Diabetic nephropathy in children

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**Introduction**

It is estimated that among 100 million European children aged 0–14 years, some 10 000 will develop insulin-dependent diabetes mellitus (IDDM) each year. Within a subset of 10–30% of IDDM patients who will ultimately develop diabetic nephropathy (DN), the earliest stages of disease can be detected within the first 4–5 years after diagnosis [1–3]. We present the risk factors for the development, the appropriate screening for early manifestations, and the strategy for prevention and treatment of DN in children and adolescents.

**Risk factors for the development of diabetic nephropathy**

A number of risk factors may influence the onset or progression of DN: duration of diabetes, metabolic control, puberty, hypertension, hyperlipidaemia, genetic influence, and smoking [2–5].

It is unusual for microalbuminuria (MA), an early sign of DN, to be present within the first 4–5 years after diagnosis. Thereafter, the prevalence of MA increases steadily with time [1,3].

Long-term glycaemic control is the most important factor for the development and severity of complications in IDDM [6]. The adolescent subgroup (13–17 years at entry) of the DCCT cohort showed a reduction of risk to develop MA by 10% following intensified treatment and achieving better glycaemic control compared with subjects on conventional treatment (primary prevention cohort); in the secondary intervention cohort, intensive therapy decreased the risk of occurrence of MA by 55%. Haemoglobin A1c levels in the intensive treatment group were, on average, ~2% lower than in subjects receiving conventional therapy [7].

Puberty enhances the development of microvascular disease. There is a significant pubertal association of the duration of diabetes with kidney volume and the prevalence of MA [3]. However, nephromegaly (an early indicator of DN) may be found in prepubertal children, indicating the importance of prepubertal course of diabetes for the development of DN during, and after puberty [3].

The first changes detectable in 24-h ambulatory blood pressure measurement (ABPM) in adolescents with MA include loss of diurnal systolic rhythm, increased systolic and diastolic pressure burden, and subtle elevation in 24-h systolic pressure [3]. High-normal or high blood pressure (BP) in adolescence is associated with higher incidence of MA and predisposes to later development of advanced DN [1,2]. Therefore, ‘tracking’ of BP should be monitored for the early detection of consistent BP increases.

No association has been found between abnormal lipids and the development of MA in adolescents nor is the influence of increased lipid levels on progression of MA known [2,3].

It is likely that selected individuals with IDDM have a genetic predisposition to developing nephropathy. The likelihood of developing DN is increased in patients with a diabetic sibling or parents who have DN. A family history of hypertension is also associated with an increased risk of DN. DD genotype of the angiotensin-converting enzyme (ACE) gene appears to be associated both with increased risk of progression of DN and reduced responsiveness to ACE inhibitors [2–4,8].

Smoking is an independent risk factor for development and progression of MA in adult with IDDM; therefore, smoking should be discouraged in young diabetics as early as possible [2,3].

**Significance and detection of microalbuminuria in paediatric patients**

Clinically detectable DN begins with the development of MA or incipient nephropathy, characterized by albumin excretion rates (AER) between 20 and 200 μg/min. MA strongly predicts overt DN.
(>300 mg of albumin/24 h), which develops in patients destined to have terminal renal failure [9].

Even slightly abnormal MA is associated with early renal and vascular damage. Thus, albumin excretion should be considered as a continuum and detecting patients having risk factors for the transition to MA would be of great benefit. It seems that poor metabolic control is a main factor in such a transition; AER in the upper normal range is another important risk marker for subsequent MA [9]. In IDDM adolescents, the degree of glomerular structural changes in the transitional stage from normo-MA to MA was positively correlated both with 5-year mean HbA1c level and nocturnal 'non-dipping' of BP [10].

The prevalence of persistent MA in children with IDDM is reported to be between 4 and 20%, depending upon a number of variables including age, glycaemic control, diabetes duration, etc. The occurrence of MA is very rare before puberty and its prevalence is low when diabetes duration is less than 3–5 years [1,3].

