

Diabetic nephropathy in children with type 1 diabetes mellitus in Bahrain

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ABSTRACT

Objectives: Children and adolescent patients with type 1 diabetes mellitus (T1DM) may have an increased risk of developing diabetic nephropathy (DNP). The incidence of DNP varies with glycaemic control, and peaks after 15-20 years of diabetes and decline thereafter. Microalbuminuria is uncommon before puberty, and usually occurs after 5 years of diabetic duration. Once overt DNP is established, a progressive decline in the glomerular filtration rate and elevation in arterial blood pressure occurs, and it is the most important disorder leading to renal failure in adult patients with diabetes in developed countries. The purpose of this study was to screen all the children and adolescent with T1DM of 5 years duration or more for DNP.

Methods: Between April 2000 and February 2001, all patients with T1DM of more than 5 years, who were diagnosed between years 1985 to 1995 and followed by pediatricians at Salmaniya Medical Complex, Kingdom of Bahrain, were screened for DNP. Medical records were reviewed for demographical data, blood for hemoglobin A1c (HbA1c), fasting sugar and renal function test. The presence of DNP, retinopathy and

nephropathy and the medications were also reviewed. DNP was diagnosed by urine microscopy, overnight urine collection for albumin to creatinine ratio, or 24-hour urine for protein, and the medications.

Results: Diabetic nephropathy was diagnosed in 10 patients (31%), 2 with microalbuminuria (incipient nephropathy), and 8 with proteinuria (clinical nephropathy). Diabetic nephropathy was diagnosed at a mean of 10.5 years after the onset of T1DM. The mean age was 18 years for the DNP. Mean HbA1c was 11.8% for DNP and 10.2% for non-nephropathy group. All the patients with DNP were treated with an angiotensin converting enzyme inhibitor, 5 of them had hypertension. None developed renal failure or retinopathy.

Conclusion: Microalbuminuria is uncommon before 5 years of the onset of T1DM. Screening for microalbuminuria should be performed in adolescent over 12 years of age, with diabetes of more than 5 years duration and persistent hyperglycemia (HbA1c > 11 %).

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Patients with diabetes onset during childhood and adolescent may have an increased risk of developing diabetic nephropathy (DNP), as well as proliferative retinopathy and cardiovascular disease. Diabetic nephropathy causes increased morbidity and mortality in patients with T1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).¹ Once overt DNP is established, a progressive decline in the glomerular filtration rate and elevation in arterial blood pressure (BP) occurs. It is

the most important single disorder leading to renal failure in adult patients with diabetes in developed countries.² The incidence of DNP varies with glycaemic control, and peaks after 15-20 years of diabetes and decline thereafter.³ Approximately one third of T1DM patients develops proteinuria. The studies uncover a number of risk factors for the development of DNP beside the glycaemic control including genetic susceptibility, high systemic BP and glomerular hyperfiltration.^{4,6} Microalbuminuria

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is defined as albumin excretion rate (AER) of 20-200 µg/minute or 30-300 mg/24 hour, it marks the onset of incipient nephropathy,^{3,7} while clinical nephropathy is defined as persistent proteinuria corresponding to an AER of more than 200 µg/minute or more than 300mg/24 hour in patients without other non-diabetic renal diseases, urinary tract infection or cardiac failure. Recent studies used 20 µg/minute as a lower limit in 2 of 3 urine samples collected over 6 months period, which heralds overt DNP.

The purpose of this study was to screen all the children and adolescent with T1DM of 5 years duration or more for diabetic nephropathy.

Methods. Between April 2000 and February 2001, a total of 57 patients were screened, the age ranged between 8-23 years (mean 15 years). All the patients diagnosed with T1DM between 1985-1995 and followed in Pediatric Diabetic and Nephrology Clinic at Salmaniya Medical Complex, Kingdom of Bahrain were included.

