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PREVALENCE OF MICROALBUMINURIA AND ASSOCIATED RISK FACTORS IN YOUNG INDIAN TYPE 2 DIABETES SUBJECTS ATTENDING A TERTIARY DIABETES CARE INSTITUTE

Dr. R. Anil Kumar*

Associate Professor and HOD Department of Endocrinology, Karnataka Institute of Endocrinology and Research Bengaluru.

***Corresponding Author: Dr. R. Anil Kumar**

Associate Professor and HOD Department of Endocrinology, Karnataka Institute of Endocrinology and Research Bengaluru.

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ABSTRACT

Aims and Objectives: To find out the prevalence of microalbuminuria in young Indian type 2 diabetes subjects with age of onset of diabetes less than 35 years. **Material and Methods:** Type 2 diabetic subjects 373 in number were selected from patients with age of onset of diabetes less than 35 years attending Karnataka institute of endocrinology and research over a period of 2 years. **Results:** Age of diabetes subjects range from 20 to 50 years with age of onset of diabetes less than 35 years in all the participants. 71.8% of diabetes subjects were males. 54.7% of subjects had BMI 18.5 to 25 and 37.8% of subjects had BMI 25 to 30. Waist circumference was 80 to 90 cms in 54.7% and 90 to 100 cm in 25.2% of subjects. Fasting plasma glucose was more than 126 mg/dl in 77.2% of the subjects. Postprandial plasma glucose of 72.9% of subjects was more than 200 mg/dl.The target HBA1c of <7% was achieved only in 18.4% of young diabetes subjects. The glycemic control of young diabetics was not good in many studies. In this study the HBA1c was more than 9% in 55.5% of the diabetes subjects. Microalbuminuria was present in 23.3% and macroalbuminuria in 4.6% of young diabetes subjects. Systolic BP, HBA1c, BMI and duration of diabetes are correlated with microalbuminuria. **Conclusions:** Microalbuminuria was present in 23.6% of young diabetes subjects with age of onset of diabetes less than 35 years. Only 18.4% of the patients HBA1C was less than 7%. The glycemic control of young diabetics was not good in many studies. In this study the HBA1c was more than 9% in 55.5% of the diabetes subjects. So it is essential to achieve Glycemic targets and blood pressure targets in young diabetes subjects to retard progression from microalbuminuria to macroalbminuria and in few patients we can revert to normoalbuminuria.

KEYWORDS: Type 2 diabetes, Microalbuminuria, Nephropathy.

INTRODUCTION

Type 2 diabetes in youth is a relatively new disease. Limited outcome data are available to predict the risk for developing nephropathy in these patients who will likely be exposed to a higher degree and duration of glycemic exposure over their lifetime. Pubertal hormones can exacerbate existing insulin resistance to accelerate β-cell failure rates and may impact renal physiology as well in youth and young adults at genetic risk for T2D. Attempts to maintain glycemic control in youth and young adults with T2D frequently coincide with medical management of obesity, hypertension, fatty liver and hyperlipidemia. Dietary and medication compliance may be limited by issues related to supervision, maturity, depression and socioeconomic circumstances. Racial/ethnic minority youth are not only at higher risk for T2D risk but may also differ in their future patterns for renovascular disease risk and therapeutic response to ACE inhibitors.

Type2 diabetes and hypertension are the two leading causes of end-stage renal disease; with risks for developing diabetic nephropathy further increased by co-existing risk factors of hyperlipidemia and/or obesity. Youth and young adults with type 2 diabetes (T2D) have increased risk for earlier onset and accelerated progression of albuminuria when compared to both their type 1 diabetes (T1D) counterparts and adults with T2D of similar duration.[1-9] Furthermore, youth and young adults with T2D have an extended lifetime exposure to these risk factors. Pubertal hormone driven extremes of insulin resistance likely contribute to the observed risk for accelerated β-cell failure and circulating growth factors may have a negative impact on nephropathy progression.[10-13] In addition, reports of worse glycemic control among teens and young adults with diabetes portend both earlier and increased cumulative microvascular complications.

Longitudinal data from the Type 2 Diabetes in Adolescents and Youth (TODAY) study predict that children and adolescents diagnosed with T2D may have a much more aggressive course of disease with an

increased risk for early hypertension and nephropathy when compared to adolescents with T1D.[5,14] A higher prevalence of hyperlipidemia, non-alcoholic fatty liver disease and inflammatory markers further contributes to the concern for cumulative lifetime nephropathy risk in youth and young adults with T2D. There is limited comparable longitudinal data regarding nephropathy outcomes for youth diagnosed with T2D. Accumulating cross-sectional and epidemiologic data reveal both increased and earlier risk for MA as well progression to nephropathy in youth and young adults with T2D.[1-3]

Sustained motivation of youth with T2D to adhere to simultaneous dietary restrictions of sodium, fat and calories is difficult. Compliance with medical therapy and lifestyle recommendations is often hampered by a multitude of contributing psychosocial, medical and physiologic factors.[1516] Effectively addressing underlying factors that contribute to deteriorating glycemic control, hypertension, and obesity during teen and young adult years is critical to reducing renovascular disease risk.

