Diabetic nephropathy: from micro- to macroalbuminuria

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Abstract. This brief review will focus on the major factors leading to incipient diabetic nephropathy (i.e. microalbuminuria) progressing to overt nephropathy (i.e. macroalbuminuria) and particularly on the role of glycaemic control and hypertension.

Both experimental and cohort studies support the role of hyperglycaemia in the development of diabetic nephropathy. Some recent long-term interventional studies in microalbuminuric patients show conflicting results regarding the role played by good metabolic control in reducing the incidence of overt nephropathy. However, strict metabolic control, which is fundamental in normoalbuminuric patients, is of little use even in microalbuminuric patients. In general, levels of glycosylated haemoglobin less than two standard deviations above the upper normal range, commonly <7.5–8%, seem to protect patients from developing nephropathy.

The results of many cross-sectional studies have shown that the progression of renal damage regularly is accompanied by arterial hypertension both in insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). Many long-term interventional studies have been performed in order to understand the effect of antihypertensive treatment on the incidence of proteinuria in both normotensive and hypertensive patients with IDDM or NIDDM. These data show a marked effect of antihypertensive therapy in preventing the onset of overt nephropathy, and suggest the superiority of angiotensin-converting enzyme (ACE) inhibitors. We believe that optimal blood pressure values are ~120/70–75 mmHg in younger patients and 125–130/80–85 mmHg in older patients. In conclusion, antihypertensive treatment, ACE inhibitors per se and possibly strict metabolic control reduce the development of nephropathy, thus playing a striking role in the secondary prevention of renal failure.

Key words: diabetic nephropathy; microalbuminuria; therapy of diabetic nephropathy

Review

Nephropathy affecting both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetic patients is one of the most frequent causes of end-stage renal failure (ESRF). In addition, diabetic nephropathy consistently is associated with high mortality cardiovascular disease [1,2].

The natural history of diabetic renal disease has been characterized in IDDM mainly by Dr C. E. Mogensen, and it may be traced, though less accurately, also in NIDDM. The presence of non-diabetic nephropathy in NIDDM can contribute to explain some discrepancies between the two types of diabetes in the natural course of renal involvement [1–3]. After 7–13 years of the disease, ‘incipient nephropathy’ develops, on average, in a third of both IDDM and NIDDM patients. It is characterized by the presence of microalbuminuria (albumin excretion rate between 20 and 200 μg/min). Overt nephropathy ensues after 10–20 years of diabetes and is characterized by persistent and increasing clinical proteinuria or macroalbuminuria. At this stage, the glomerular filtration rate (GFR) begins to decline and arterial hypertension progressively appears.

There are many studies dealing with the prevalence of persistent microalbuminuria in both IDDM and NIDDM. However, only results obtained from sufficiently large cohorts of diabetic patients, by using reliable methods and several urine collections are considered here [4–13]. In these selected papers, the prevalence of persistent microalbuminuria in non-proteinuric patients with IDDM varies from 10 to 28% in various populations [4–8]. The most recent paper by The Italian Microalbuminuria Study Group [8] reports the prevalence in Italy. In the largest population studied to date (>300 patients), an 11% prevalence was found. Only very few studies of NIDDM, for example the study carried out in the Genova area [13], included collection of more than one urine sample. However, a prevalence similar to IDDM was found in all studies, i.e. 13–30% and 17% in Italy [9–13].

Successfully carried out prospective studies in IDDM demonstrated the predictive role of microalbuminuria for overt nephropathy. Figure 1 shows the incidence of overt nephropathy in microalbuminuric and in
normoalbuminuric patients [14–22]. Positive predictive power is also shown in cohorts with long lasting follow-up (10 years or more) [14,15,19]. Data obtained for both IDDM and NIDDM patients demonstrate that 6–8% of microalbuminuric patients develop overt nephropathy every year, whereas <2% of normoalbuminuric patients reach this stage. The discriminating level and the predictive power of microalbuminuria for overt nephropathy must be confirmed by large and prolonged longitudinal studies, particularly in NIDDM.

The most reliable approach to evaluating the frequency of diabetic nephropathy is to study the cumulative incidence of overt nephropathy. Contrary to common opinion, the cumulative incidence in NIDDM on the basis of duration of diabetes is similar to that in IDDM [23–28]. During the first 5 years, very few patients develop nephropathy. The cumulative incidence increases thereafter, reaching 25–45% after 25 years of diabetes. Longer studies from the USA, Denmark and Japan show a 40 year cumulative incidence of between 35 and 45%.

Major risk factors for renal damage in diabetes and particularly for the progression from micro- to macroalbuminuria are: poor glycaemic control, systemic hypertension, diabetes of long duration, genetic factors, abnormalities in the lipid spectrum and haemostatic parameters, possibly smoking habits and, lastly, albuminuria per se [1–3]. However, their relative roles and mechanisms are far from being certain and, what is more, the effect of some factors is often interactive and difficult to dissect. Clearer indications on intervention strategies have been derived from large, long-term (2–3 years) prospective or interventional studies which used valid end-points, for example incidence of albuminuria increase ≥50% yearly, rate of incidence of proteinuria, and/or structural end-points. Theoretically, the rate of change in the GFR and also the incidence of ESRF or mortality are the best end-points which would, however, require excessively prolonged studies.