The medical records were reviewed for the following data: demographic data, duration of diabetes, BP (130/85 mm Hg was considered high), fasting blood sugar hemoglobin A1c (HbA1c) (of >7.5% was considered high), serum cholesterol (>5.7 mmol/l was considered high), triglyceride, total protein, albumin, renal function test, urinalysis for protein, red blood cells, white blood cells, and according to the results we proceeded to either overnight 12 hour urine for microalbuminuria (AER of >20 mg/minute was considered abnormal), average 2-3 results within 6-months duration, or 24 hour urine for protein and creatinine for those with persistent proteinuria or those patients who had positive urinalysis for protein, the file was reviewed for date of first abnormal urine test and considered it as the time of diagnosis of DNP. Urine culture, serology tests and C₃, C₄ were requested for those with persistent proteinuria or clinical nephropathy (an AER of more than 200µg/minute or more than 300mg/24 hour) to exclude urinary tract infection and other causes of nephropathy, as well as renal ultrasound and renal biopsy if indicated, and medications. The presence of other diabetic complications including retinopathy by latest eye examination in diabetic eye clinic, or neuropathy were included.

Statistical analysis. Data was analyzed using the Statistical Package for Social Sciences (SPSS) for windows version 12.0 and Number Cruncher Statistical Software (NCSST). Patients were categorized into DNP-positive (n=9) and DNP-negative (n = 47). Statistical significance for differences in quantitative variables was tested by the Fisher's exact test, and for differences in the frequencies the Yates chi square test was used. P-value was used to determine significance at level =0.05.

Results. Diabetic nephropathy was reported in 10 patients, one was excluded as the patient died with incomplete data, 2 patients had microalbuminuria (AER 20-200 mg/minute), the remaining 8 had proteinuria (>300 mg/day). The mean urinary protein was 1.42±0.73 gm/day. Urinalysis was repeated for 45/53 patients, while 12 hour urine for microalbumin was checked for 23 patients and 24 hour urine for protein was checked for 8 patients, those with positive urinalysis for protein. The age at diagnosis of the DNP group ranged between 15-23 years (mean 18) and it was diagnosed 6-15 years after the onset of T1DM (mean 10.12) (Table 1). The DNP duration ranged between 1-28 months (mean 12). The mean HbA1c was 11.84% ± 2.91 for the DNP group and 10.19% ± 3.05 for the non-DNP group (p=0.18). Hypertension was reported in 5 patients of the DNP group. The mean systolic BP was 141 ± 11.40 mm Hg and the mean diastolic BP was 91 ± 15 mm Hg. None developed renal failure. Renal biopsy was performed on 3 patients; all had their biopsy consistent with diabetic glomerulosclerosis, in addition, one had secondary focal segmental glomerulosclerosis, and the second had fibrillary glomerulosclerosis (Table 1). The entire DNP group was treated with an angiotensin converting enzyme (ACE) inhibitor in the form of Captopril, Enalapril or Lisinopril to control both the DNP as well as the

Table 1 - Characteristics of study participants.

Characteristics	DNP-Negative*	DNP-Positive*	P value
N of patients	47	9	
Male to female ratio	23:24	4:5	0.518 [†]
Age at T1DM diagnosis	7.14 ± 3.06	7.25 ± 2.05	0.924
Duration of T1DM	9.17 ± 2.78	10.12 ± 2.74	0.385
HbA1c	10.19 ± 3.05	11.84 ± 2.91	0.18
Urinary protein			
Negative	38/44	2/9	
Positive	2/44	7/9	
Not determined	4/44	0/9	
Cholesterol	5.83 ± 3.17	6.61 ± 1.57	0.642 [†]
Triglycerides	1.51 ± 1.01	1.50 ± 0.70	0.983 [†]
Complications			
Neuropathy	1/47	0/9	0.351 [†]
Edema	0/47	2/9	0.021 [†]
Retinopathy	1/41	0/9	0.400 [†]
Hypertension	0/43	5/9	<0.001 [†]

*indicates patients with available data.
[†]Fisher's exact test, [†]Yates chi square test.
[‡]had a positive protein in only one occasion, had no DNP.
DNP - diabetic nephropathy, T1DM - type I diabetes mellitus, HbA1c - hemoglobin A1c

hypertension. Eye examination for retinopathy was repeated for 51/56 patients, one patient had retinopathy and neuropathy but did not have nephropathy. From the DNP group, none had diabetic retinopathy or neuropathy.