Microalbuminuria is an early marker of nephropathy, cardiovascular diseases and severe ocular morbidity in adults with diabetes.[17–21] It is a subclinical condition that is associated with high morbidity and mortality.[21,22] The presence of microalbuminuria precedes the development of overt diabetic nephropathy by 10–14 years. It is at this stage that one can reverse diabetic nephropathy or prevent its progression.[21,23,24,25] Diabetic nephropathy, the end result of microalbuminuria, is a major cause of morbidity, premature mortality, end stage renal disease, need for renal replacement therapy, cardiovascular diseases, and escalating health-care costs in diabetic patients.[26, 28–32] The prevalence of DN is increasing steeply along with the diabetes epidemic.[15] Approximately one third to half of patients with diabetes develops renal manifestations.[28,29,33]

The following study is undertaken to know the prevalence of microalbuminuria in young type 2 diabetics with age of onset of diabetes less than 35 years.

AIMS AND OBJECTIVES

To find out the prevalence of microalbuminuria in young Indian type 2 diabetes subjects with age of onset of diabetes less than 35 years.

MATERIAL AND METHODS

Type 2 diabetic subjects 373 in number were selected from patients with age of onset of diabetes less than 35 years attending Karnataka institute of endocrinology and research over 2 years.

Clinical and biochemical studies

Measurements of weight, height, and waist circumference were obtained using standardized techniques. The BMI was calculated using the following formula: weight (kg)/height (m^2). Blood pressure was recorded in the sitting position in the right arm. Two readings were taken 5 min apart, and the mean of the two was taken as the final blood pressure reading. The study was approved and informed consent was obtained from all the participants.

A fasting and post prandial blood sample was taken for estimation of plasma glucose by hexokinase method. HBA1C was measured by the high-performance liquid chromatography method using the Bio-rad Variant 2 turbo analyser.

Diagnosis of diabetes was made by using criteria of fasting plasma glucose ≥126 mg/dl and HBA1c ≥6.5%.

Estimation of microalbuminuria

Microalbumin concentration was measured in a fasting urine sample using immunoturbidometric assay (Hitachi C311 autoanalyser; Roche Diagnostics).

Microalbuminuria

Microalbuminuria was diagnosed if the albumin excretion was between 30 and 299 µg/mg of creatinine. Macroalbuninuria was diagnosed if albumin excretion was ≥300 µg/mg of creatinine.

Statistical Methods: Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance. A t-test is a statistical test that is used to compare the means of two groups. It is often used in hypothesis testing to determine whether a process or treatment actually has an effect on the population of interest, or whether two groups are different from one anotherwith the null hypothesis (H_0) is that the true difference between these group means is zero and the alternate hypothesis (H_a) is that the true difference is different from zero.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value:0.01<P ≤ 0.05)
** Strongly significant (P value: P≤0.01)

Statistical software: The Statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

Age of diabetes subjects range from 20 to 50 years with age of onset of diabetes less than 35 years in all the participants. 71.8% of diabetes subjects were males. 54.7% of subjects had BMI 18.5 to 25 and 37.8% of subjects had BMI 25 to 30. Waist circumference was 80 to 90 cms in 54.7% and 90 to 100 cm in 25.2% of subjects. Fasting plasma glucose was more than 126 mg/dl in 77.2% of the subjects. Postprandial plasma glucose of 72.9% of subjects was more than 200 mg/dl. (Table 1-6)

The target HBA1c of <7% was achieved only in 18.4% of young diabetes subjects. The glycemic control of young diabetics was not good in many studies. In this study the HBA1c was more than 9% in 55.5% of the diabetes subjects. Microalbuminuria was present in 23.3% and macroalbuminuria in 4.6% of young diabetes subjects. Systolic BP, HBA1c, BMI and duration of diabetes are correlated with microalbuminuria. (Table 7 to 10)

Table 1: Age distribution of patients studied.

Age in years	No. of patients	%
<20	13	3.5
20-30	128	34.3
31-40	227	60.9
41-50	5	1.3
Total	373	100.0

Table 2: Gender distribution of patients studied

Gender	No. of patients	%
Male	268	71.8
Female	105	28.2
Total	373	100.0

Table 3: Age distribution of patients studied

Age in years	Gender		Total
	Male	Female	
<20	8(3%)	5(4.8%)	13(3.5%)
20-30	80(29.9%)	48(45.7%)	128(34.3%)
31-40	177(66%)	50(47.6%)	227(60.9%)
41-50	3(1.1%)	2(1.9%)	5(1.3%)
Total	268(100%)	105(100%)	373(100%)
Mean ± SD	31.85±5.19	29.97±6.21	31.32±5.55

P=0.003**

Table 4: Age at onset of diabetes in years-distribution of patients studied.

