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Prevention of Diabetic Nephropathy in Children and Adolescents: How Effective are the Current Strategies?

Review Article

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Abstract

This paper aims to review the risk factors for diabetic nephropathy (DN) and the effectiveness of the current strategies for its prevention. Type 1 diabetes mellitus (T1DM) is the predominant form of diabetes in children and adolescents, but the prevalence of Type 2 diabetes mellitus (T2DM) in these age groups is currently increasing worldwide. One of the major challenges of T1DM is the development of DN among other microvascular complications. DN evolves over a long period of time starting from microalbuminuria and progressing to end stage renal failure. While microalbuminuria in children is reversible and may not evolve to end-stage renal failure, macroalbuminuria inevitably progresses to end-stage renal failure irrespective of any known treatment. Several modifiable and non-modifiable risk factors are well documented in the literature but addressing a few are critical in the prevention of DN.

For instance, tight glycemic control and intensive control of hypertension have significant impact on prevention and progression of DN. From several studies, tight glycemic control has been shown to decrease the risk of microvascular disease in both T1DM and T2DM. Thus, poor glycemic control is critical in the etiology of DN. While tight glycemic control in patients with T1DM reduces the incidence of microalbuminuria and the progression from microalbuminuria to macroalbuminuria, there is overwhelming evidence to show that antihypertensive treatment with angiotensin converting enzyme (ACE) inhibitors is important in both preventing and treating microalbuminuria, and thus preventing progression to overt DN. Dietary protein restriction is also an adjunct strategy in retarding the progression of DN. Other novel therapeutic strategies have been recently tried and found potentially effective. Research is ongoing to establish the clinical efficacy and usefulness of some of these new agents in future.

Keywords: Childhood Diabetes; Diabetic Nephropathy; Microvascular Complications; Risk Factors; Prevention.

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Introduction

Type 1 diabetes mellitus (T1DM) is the predominant form of diabetes mellitus (DM) in children and adolescents [1], but the prevalence of Type 2 diabetes mellitus (T2DM) in these age groups is currently increasing worldwide [2]. The presence of persistent microalbuminuria in T1DM is strongly predictive of overt proteinuria (macroalbuminuria), subsequent end-stage renal failure and occasionally of cardiovascular disease [2, 3]. On the other hand, T2DM is a major risk factor for cardiovascular events. Specifically, in patients with T1DM, hypertension and decline in renal function occur after the onset of macroalbuminuria; but in those with T2DM, hypertension and a decline in renal function may occur when there is microalbuminuria [2].

One of the major challenges of T1DM or even T2DM is the development of diabetic nephropathy (DN) [4]. DN is a clinical syndrome characterized by persistent albuminuria (> 300 mg/d or 200μg/min) confirmed on at least two occasions 3 to 6 months apart, progressive decline in glomerular filtration rate (GFR), and hypertension. DN is categorized into stages: microalbuminuria (urine albumin excretion of >20 μg/min and ≤ 199 μg/minor an albumin to creatinine ratio (mg/mmol) of 2.5 to 25 in males and 3.5 to 35 in females) [2], and macroalbuminuria (urine albumin excretion of ≥ 200μg/min). DN evolves over a long period of time-usually over 10 to 20 years-starting from microalbuminuria and progressing to end stage renal failure [1]. While microalbuminuria in children is reversible and may not therefore evolve to end-stage renal failure, macroalbuminuria inevitably progresses to end-stage renal failure irrespective of any known treatment [1].

Overt DN is thus very rare in the pediatric age group [5, 6], because renal involvement occurs in five stages which are related to the duration of T1DM [4, 5]. Stage 1 occurs with the onset of diabetes and is characterized by enlarged kidneys and hyperfiltration

with increased GFR. Stage 2 occurs over 2 to 5 years; although similar to Stage 1, histopathologic abnormalities are however seen on renal biopsy. Stage 3 or incipient DN is characterized by microalbuminuria and normal renal function. With the onset of this stage about 5 years after diagnosis of diabetes, hypertension and progressive decline in GFR develop. Stage 4 or overt DN is the stage of dipstick positive proteinuria (macroalbuminuria) and rapid decline in GFR. Within 10 years of Stage 4, Stage 5 or end-stage renal failure sets in. Therefore, a consensus guideline recommends commencement of screening for microalbuminuria after 5 years of diabetes [4, 7, 8].

