Full Length Research

Early microalbuminuria in adolescent Type 1 diabetic patients: Experience from a pediatric endocrine clinic in a developing country

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There are no studies of early microalbuminuria in adolescent Type 1 diabetic patients in the developing world where patients are considerably undernourished and follow conventional treatment regimens in most part. The objective was to assess the presence of microalbuminuria in Type 1 adolescent diabetes mellitus (DM) patients where patients still use conventional treatment regimen. The subjects (n = 30), in the age group of 10 to 18 years, were divided into two groups - good glycaemic (n = 16) and poor glycaemic (n = 14) control groups during end of study period based on their mean HbA1c value (<8.5 vs. ≥8.5, mean value over one year period). Though no subject with good glycaemic control developed microalbuminuria, 5 (35.7%) of the total 14 poor glycaemic control patients had microalbuminuria. Both systolic and diastolic blood pressures were higher in the microalbuminuric group. It is concluded that malnourished adolescent Type 1 diabetic patients who follow conventional treatment regimen and are poorly controlled, may develop very early microalbuminuria.

Key words: Diabetic nephropathy, early diagnosis, microalbuminuria.

INTRODUCTION

Diabetic nephropathy, one of the leading causes of end stage renal disease, affects 20 to 30% patients with Type1 diabetes mellitus (DM). The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate of 30 to 300 mg/24 h (microalbuminuria) constitutes an early stage of nephropathy, especially when it becomes persistent (at least 2 of 3 consecutive urine samples) (Mogensen et al., 1985).

The prevalence of microalbuminuria in childhood and adolescence is 7.6 to 20% (Cook and Daneman, 1990; Quattrin et al., 1995; Mathiesen et al., 1986). Progression of microalbuminuria is usually associated with sustained hyperglycemia and elevated systolic blood pressure

(SBP) and can be normalized with better prevailing metabolic control and lower diastolic blood pressure (DBP) (Mogensen and Christensen, 1984). If glycosylated hemoglobin value is maintained below 8.1%, the number of patients in whom microalbuminuria develops should decline substantially, which in turn lowers the number in whom overt proteinuria and end stage renal disease develops (Wang et al., 1993; Diabetes Control and Complications Trial Research Group, 1993).

In the adolescent population, microalbuminuria detected in the first decade of disease will persist or progress in the second decade in approximately two thirds of patients and new microalbuminuria will develop in a third of those initially normoalbuminuric (Gorman et al., 1999). This underlines the need for regular microalbuminuria screening to be started early during this period.

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According to the statement of the American Diabetes Association (ADA), annual screening for microalbuminuria should be initiated once the child is 10 years of age and has had diabetes for 5 years, more frequent testing is indicated if values are increasing (Silverstein et al., 2005). Due to intensive treatment in the post DCCT (diabetes control and complications trial) era, glycaemic control is much better than before in developed countries and prevalence of different microvascular complications are in decreasing secular trend.

But in developing countries like ours, the picture is not that rosy due to financial constraints and lack of health insurance schemes. In developing countries, conventional therapy is used instead of intensive therapy, regular insulin and Neutral Protamine Hagedorn (NPH) insulin is given at breakfast and supper which produces the least physiologic profile with large excess before lunch and during the early night, combined with poor coverage before supper and breakfast. Alot is not known about prevalence of microalbuminuria in Type 1 DM in India where conventional treatment regimens are still mainly being followed.

There are hardly any studies in India showing the importance of screening for complications in adolescent population by analyzing different laboratory data (like albumin excretion rate, blood pressure and glycosylated hemoglobin, etc.) when the disease manifestations are subclinical, reversible and treatable. Definite emphasis on malnutrition is lacking in most of the microalbuminuria studies done so far.

MATERIALS AND METHODS

Cross sectional analytical type of study was conducted on 30 Type 1 diabetic patients in the age group of 10 to 18 years attending the pediatric endocrine clinic over a period of one year in Lok Nayak Hospital, New Delhi, India. The study protocol was approved by institutional ethics committee and patients consented to participate in the study.