In adolescents and young adults, MA does not necessarily proceed to persistent proteinuria. The elevated AER may occur transiently or intermittently and in a considerable number of patients (up to 40–50%) it can regress to normal [2,11,12]. Adolescents with permanent MA had significantly poorer metabolic control, higher BP, longer diabetes duration and more frequent background retinopathy than those with only transient elevations of the AER [2,13]. A significant number of adolescents with persistent MA may revert to NA; these patients were younger at onset of MA and had both HbA1c and diastolic BP lower than those who remained microalbuminuric [13]. No consistent data exist on patients with intermittent MA.

Screening of children and adolescents for MA is preferably performed determining AER in a timed overnight urine collection. The high day-to-day variability in AER (up to 40%) makes it essential that at least two urine collections are obtained; if AER is high in one of them, a third sample is taken to determine whether the patient has MA [1–3,5,8,11]. The albumin/creatinine ratio in the first morning urine is felt to be the most reliable method of screening by some [5,11], but less reliable by others [2,3]. This ratio is generally not recommended in random urine samples [2,3,11]. Screening should be postponed in situations known to transiently increase urinary albumin excretion [14].

A general consensus has been reached for the quantitative definition of MA in adults [14], but this is not been the case in paediatric patients where the cut-offs for AER of 15, 20, or 30 μg/min were used [3,5,12]. These values are somewhat arbitrary because the reported upper limits of AER in healthy children range from 5 to 10 μg/min below the defined predictive level of MA (20 μg/min) in adults [1–3,11]. The reference value of 15–200 [1] or 20–200 μg/min [2,3,11] of AER in timed overnight urines and 20–200 μg/min (30–300 μg/24 h) in 24 h urine collections [1,3,5] are quoted as the limits of definition of MA. MA is present when AER is found within the defined limits in at least two out of three urine samples, preferably within a 1–6 month period. First morning urinary albumin to creatinine ratio predicting MA is considered to be above 3.5 mg/mmol [11]. The predictive values of a positive test for MA increase as the cut-off increase but it appears that the reference value of 20 μg/min is useful in predicting the development of permanent MA [2].

For screening purposes, AER determination should be started in 6–12-monthly intervals in a child 11–12 years old or a child who shows evidence of puberty and with a diabetes duration of 4–5 years. If AER is above normal limits, diagnosis of MA has to be substantiated by repeated testing in 3–6 months [2,3,5,11].

**Primary prevention and secondary intervention**

The major interventions include intensive diabetes management to achieve and maintain tight metabolic control and antihypertensive therapy. Other interventions (exercise programme, diet, lifestyle changes) are less well studied [3].

The DCCT demonstrated an impressive effect of improved metabolic control in both delaying the onset and slowing of the progression of microvascular complications [6,7]. It is crucial that this control is achieved before the onset or in the early stages of MA [2,3,8,10].

The renoprotective properties of ACE inhibitors extend beyond their antihypertensive effect: they reduce the progression of both MA and overt proteinuria in hypertensive diabetics and significantly reduce progression from normoalbuminuria to MA. They also increase the chances of regression of MA regardless of other variables in normotensive adults [4,9,14,15].

The point at which ACE inhibitors should be started in young diabetic people has yet to be defined. Risk factors for progression of normoalbuminuria to MA, such as AER in the upper normal range and/or a trend to high-normal BP during follow-up may indicate initiation of treatment; genetic predisposition to hypertension and/or a family history of DN would support a decision [8]. ACE inhibitors should be started when MA persists despite 6–12 months of improved metabolic control [1,5,8]. In hypertensive IDDM adolescents an ACE inhibitor is also a drug of choice. The second-line drugs include calcium channel inhibitors, alpha-receptor blockers or low-dose thiazides [2,3,5,8].

A protein intake of 1 g/kg body weight is sufficient also in growing children; a low-fat diet is advisable for older children [2,8].

**Conclusion**

The goals of monitoring and therapy in children and adolescents with IDDM are to maintain good metabolic control, monitor AER, aggressively control of BP, use of ACE inhibitors for persistent MA and
consideration of diet modification or lifestyle changes. Early detection of renal injury in IDDM by screening for MA enables therapeutic measures to be instituted aiming at reducing or even reverting MA and possibly preventing the development of DN.

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References