Apart from the duration of diabetes, and normal glycaemic control, there are other risk factors which may influence the onset and progression of DN. This paper aims to review these risk factors and the effectiveness of the current strategies for prevention of DN in childhood diabetes.

Literature search was conducted on Google and PubMed databases using appropriate search terms.

Risk factors for diabetic nephropathy

Although DN with consequent end-stage renal failure constitutes one of the leading causes of mortality in T1DM [5], overt DN is very uncommon in the paediatric age group [6]. However, one report described a 13 year-old female adolescent with poorly-controlled T1DM who developed overt DN only after 4 years of diabetes despite the absence of microvascular complications such as diabetic retinopathy [9]. Previous reports have also confirmed the possibility of overt DN before 5 years of diabetes in pre-pubertal, poorly-controlled patients with T1DM [10, 11]. Conversely, renal function can be impaired even in T2DM patients with normoalbuminuria and microalbuminuria as well-known cardiovascular risk factors such as hypertension and arteriosclerosis appear to have a close relationship with renal damage in T2DM [12]. Consequently, some authors have suggested that screening for microalbuminuria in T1DM should be done at an earlier age than is currently recommended-especially in patients with identified risk factors for DN such as poor glycemic control and pubertal growth spurt [9]. Unlike in T1DM, where the strict glycemic control is the main preventive strategy for DN, in T2DM, the control of modifiable risk factors such as hypertension, hyperlipidemia, and obesity may assume priority [12]. In fact, some investigators have demonstrated a strong relationship between microalbuminuria and adolescent years, thus suggesting that adolescence and puberty are non-modifiable risk factors for progression of DN in T1DM [13]. Apart from hypertension and hyperlipidemia, smoking habits, albuminuria per se, as well as genetic predisposition are also known risk factors [5, 7, 14, 15]. Epidemiological [16] and familial studies [17-21] have demonstrated that genetic predisposition contributes to the development of DN in patients with both T1DM and T2DM. Additional findings supporting this observation include the report that diabetic siblings of patients with diabetes and renal disease are five times more likely to develop nephropathy than diabetic siblings of diabetic patients without renal disease [22], and the existence of a strong concordance of both nephropathy and renal histopathology in twins with T1DM [23]. In a study of Brazilian families with two or more diabetic members, the presence of diabetic nephropathy in the probands was significantly associated with a 3.75-fold increased risk of diabetic nephropathy in the diabetic siblings [21].

Furthermore, low levels of high-density lipoprotein, low socioeconomic status, and male gender reportedly had significant association with DN in subjects with T2DM while the combination of blood pressure values in the high-normal range with moderately elevated levels of total cholesterol and hemoglobin A1c (a marker for average glycemic levels over the previous 3 months) defines a high-risk group for the progression to DN and for clinical events related to arteriosclerotic cardiovascular disease [24]. These observations are corroborated by a group of researchers in Thailand who documented duration of diabetes, HbA1c levels and uncontrolled hypertension as risk factors for DN in T2DM [25]. Admittedly, most of these studies on T2DM were conducted on adult subjects; nevertheless the findings could equally apply to children and adolescents among whom the global prevalence is rising [26].

Diabetic nephropathy and microvascular complications in T1DM and T2DM: the differences

Patients with DN and T1DM almost always have other signs of diabetic microvascular disease, such as retinopathy and neuropathy. The retinopathy-which is easy to detect clinically-usually precedes the onset of overt DN in these patients. By the time advanced retinopathy has occurred, there are usually histologic changes in the glomeruli, as well as evidence of microalbuminuria. However, there are some patients with advanced retinopathy who have little or no renal disease as evaluated by renal biopsy and proteinuria. Rarely, T1DM may present with DN without preceding or associated retinopathy [9]. On the other hand, T2DM patients with marked proteinuria and retinopathy most likely have DN while those without retinopathy have a high incidence of non-diabetic glomerular disease.