Age at onset yrs	Gender		Total
	Male	Female	
<20	14(5.2%)	17(16.2%)	31(8.3%)
20-30	134(50%)	63(60%)	197(52.8%)
31-40	120(44.8%)	25(23.8%)	145(38.9%)
Total	268(100%)	105(100%)	373(100%)

Table 5: BMI (kg/m^2)-distribution of patients studied.

BMI (kg/m^2)	Gender		Total
	Male	Female	
<18.5	13(4.9%)	5(4.8%)	18(4.8%)
18.5-25	157(58.6%)	47(44.8%)	204(54.7%)
25-30	94(35.1%)	47(44.8%)	141(37.8%)
>30	4(1.5%)	6(5.7%)	10(2.7%)
Total	268(100%)	105(100%)	373(100%)

Table 6: Waist Circumference in cm.

Waist Circumference in cm	Gender		Total
	Male	Female	
<80	40(14.9%)	15(14.3%)	55(14.7%)
80-90	152(56.7%)	52(49.5%)	204(54.7%)
90-100	65(24.3%)	29(27.6%)	94(25.2%)
100-110	11(4.1%)	9(8.6%)	20(5.4%)
Total	268(100%)	105(100%)	373(100%)

P=0.275, Not Significant, Chi-Square Test

Table 7: Comparison of BMI/WC/SBP/DBP.

	Gender		Total	P value
	Male	Female		
BMI (kg/m^2)	33.29±151.64	24.85±3.42	30.92±128.54	0.569
Waist Circumference in cm	86.36±7.60	88.81±8.37	87.05±7.89	0.007**
SBP (mm Hg)	127.82±15.22	121.10±14.48	125.93±15.30	<0.001**
DBP (mm Hg)	83.17±40.33	77.73±10.13	81.64±34.68	0.174

Table 8: FPG/PPG distribution of patients studied.

	Gender		Total (n=373)
	Male (n=268)	Female (n=105)	
FPG			
• <100	16(6%)	12(11.4%)	28(7.5%)
• 100-126	39(14.6%)	18(17.1%)	57(15.3%)
• >126	213(79.5%)	75(71.4%)	288(77.2%)
PPG			
• <140	19(7.1%)	13(12.4%)	32(8.6%)
• 140-200	52(19.4%)	17(16.2%)	69(18.5%)
• >200	197(73.5%)	75(71.4%)	272(72.9%)

Table 9: HbA1c%distribution of patients studied.

HbA1c%	Gender		Total
	Male	Female	
<6	9(3.4%)	2(1.9%)	11(2.9%)
6-7	44(16.4%)	14(13.3%)	58(15.5%)
7-8	35(13.1%)	17(16.2%)	52(13.9%)
8-9	31(11.6%)	14(13.3%)	45(12.1%)
9-10	34(12.7%)	16(15.2%)	50(13.4%)
>10	115(42.9%)	42(40%)	157(42.1%)
Total	268(100%)	105(100%)	373(100%)
Mean ± SD	9.73±2.70	10.39±8.59	9.92±5.10

P=0.258

Table 10: Serum creatinine and Albumin distribution of patients studied

	Gender		Total (n=373)	P value
	Male (n=268)	Female (n=105)		
Serum Creatinine (mg/dl)				
• <1.1	257(95.9%)	105(100%)	362(97.1%)	0.035*
• >1.1	11(4.1%)	0(0%)	11(2.9%)	
Albuminuria				
• <29	185(69%)	84(80%)	269(72.1%)	0.037*
• 30-299	67(25%)	20(19%)	87(23.3%)	
• >300	16(6%)	1(1%)	17(4.6%)	

Chi-Square/Fisher Exact Test

DISCUSSION

The TODAY Study provides unique prospective longitudinal data regarding HTN and MA in a large multi-ethnic cohort of well characterized youth with T2D (ages 10–17 years). Participants were enrolled within two years of their T2D diagnosis and provided comprehensive diabetes care that included aggressive protocol-driven treatment of confirmed HTN and MA. The incidence of hypertension rose from 11.6% at baseline to 33.8% within only 3.9 years average duration of TODAY study participation. Consistent with adult T2D findings, males had a significantly higher risk for developing hypertension. The risk for hypertension increased by 14% per additional year of age and by 6% per additional unit of BMI at baseline. In contrast, the risk for microalbuminuria was similar between genders with a prevalence of 3% at baseline rising to 16.6%. The only significant factor influencing MA progression in TODAY participants was glycemic control; there was a 17% increased risk of developing MA for every 1% rise in A1C. Overall, 8% of participants developed macroalbuminuria and one-third of those advanced to proteinuria during the duration of the study.[5]

Youth with T2D should be carefully monitored at quarterly visits for glycemic control, weight gain, and blood pressure (BP) with annual screenings of urinary microalbuminuria (MA) and serum lipids.[34,35]

Therapeutic interventions which reverse microalbuminuria include intensified glycemic control, use of ACE inhibitors, use of SGLT 2 inhibitors and these should be initiated in diabetics with microalbuminuria to prevent progress to overt diabetic nephropathy.