Major eligibility criteria included insulin dependence as evidenced by deficient c- peptide secretion, no hypertension or dyslipidaemia, and no other major medical conditions. All patients were taking conventional treatments due to poor economic standard. Anthropometry and Tanner staging were performed in all patients. Patients were not divided at the beginning of the study according to glycaemic control. They were classified into 2 groups at the time of statistical analysis (end of one year or study period) depending on the mean glycosylated hemoglobin during the study period. The following tests were performed during the study period:

1) Fasting and post prandial blood glucose (determination of true glucose, based on enzymatic method using glucose oxidase and peroxidase)
2) Glycosylated hemoglobin level (HbA1c) (fast ion exchange resin separation method)
3) Urinary albumin excretion rate to detect microalbuminuria (30 to 300 µg/mg of creatinine) by immunoturbidimetric quantitative analysis. In all these patients, microalbuminuria was detected by a total of three timed urine (1st voided early morning) collections, performed within 6 months in order to reliably establish the presence of persistent microalbuminuria (at least two of three tests show elevation).
4) Blood pressure measurement using an appropriately sized cuff and with the patient relaxed and seated.

Statistical analysis

Data were presented as mean ± SD. Fischer exact test was used for comparing the statistical significance of categorical variables. The Student t test was used for comparing the statistical significance of continuous variables following a Gaussian distribution, whereas Wilcoxan Mann-Whitney tests was done for non-Gaussian distribution. For comparison of three or more unmatched groups, one way ANOVA analysis was used. The level of significance was set as 5% in all comparisons. All tests were 2-sided.

RESULTS

The subjects (n = 30) were divided into two groups, that is, good glycaemic and poor glycaemic control groups, based on their mean HbA1c value (<8.5 vs. ≥8.5) averaged over the 1 year time period. In the good glycaemic control group, the average glycosylated hemoglobin level (%) was 7.89±0.68. In the poor glycaemic control group, the average glycosylated hemoglobin level (%) was 11.25±0.35, which was significant (0.01)

In the good glycaemic control group, there were 9 females and 7 males with a mean age of 13±2.58 years. Sixteen subjects were equally divided into pre-pubertal and pubertal stage (8 subjects in each group). In the poor glycaemic control group, there were 7 females and 7 males, with a mean age of 13.71±2.3y ears. Five subjects were pre-pubertal and the remaining nine were in puberty. Age, sex, pubertal status, diabetes duration and body mass index (BMI) were comparable in these two groups. Baseline characteristics of these groups are displayed in Table 1.

Though no subject with good glycaemic control developed microalbuminuria, 5(35.7%) of the total 14 poor glycaemic control patients developed microalbuminuria. Nine (64.3%) of the 14 poor control patients were still normoalbuminric. All 5 patients with microalbuminuria were male and four had attained puberty. Among 7 males of the poor control group, only 2 (22.2%) were normoalbuminuric. This male predominance in the microalbuminuric group is statistically significant (p = 0.02). The average age of these microalbuminuric subjects was 14.6±1.8 years, comparable to the subjects who did not develop microalbuminuria (p = 0.30). Average diabetes duration (in years) and mean HbA1c (%) of microalbuminuric subjects were 5.4±3.64 and 11.62±1.23 respectively, these were not statistically different from poor control normoalbuminuric subjects (p = 0.257 and 0.193 respectively). Comparison of blood pressures among 16 subjects with good glycaemic control, 5 subjects with

Table 1. Baseline characteristics of good and poor glycaemic control groups.

Variable	Good glycaemic control (avg. HbA1c<8.5) [n = 16]	Poor glycaemic control (avg. HbA1c>8.5) [n = 14]	P value
Age (years)	13±2.58	13.71±2.3	0.430
Female (%)	56.3	50	0.500
Puberty (%)	50	64.3	0.484
Diabetes Duration(years)	3.18±1.72	3.93±2.62	0.470
Insulin dosage (unit/kg/day)	1.19±0.19	1.24±0.21	0.587
Wt(kgs)	31.27±10.19	32.54±10.83	0.741
Ht(cms)	136.1±13.93	143.39±17.76	0.216
BMI(kg/m^2)	16.3±2.54	15.37±2.49	0.522
Glycosylated Hb(HbA1C)	7.89 ± 0.68	9.37±1.89%	0.010
Fasting blood sugars (mg/dl)	261.6±88.7	370.0±70.3	0.007
Post prandial	306.6±85.5	401.6±45.9	0.010

Table 2. Comparison of blood pressure among good glycaemic control, poor glycaemic with and without microalbuminuria groups.