Glomerular hyperperfusion is among the earliest changes demonstrable in DN-which is accompanied by microalbuminuria. Microalbuminuria not only serves as a sensitive early indicator of DN but also a powerful predictor of its subsequent progression. Eighty percent of T1DM patients with microalbuminuria will progress to overt nephropathy within 10-15 years. Of these patients, 50% will develop ESRD within 10 years and 75% within 20 years in the absence of specific interventions [27]. Among patients with T2DM, 20-40% of patients with microalbuminuria will progress to overt nephropathy, though only 20% of those patients will go on to ESRD within the next 20 years [27]. Microalbuminuria is also a powerful predictor of cardiovascular disease in both T1DM and T2DM. Thus, in T1DM, yearly screening should begin after puberty and 5 years after initial diagnosis. In T2DM, yearly screening for microalbuminuria should begin at the time of diagnosis because of the likelihood that diabetes has been present for several years by the time it is diagnosed.

Prevention and treatment strategies for diabetic nephropathy

Both tight glycemic control and intensive control of elevated blood pressure have significant impact on prevention and progression of DN [28]. In general, the goal for glycemic control is a blood glucose level as close to normal (HbA1c <7%) as possible without causing dangerous hypoglycemia [29]. The importance of

prevention cannot be overemphasized; once overt nephropathy is present, progression cannot be halted but only retarded. It is much more effective to screen for early nephropathy with sensitive tests for microalbuminuria and to prevent or halt the earliest stages of renal damage by tight glycemic control and control of hypertension [29].

From several studies, tight glycemic control has been shown to decrease the risk of microvascular disease in both T1DM and T2DM [14, 30-32]. It is well established that poor glycemic control is critical in the etiology of diabetic nephropathy. For instance, DN is rare in patients with HbA1c consistently <7.5-8.0% [4, 14].

In the Diabetes Control and Complications Trial (DCCT), tight glycemic control in patients with T1DM reduced the incidence of microalbuminuria by 39% in the primary prevention group and reduced the progression from microalbuminuria to macroalbuminuria by 54% in the secondary prevention group [30]. Furthermore, in the United Kingdom Prospective Diabetes Study (UKPDS), there was a 34% decrease in the risk of microalbuminuria in patients with T2DM treated more intensively for glycemic control [31]. Thus, there is a strong clinical evidence for the effectiveness of tight glycemic control in the prevention of DN.

Secondly, hypertension is a well established contributory cause of diabetic microvascular complications [33], and its control decreases albuminuria, delays nephropathy, and improves survival in both T1DM and T2DM [34]. Notably, the renin-angiotensin system is the target of the most effective strategy for both control of hypertension and, independently, for reduction of the pathophysiologic abnormalities which result in proteinuria [35]. This is best established in T1DM, but there is increasing evidence that the same pathophysiologic principles and treatment also apply in T2DM [33]. In addition, hypertension may be a common primary risk for the renal and other nonrenal cardiovascular complications of diabetes [36, 37]. One review has noted that apart from good glycemic control, antihypertensive treatment especially with angiotensin converting enzyme (ACE) inhibitors, often combined with other agents is quite effective in preventing progression of DN in all its stages [38]. In T2DM, hypertension is often an early finding, and blood pressure significantly increases according to the degree of albuminuria, normo-microalbuminuria and clinical proteinuria (macroalbuminuria) [38]. Hypertension is an important risk for both DN and cardiovascular disease. The author further notes that based on several studies, antihypertensive treatment - particularly with ACE-inhibitors-is important in both preventing and treating microalbuminuria, and thus preventing progression to overt DN [38]. Indeed, there is accumulating evidence to suggest that the use of antihypertensive agents which target the renin-angiotensin system can retard the progression of DN, as well as provide cardioprotection in patients with T2DM and microalbuminuria [2]. Antihypertensive treatment in patients with microalbuminuria and T2DM should therefore be initiated with angiotensin converting enzyme (ACE) inhibitors or angiotensin-II type 1 receptor blockers [2]. Nevertheless, neither ACE inhibitor nor ARB is currently recommended in normotensive, normoalbuminuric diabetics for primary prevention of DN.