Both experimental and cohort studies support the role of hyperglycaemia in the development of diabetic nephropathy [1,2,23,29]. The effect of hyperglycaemia may be mediated by a number of factors, such as promoting glomerular hypertension, and inducing a number of intracellular and extracellular biochemical consequences. Subsequently, abnormal synthesis and/or degradation of proteins in the extracellular matrix ensues. Haemodynamic and biochemical abnormalities lead to changes in basal membrane thickness and selectivity, as well as to expansion of both the mesangial and interstitial matrix, culminating in glomerulosclerosis and tubulo-interstitial fibrosis [1,2,31].

Some recent, long-term interventional studies show conflicting results regarding the role that good metabolic control plays in reducing the incidence of overt nephropathy when therapy is commenced in the microalbuminuric phase [3]. A recent re-evaluation of The Diabetes Control and Complications (DCCT) data [32] does not demonstrate a significant reduction in the incidence of proteinuria in these patients. Furthermore, in two other studies, arterial blood pressure is shown to have a confounding influence: it amplifies the positive side of good metabolic control in the Danish study [33], whereas it masks this role in the English one [34]. Results obtained from a few Japanese NIDDM patients suggested that the incidence

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**Fig. 1.** Incidence density of overt nephropathy in microalbuminuric (■) and normoalbuminuric (▲) diabetic patients. P.P.P. = positive predictive power. Values at the base of columns indicate reference numbers.
density of proteinuria in patients with good control is nearly half of that observed in patients with poor control [20]. A recent paper using structural endpoints emphasized this assumption [35].

In conclusion, strict metabolic control, which is fundamental in normoalbuminuric patients [1,3], is likely to be useful even in microalbuminuric patients. In general, glycosylated haemoglobin of less than two standard deviations above the upper normal range, commonly <7.5–8%, seems to protect patients from developing nephropathy. However, it must be stressed that intensified insulin therapy is associated with increased episodes of severe hypoglycaemia [36], thus reliable estimates of both benefits and harmful effects are required.

Results of many cross-sectional studies have shown that progression of renal damage regularly is accompanied by arterial hypertension both in IDDM and...
NIDDM [1,2,8,13]. Arterial hypertension is an important risk factor in the development and progression of renal damage in diabetes [29,30] and also for the life expectancy of these patients [1,2]. Recently, interest in this risk factor has increased progressively and, in fact, effective and 'safe' antihypertensive treatment has become available. Furthermore, while converting hypertensive patients to become normotensive is a relatively simple and inexpensive procedure in diabetic patients, achieving a constant degree of normoglycaemia is far more difficult and expensive. High blood pressure together with chronic hyperglycaemia further increase glomerular hypertension [31].

Many long-term interventional studies have been performed to understand the effect that antihypertensive treatment has on the incidence of proteinuria in both normotensive and hypertensive patients with IDDM or NIDDM. In both normotensive (Figure 2) and hypertensive (Figure 3) patients, angiotensin-converting enzyme (ACE) inhibitors markedly reduced the incidence of overt nephropathy [37–45]. Interestingly, ACE inhibitors are effective in accomplishing this independently of blood pressure, although, in studies by Viberti et al. [37], Lafel et al. [39]. The Microalbuminuria Captopril Study Group [40] and Lebovitz et al. [43], blood pressure is marginally yet significantly lower in the ACE inhibitor-treated group. In hypertensive patients, decreasing blood pressure to ~140/90 mmHg or slightly lower, even by using dihydropyridinic Ca-blockers [44,45], showed beneficial effects. A recent study by The Italian Microalbuminuric Study Group [46] on 137 microalbuminuric IDDM patients with basal blood pressure <140/90 mmHg also demonstrated the significant role of ACE inhibitors in reducing the incidence of progression towards macroalbuminuria.

When taken together, these data show a marked effect of antihypertensive therapy in preventing or delaying the onset of overt nephropathy both in IDDM and NIDDM, and suggest the superiority of ACE inhibitors. Longer follow-up, however, is mandatory to determine whether this favourable effect will preserve normal GFR and lead to a greater survival rate. ACE inhibitors can also be used in patients with blood pressure <140/90, but >115/75 mmHg if they are <50 years old and >120/80 mmHg if they are >50 years old, owing to their well-known renoprotective effect [3]. We believe that optimal values of blood pressure are ~120–70–75 mmHg in patients <50 years of age, and 125–130/80–85 mmHg in patients >50 years [3]. These guidelines are similar to those suggested by some recent consensus papers [47–49].

Finally, at the microalbuminuric stage, metabolic control and, more importantly, blood pressure are important risk factors for overt nephropathy. Antihypertensive treatment, ACE inhibitors per se and perhaps strict metabolic control reduce the development of nephropathy, thus playing a striking role in secondary prevention of ESRF.

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