marker for increased risk of cardiovascular disease in these patients [9]. The aerobic work capacity is impaired in patients with persistent microalbuminuria [10], which suggests that microangiopathy or other pathological process is affecting myocardium. The increase in the ratio of low-density and high-density lipoprotein has been described [11], indicating atherogenic lipid profile. Impaired fibrinolytic activity and elevated plasma levels of fibrinogen and von Willebrand factor are present in patients with microalbuminuria, suggesting generalized endothelial injury [9]. Microalbuminuria is regarded as a marker of generalized endothelial damage, it reflects transvascular albumin leakage and has been proposed to indicate increased endothelial permeability, now recognized as an early event in atherogenesis [11,12]. It was demonstrated that microalbuminuria precedes the increase in arterial blood pressure, and a concomitant increase in UAER and blood pressure was observed with the estimated mean annual increase in blood pressure of 2.7 mmHg [13,14]. Elevated blood pressure is additional risk factor for development of cardiovascular complications in patients with type 1 diabetes and microalbuminuria. The prevalence of arterial hypertension (blood pressure values ≥140/90 mmHg) in adult type 1 diabetic patients with microalbuminuria is 52%, and is increased when compared to patients with normoalbuminuria in whom was estimated as 42% [15,16]. Several studies have reported that sodium and water retention play a dominant role in the initiation and maintenance of systemic hypertension in patients with microalbuminuria, whereas the contribution of the renin-angiotensin-aldosterone system is smaller [1]. A genetic predisposition to hypertension in type 1 diabetic patients developing diabetic nephropathy was suggested and confirmed recently [17]. It was also demonstrated that the D allele associated with the insertion (I)/deletion (D) polymorphism of the gene for angiotensin-converting enzyme (ACE) and DD homozygocity are risk factors for an accelerated course of diabetic nephropathy in patients with type 1 diabetes. Of particular interest is that deletion polymorphism in the ACE gene is associated with coronary heart disease (CHD) in type 1 diabetic patients with nephropathy [18] as well as in nondiabetic patients [19]. The DD genotype appeared also to increase mortality once dialysis treatment was initiated. Since plasma ACE level (and also tissue ACE activity, as demonstrated in experimental studies) in DD subjects is about twice that of II subjects, with ID subjects having intermediate levels [20], it strongly suggests that increased generation of the angiotensin II (Ang II) unfavourably influences development of both renal and vascular changes and that inhibition of Ang II activity should have important protective effects. These protective effects associated with the use of ACE inhibitors or/and the antagonists of $AT_1$ receptors of Ang II were confirmed in several prospective studies in diabetic patients with nephropathy.

The generalized vascular lesions, the atherogenic changes in the lipid profile and elevated blood pressure that characterize patients with type 1 diabetes and microalbuminuria may lead to increased incidence of cardiovascular events and even to death from vascular disease, but it is still not proven whether microalbuminuria in it self is associated with an excess mortality in these patients, or whether it is so only because it is a predictor of clinical nephropathy and end-stage renal disease (ESRD). It is also not directly proven whether regression of microalbuminuria is associated with the reduced incidence of cardiovascular events, although it seems very probable. It has been demonstrated microalbuminuria independently predicts all-cause and cardiovascular mortality in general population [21].

It is also well documented that microalbuminuria in patients with type 2 diabetes is a predictor of cardiovascular complications and death [22,23]. The prevalence of microalbuminuria averaged 27% in cross-sectional evaluation of type 2 diabetic patients. Several traditional cardiovascular risk factors, including elevated hemoglobin $A1_C$ ($HbA_{1C}$) levels, obesity and hypertension were found with increased frequency in patients with type 2 diabetes and microalbuminuria and increased frequency of the CHD was observed as well [24]. Particularly high prevalence of arterial hypertension averaging 90% of the subjects has been found in type 2 diabetic patients with microalbuminuria [16] and very often hypertension preceded the development of microalbuminuria for many years. The mean 24 h systolic blood pressure showed a significant positive correlation with UAER within the microalbuminuric patients with type 2 diabetes [25]. Persistent microalbuminuria appeared to predict and aggravate lipoprotein abnormalities in type 2 diabetic patients. In these patients, a significant increase in very-low-density lipoprotein (VLDL) cholesterol, VLDL and low-density lipoprotein (LDL) trigliceride levels and a decrease in high-density lipoprotein (HDL) cholesterol levels were seen after the 5-year follow-up [26]. In many subjects the components of metabolic syndrome (central obesity, the resistance of periferal tissues to insulin, hyperinsulinemia, hypertension and the atherogenic lipid profile) precedes the development of type 2 diabetes and recently microalbuminuria was included as an additional factor in the criteria for diagnosis of this syndrome [27]. A variety of hemostatic abnormalities have been shown to correlate significantly

with UAER in diabetic patients, including plasma fibrinogen, factor VII activity, factor VII antigen, protein C, lipid peroxides and others [28,29] indicating a tendency to hypercoagulability in microalbuminuric type 2 diabetic patients.

It is generally accepted that increased blood pressure levels, hyperlipidemia and hemostatic abnormalities constitute the set of factors with are responsible for the significantly increased risk of developing macrovascular disease in type 2 diabetic patients with microalbuminuria, which indicate the endothelial damage [9]. Deckert et al. [30] suggested a common pathogenic mechanism of microalbuminuria and premature atherosclerosis because of the similarity and functional alterations of glomeruli and large vessel walls in patients with albuminuria.