Currently, most evidence and published guidelines suggest ACE inhibitors as first-choice antihypertensives in patients with diabetes [27, 39]. Notably, the degree of blood-pressure reduction rather than the class of antihypertensive agent used appears to be the most important factor in renoprotection. Calcium-channel blockers have been demonstrated to have beneficial effects [40] and combinations of ACE inhibition and calcium-channel blockade have shown positive results [41].

Dyslipidemia is also one of the putative risk factors for DN in patients with diabetes [42]. In addition, it is known to hasten the atherosclerotic process and is thus one of the major risk factors for cardiovascular disease in diabetes. A recent strategy is the use of nutraceuticals and functional foods which have been reported to reduce the overall cardiovascular risk induced by dyslipidemia by acting in synergy with statins [43]. Nutraceuticals refer to foods or food components which provide medical benefits including prevention and/or treatment of disease while functional foods are any foods or food ingredients which may provide health benefit beyond the traditional nutrients they contain [43]. Furthermore, dietary omega-3 polyunsaturated fatty acids could improve endothelial function and structure early in life, and therefore reduce cardiovascular risk profile later in life since endothelial dysfunction is an early marker of atherosclerosis [44].

The diabetic milieu is a complex environment where a number of interventions may be utilized to target various pathological processes. Given that no single therapy completely ameliorates DN, novel strategies are needed to complement existing interventions [45]. Some of these novel agents include the following; allopurinol -uric acid antagonist-(which improves endothelial dysfunction and reduces urinary TGF-β in DN) [46-48], vitamin D (which reduces albuminuria) [49], renin inhibitors such as aliskiren (which lowers blood pressure and reduces albuminuria) [50], and endothelial inhibitors such as atrasentan (which also lowers blood pressure and reduces albuminuria) [51].

Finally, high dietary protein has renal hemodynamic effects that include increased glomerular filtration rate (GFR), hyperfiltration, and increased intraglomerular pressure which are probably accentuated by poor glycemic control [29]. Dietary protein restriction has been shown to decrease renal functional deterioration in both T1DM and T2DM [52, 53]. For example, in a 5-year prospective study of patients with T1DM, those on a protein- and phosphate-restricted diet showed a decline of GFR of only 0.26 ml/min/month compared with 1.01 ml/min/month in those on unrestricted diets [54].

Current recommendations are for dietary protein at the level of the Recommended Dietary Allowance of 0.8 g/kg/day, accounting for 10% of total calories. In selected patients with decreasing GFR, it may be useful to decrease the prescribed protein intake to 0.6 g/kg/day as directed by a professional nutritionist [29].

Conclusion

Among the microvascular complications of diabetes in children and adolescents, DN remains the most important contributor of mortality. DN evolves over a long period of time-usually over 10 to 20 years- starting from microalbuminuria and progressing to end stage renal failure. Both tight glycemic control and intensive control of hypertension have significant impact on prevention and progression of DN. While tight glycemic control in patients with T1DM reduces the incidence of microalbuminuria and the

progression from microalbuminuria to macroalbuminuria, there is overwhelming evidence to show that antihypertensive treatment - particularly with ACE-inhibitors- is important in both preventing and treating microalbuminuria, and thus preventing progression to overt DN. Dietary protein restriction is also a useful adjunct strategy in retarding the progression of DN. Based on evidence in the literature, the current strategies for the prevention of DN in childhood diabetes are still effective and should remain part of the standard management guidelines. Other novel therapeutic strategies have been recently tried and found potentially effective. Research is ongoing to establish the clinical efficacy and usefulness of some of these new agents in future.

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Special Issue on

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