DISCUSSION. The natural history of DNP progresses from earlier stages of glomerular hyperfiltration and hypertension to microalbuminuria, proteinuria, and, if untreated, end-stage renal disease (ESRD) which requires dialysis and transplantation. It has been suggested that 25-45% of patients will, during their lifetime, develop clinically evident DNP,⁸ this correlates with the clinical data obtained in this trial in which 31% of patients developed DNP. The prevalence of DNP associated with T1DM increased with a longer duration of diabetes, but microalbuminuria is uncommon before puberty, and usually occurs after 5 years of diabetic duration.³ In this study, the DNP was reported 6-15 years post-onset of diabetes with a mean duration of 10.12 years. The Diabetes Control and Complications Trial Research Group (DCCTRG, 1993), which is one of the largest controlled trials on subjects aged 13-39 years with T1DM, identifies many risk factors for DNP. These included poor glycaemic control (HbA1c more than 11% are at higher risk), early age of diagnosis, genetic predisposition with positive family history, family history of hypertension, elevated AER, hypertension, relative insulin resistance and smoking. The DCCTRG trial resulted in more than 75% reduction in long-term complications compared with the conventional therapy and reduced the risk of microalbuminuria by 55% in the secondary intervention cohort.^{3,8,9} They concluded that most patients with T1DM should be treated as early as possible with the aim of maintaining glycaemia as close to the normal range as safely as possible. The target level for glycaemic control is HbA1c of 7-7.5% seems reasonable since lower level increases the risk for severe hypoglycaemia.⁹⁻¹¹ However, such target is difficult to achieve in children and adolescent since most children have poor glycaemic control. The mean HbA1c in our patients was 11.8% for the DNP group and 10.2% for the whole group, which indicates poor glycaemic control in this age group as a whole. Age at diagnosis is also a risk factor, the younger the age at diagnosis of diabetes; the higher is the risk.^{6,10} In our group of DNP the age at diagnosis was 7.60 ± 2.40 years compare to 7.12 ± 3.10 for the DNP negative group ($p=0.64$). The difference was not significant, and the age at the time of DNP diagnosis was the mean of 18 years, and none developed renal failure.

Hypertension is not, in itself, a risk factor for initiating nephropathy but generally considered to be a consequence of it. Patients with glomerular

hyperfiltration appear to be at increased risk in diabetic renal disease.^{8,9} Many clinical trials have shown that intensified anti-hypertensive therapy is associated with improved survival and decreased mortality rates in this population. Most of these studies have demonstrated a beneficial effect of anti-hypertensive therapies, including a variety of ACE inhibitor, on discrete stages of DNP.^{7,12} Increasing evidence indicates that early intervention delays the progression of nephropathy. It has become apparent that trace albuminuria provides a unique opportunity to recognize incipient renal involvement in early onset, particularly in T1DM.¹³ Angiotensin converting enzyme inhibitors have had a particular role to play in the prevention of DNP with and without hypertension.^{10,14,15} The European Microalbuminuria Captopril Study Group reported that captopril treatment significantly impeded progression to clinical proteinuria and prevented the increase in AER in normotensive adult diabetics with persistent microalbuminuria. It also postponed the development of overt diabetic nephropathy in normotensive T1DM patients. Captopril was also shown to be effective in decreasing AER in normotensive children with microalbuminuria. The drug protects against deterioration in renal function in T1DM nephropathy and is significantly more effective than BP control alone.^{16,21}

Five patients in this trial had high BP of more than 130/90 (authors consider a BP of <130/85 mm Hg to be optimal for diabetic patients). All patients in this trial were started on ACE inhibitors as soon as they were diagnosed with DNP with or without hypertension. This was started with Captopril therapy and, with the availability of new types of ACE inhibitors, it was changed to Enalapril or Lisinopril in an effort to increase patient's compliance as these were given once daily. The change in insulin resistance as an effect of the given drugs was not studied.

In conclusion, early detection and intervention of DNP is advisable, and to prevent the long-term morbidity and mortality, screening for microalbuminuria should be performed in adolescent over 12 years of age, with diabetes of more than 5 years duration, hypertension and persistent hyperglycaemia (HbA1c >11%).

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