Although preliminary T2D outcome data is limited at this time, the known relationship between nephropathy and cardiovascular morbidity predicts youth and young adults diagnosed with T2D may experience severe, chronic complications of Type 2 diabetes by their 40s with a loss of approximately 15 years from average remaining life expectancy.[36]

In general, all major classes of BP medications have been proven to provide CV protection when adequate BP control is achieved. In contrast, special renoprotection is seen with blockade of the RAAS, which is the cornerstone of treatment for the prevention and progression of renal disease in diabetes patients. Though the level of evidence may be stronger for ACE inhibitors in T1D and ARB's in T2D, either can be used. Head to head data are not robust, but in one underpowered trial, GFR change over 5 years was not different between an ACE inhibitor or ARB. Combination therapy with RAAS drugs is not recommended as additional renal or CV protection has not been documented and potential harm from adverse reactions of hyperkalemia may be increased.[37]

Timing of dosing can also be important. In an adult group with CKD, taking at least one BP drug at bedtime improved BP control and "dipping" of blood pressure as measured by 24 hour ambulatory blood pressure monitoring. Importantly, it also decreased the composite risk of CV death, MI, and stroke (adjusted HR, 0.28; 95% CI, 0.13–0.61; P<.001). This is a simple intervention with potentially important implications to patients. (38) This advice is likely relevant to youth and young adults with T2D who are already at risk for impaired nocturnal "dipping" of both systolic and diastolic BP, early left ventricular hypertrophy, posterior and septal wall thickening and increased arterial stiffness. Autonomic neuropathy is also responsible for impaired nocturnal dipping in many type 2 diabetes subjects.

Diabetes is the commonest cause of end stage renal disease. If a young type 2 diabetic develops microalbuminuria very early in the course of disease the chances of developing overt nephropathy is high, so for all young type 2 diabetics the urine microalbuminuria test should be done annually both in urban and rural areas so that we can reduce the percentage of type 2 diabetics developing ESRD.

Microalbuminuria is usually regarded as a marker of organ damage, reflecting the degree of cardiovascular damage induced by hypertension or diabetes mellitus. Apart from the general population, microalbuminuria is also an independent risk factor for CVD, and cardiovascular and all-cause mortality in diabetics.[39,40] and hypertensive.[41] The mechanisms underlying the association between microalbuminuria and cardiovascular disease or all-cause mortality are largely unknown but are thought to reflect endothelial dysfunction and microvascular damage.[42] and possibly inflammation.[43] So young diabetics with microalbuminuria should be evaluated regularly for presence of coronary artery disease and treated accordingly.

In our study only 18.4% of the subjects have achieved HBA1c target of less than 7%. Microalbuminuria was present in 23.6% of the subjects. Systolic blood pressure, BMI, duration of diabetes and HBA1c correlate with microalbuminuria. If the glycemic and blood pressure targets are achieved the progression of microalbuminuria to overt diabetic nephropathy can be prevented. Macroalbuminuria was present in 4.6% of subjects and these diabetes subjects should be investigated to find out the non diabetic causes of macroalbuminuria. All the diabetes subjects were on treatment by their respective diabetologists.

CONCLUSIONS

Microalbuminuria was present in 23.6% of young diabetes subjects with age of onset of diabetes less than 35 years. Only 18.4% of the patients HBA1C were less than 7%. The glycemic control of young diabetics was

not good in many studies. In this study the HBA1c was more than 9% in 55.5% of the diabetes subjects. So it is essential to achieve Glycemic targets and blood pressure targets in young diabetes subjects to retard progression from microalbuminuria to macroalbminuria and in few patients we can revert to normoalbuminuria.

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Abbreviations-
T2DM-Type 2 diabetes mellitus.
TIDM-Type 1 diabetes mellitus.
MA-Microalbuminuria.
BMI-Body mass index.
ACE-Angiotensin converting enzyme.
ARB-Angiotensin receptor blocker.
GFR-Glomerular filteration rate.
BP-Blood pressure.
CV-Cardiovascular
MI-Myocardial infarction.
CKD-Chronic kidney disease.
SGLT –Sodium glucose transporter.

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