Variable		Good glycaemic control (n = 16)	Poor glycaemic control and microalbuminuric (n = 5)	Poor glycaemic control and normoalbuminuric (n = 9)	P Value
SBP(mm Hg)	Mean ± SD	109.50±6.713	119.2±11.37	110.67±6.56	0.04
DBP(mm Hg)	Mean ± SD	69.75±5.158	77.2±4.6	72±2	0.009

SBP = systolic blood pressure; DBP = diastolic blood pressure.

microalbuminuria and 9 subjects without microalbuminuria groups (last 2 groups were from poor glycaemic control group) is displayed in Table 2. Comparison of SBP and DBP in the three groups by ANOVA showed that there were statistically significant differences in both SBP and DBP between the three groups.

DISCUSSION

The diabetes control and complications trial (DCCT), released in 1993, was the first significant randomized intensive therapy trial in Type 1 diabetes (Diabetes Control and Complications Trial Research Group, 1993). It confirmed conclusively that there was a direct and continuous relationship between diabetes control and the risk of complications. But the recent status of glycaemic control in adolescent diabetic population of developing countries is not critically analyzed against the secular trend of improving glycaemic control in developed counties in the post-DCCT era.

Our study population was significantly malnourished (16.3± 2.54 and 15.37±2.49 kg/m^2 in good and poorly controlled subjects respectively) compared to DCCT study where BMI in male and female in primary prevention cohort were 21±2 and 22±3 kg/m^2 respectively. This is similar to one study from South India in which 70% of patients with insulin-dependent diabetes

mellitus (IDDM) also had a BMI of less than 18 (Ramachandran et al., 1988). Study by Arbona et al. (1990) also showed that in Type 1 diabetes, protein malnutrition was found in 50% of the evaluated subjects, with a significant relation between the degree of metabolic control and the prevalence of protein malnutrition. Chronic undernutrition is an important determinant of diabetes in an individual, either by progressively impairing beta cell function or by increasing the susceptibility of the individual to other genetic and environmental diabetogenic influences. This issue is drastically different from developed countries where Type 1 DM is also associated with adiposity and both Type 1 and 2 are taken as the same disorder of insulin resistance set against different genetic background.

Enthusiasm for accepting the target achieved by the intensively treated adult cohort of the DCCT is counterbalanced by the recent results of epidemiology of diabetes interventions and complications (EDIC) - the follow up study of DCCT participants where most participants were on intensive treatment (Epidemiology of Diabetes Interventions and Complications, 1999).

The EDIC study showed an increase in A1C level in those adolescents in the intensive treatment group (from 8.1 to 8.4%) and a decrease in those in the conventional group (from 9.8 to 8.5%) after the end of the study. These data suggest that intensification of treatment outside of a clinical trial can decrease A1C significantly, but that it may be difficult to achieve an A1C consistently < 8%

without the resources of a clinical trial. In addition, the benefits of improved glycaemic control in children must be balanced with careful consideration of the child's unique vulnerability to hypoglycemia. As it is clear that hypoglycemic risk is not confined to young children, maintaining optimal HbA1c by frequent blood glucose monitoring is not possible.

In our setup, maintenance of HbA1C < 8 (in 10 to 12 years) and < 7.5% (13 to 18 years) according to ADA guidelines is not practical for several reasons like:

 i. Mainly twice daily dose of insulin used.
ii. Less frequent blood glucose monitoring.
iii. Less motivated population.

Thus, due to lack of a tight control, we took 8.5% as cut off and HbA1C < 8.5% was considered as good control and > 8.5% as poor control (Epidemiology of Diabetes Interventions and Complications, 1999). However, the average HbA1c of the population with good glycaemic control was 7.89± 0.68 and had a mean age of 13±2.58 years.