There is growing support for the suggestion that microalbuminuria may be reflection of generalized endothelial dysfunction in capillaries (e.g. glomeruli) and arteries [31,32], and that leakage of albumin though the glomerular wall might be a marker of preclinical atheriosclerosis [33]. Theoretically, such a leakiness may allow for an increased lipid insudation into the large vessel wall, thereby linking microalbuminuria to atherogenesis [21,23].

Recently, an association of cardiovascular disease with the markers of inflammation was demonstrated both in non-diabetic and diabetic populations [23]. Stehouwer et al. [34] prospectively followed markers of chronic inflammation and endothelial dysfunction in a large group of patients with type 2 diabetes for 9 years. Markers for both endothelial dysfunction and chronic inflammation, as well as microalbuminuria, were found to be interrelated, to have developed in parallel, progressed with time, and were related to death. It may be concluded that a sensitive marker of (sub)clinical inflammation, such C-reactive protein (CRP) and microalbuminuria reflect intimately related components of the atheroslcerotic disease process [35]. It was demonstrated that elevated CRP levels enhances the relationship between blood pressure (which has been shown to be the main determinant of microalbuminuria in diabetes and hypertension) and microalbuminuria. This interaction was found independently of other factors. It was suggested that CRP may be a marker of vascular disease, which indicates impaired autoregulation of glomerular pressure and/or dysfunction of glomerular endothelinum. Both of these factors may enhance microalbuminuria. It is of interest, that CRP and microalbuminuria both predict incident cases of type 2 diabetes, which underlines their role in insulin resistance [6,37].

The results of the recent study [38] have suggested that the link between cardiovascular risk factors and microalbuminuria may originate from elevated vascular endothelial growth factor (VEGF) levels. It was shown that hyperglicemia plays an important role in increasing VEGF plasma concentrations and VEGF levels are increased in patients with diabetes. Elevated circulating VEGF levels, increased additionally when hypertension is present, may cause increased vascular permeability, which results in microalbuminuria in the kidney. It was concluded that there is a relation between increased VEGF levels and subsequent occurrence of microalbuminuria and the increased cardiovascular risk. The significant association between microalbuminuria and VEGF was dependent on cardiovascular risk factors [38].

Independently of the mechanisms involved in the development of microalbuminuria in type 2 diabetic patients, several retrospective and prospective studies have shown that microalbuminuria is not only predictor for proteinuria and progressive diabetic nephropathy but also a prognostic indicator of early mortality from cardiovascular disease. In the prospective study of elderly diabetic patients, UAER was the best prognostic factor for long-term mortality [39]. In another study [40] the excess mortality in type 2 diabetic patients was highly significantly increased among those with microalbuminuria (28%), compared with those with normal UAER (5%), and the predictive power of microalbuminuria persisted after adjustment for the effect of major risk factors. It was also demonstrated that albuminuria was much strongly associated with premature death from cardiovascular diseases than with end-stage renal disease (ESRD): after 10 years of follow-up 69% of patients died from acute myocardial infarction, cardiac failure, or stroke, while only 7% patients died from ESRD [1]. It may be concluded that microalbuminuria in type 2 diabetic patients appeared to be more relevant as a marker for cardiovascular disease and death than for renal failure [9].

The patients with both type 1 and type 2 diabetes complicated by overt nephropathy with proteinuria demonstrate even higher risk of cardiovascular complications than the patients with microalbuminuria, due to the effects of the same factors influencing prognosis in patients with microalbuminuria. It was demonstrated, however, that the survival of type 1 diabetic patients with overt nephropathy improved substantially because early antihypertensive treatment. In the long-term observational follow-up study it was shown that the median survival time was 13.9 years in type 1 diabetic patients with diabetic nephropathy [39]. The study also revealed that death due to ESRD was reduced to 35%. When the cumulative death rate during the natural history of diabetic nephropathy in type 1 patients were compared before and after introduction of effective antihypertensive treatment, it appeared that the mean survival times increased from 5-7 years before to >16 years after introduction on modern hypertensive treatment [1]. The recent meta-analysis of the prospective studies evaluating the effect of the antagonist of the Ang II AT 1 receptors (ARB) in type 2 diabetic patients either with micro- or macroalbuminuria, hypertension and even elevated blood preasure levels, revealed a significant risk reduction of 15% of cardiovascular events as compared with patients treated with other hypotensive agents [1], along with marked renoprotective effect of ARBs.

There are several additional risk factors for cardiovascular complications in patients with type 1 and type 2 diabetes and nephropathy, including diabetic cardiomyopathy, autonomic neuropathy of cardiovascular system, left ventricular hypertrophy and cardiac rhythm abnormalities (which predispose to sudden death), which were not discussed in this paper. The presented data seems, however, sufficient to support the conclusion that early detection of microalbuminuria or proteinuria in a patient with diabetes indicates not only a potential risk for the development of progressive kidney function impairment, but is also a marker of high risk of cardiovascular complications. These patients should receive a multifactorial treatment and should be monitored carefully to prevent or slow down the progression of both kidney and cardiovascular complications.

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