In our study, 16.67% (5 among 30 subjects) developed microalbuminuria, all of them were from poor control group. In the primary prevention cohort of DCCT, the subjects in the intensive treatment group had 5.8 episodes of microalbuminuria per 100 patient-years compared with 7.1 episodes per 100 patient-years in the conventional treatment subjects. In the study performed by Cook et al. (1990), 7.6% adolescents with IDDM showed persistent microalbuminuria (Cook and Daneman, 1990). In the MIDAC research group study, among a total of 1007 patients, ninety eight (9.7%) had microalbuminuria (Moore and Shield, 2000). Study by Cosmescu et al. (2003) showed that persistent microalbuminuria was detected in 9% and intermittent microalbuminuria in 11.8% of patients. A similar study by Yoo et al. (2004) showed that persistent microalbuminuria and macroalbuminuria were observed in 11.3 and 2.8% of patients with DM1. But the study of Kong et al. (2005) on post DCCT showed that prevalence of persistent microalbuminuria was 2% in an adolescent cohort with diabetes duration >5 years due to intensive treatment and the decreased rate of complication. This decreasing trend of microvascular complications was also proved by Mohsin et al. (2005) by doing further cross sectional analysis of complications from 1990 to 2002.

The results of the largest cross sectional study (the study of EURODIAB IDDM complications) confirmed the early development of microangiopathy (Karamanos et al., 2000). This study also showed that standardized and validated methodology would detect complications more accurately. The presence of microalbuminuria was documented very early in almost a quarter of patients against the popular belief that microangiopathy do not appear very early. There is strong evidence of development of persistent microalbuminuria with poor glycaemic control even in longitudinal studies (Stone et al., 2006).

This higher percentage of early nephropathy in our study population was mostly attributable due to poor glycaemic control but significantly malnourished state might also make the situation worse. Another interesting observation is that, in our study, there was a statistically significant difference with respect to sex in microalbuminuria group as all the microalbuminuric were male. Similarly, in the study by Patel et al. (1999) microalbuminuria was significantly more prevalent among the males. But this finding is in contrast to the finding of Moore and Shield (2000) whose study showed that significantly more girls than boys had abnormal albumin excretion. Although average diabetes duration of microalbuminuric subjects were 5.4±3.64 years, two subjects were only 12 years old and had diabetes for only 3 years. Thus, in these children with higher HbA1C, that is, very poorly controlled subjects, starting of screening after 5 years of diagnosis according to the ADA guideline may be a bit late and consideration should be given to start an earlier screening for microalbuminuria; perhaps after 2 to 3 years of diagnosis.

The natural history of blood pressure (BP) changes prior to the development of microalbuminuria is less well defined, but in the microalbuminuric stage, blood pressure progressively rises. Diastolic BP was significantly more in microalbuminuric subjects in our study group compared to non microalbuminuric poor control group (p=0.011). Both SBP and DBP were significantly higher in microalbuminuric group when compared with good control group. A study by Mathiesen et al. (1995) showed that initially, there was no difference between SBP and DBP between microalbuminuric and non-microalbuminuric Type 1 diabetic subjects but later, significant elevation of DBP occurred. Khan et al. (1994) showed that Type 1 diabetic with persistent microalbuminuria had higher systolic and diastolic blood pressure though all of them were normotensive. Study by Quattrin et al. (1995) also showed that systolic and diastolic blood pressures were significantly higher in the incipient and overt nephropathy group when compared with the normal group.The changing pattern of metabolic control in highly motivated diabetics has a profound influence on reducing the incidence and severity of complications. But in developing countries, stringent blood glucose control is not easy because of poor financial support system. So, screening for complications becomes much more important here as reversal of poor glycaemic control and special complication directed therapy like ACE inhibitors for nephropathy actually improves outcome.

LIMITATIONS

There are several shortcomings of this study and the

most important is low sample size. Although it may serve as a starting point of a large scale epidemiological study along with strict anthropometric variables to conclusively prove or disprove role of malnutrition in diabetes control. Also, we could not access the duration of puberty in subjects; this seems to be one of the important factors for appearance of complications. In spite of being a small study, we tried to bring up the real situation of Type 1 diabetes population in a poor developing country in the post-DCCT era where practical problem to achieve the glycaemic control according to the ADA guideline is very difficult. We also raised two valid questions to explore if malnourished state contributes along with poor glycaemic control to augment early appearance of microvascular complications and what would be the appropriate time for microalbuminuria screening in our set up where conventional treatment is being followed.

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