Original Article

Microalbuminuria in Newly detected Type 2 Diabetic Subjects with Familial Predisposition to Hypertension

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Abstract:
Background and aim: *The majority of the diabetes mellitus subjects belongs to type 2 diabetes. Microalbuminuria is an early marker of nephropathy in type 2 diabetes. This study in Bangladeshi type 2 diabetic patients was to evaluate whether microalbuminuria is influenced by familial predisposition to hypertension in presence or absence of hypertension.* ***Method:*** *Sixty three newly diagnosed Bangladeshi type 2 diabetic patients (age in years 45±4; BMI 24.0±3.4 kg/m^2) and twenty age and BMI matched control subjects (age 47±9, BMI 22.4±3.8) without any family history of diabetes and hypertension were investigated. The diabetic subjects were divided into two groups as diabetes with family history of hypertension (n=37) and diabetes without family history of hypertension (n=26). Diabetic subjects were further divided into normotensive (n=46) and hypertensive (n=17) subgroups. Serum glucose was measured by glucose-oxidase; blood urea, serum creatinine and urinary creatinine by enzymatic-colorimetric method and urinary albumin by immunoturbidimetry method.* ***Results:*** *Microalbuminuria was significantly elevated in diabetic subjects with familial predisposition to hypertension when compared to diabetic subjects without familial predisposition to hypertension [median (range) 2.23 (0.28-9.43) vs 1.52 (0.29-3.91) mg/mmol p<0.03]. When diabetic normotensive subjects were compared with diabetic hypertensive subjects for microalbuminuria, no significant difference was found among themselves [median (range) 1.67 (0.17-8.62) vs 1.70 (0.28-9.43) mg/mmol p=NS].* ***Conclusion:*** *Microalbuminuria, a marker of early diabetic nephropathy is more influenced by familial predisposition to hypertension in diabetic population irrespective of presence of hypertension.*

Key words: microalbuminuria, diabetes mellitus, familial predisposition to hypertension, nephropathy

Introduction:
Diabetes mellitus is a global health problem and a major cause of morbidity and mortality because of its long-term complications[1]. Diabetic nephropathy is one of those complications which has a prevalence of 7% to 21% reported in different studies conducted in Asia[2]. The prevalence of diabetic nephropathy in Bangladesh is 17.9% among those who are diabetic for >10 years[3]. Though the likelihood of developing the end stage renal disease (ESRD) is much less in type 2 (5 to 10%) compared to type 1 diabetes (40%)[4]. The actual number of type 2 diabetes developing ESRD is greater in Bangladesh since 95% of diabetic subjects in this population are of type 2 variety.

Diabetic nephropathy is the leading cause of ESRD requiring dialysis in developed countries and it is the second common cause of ESRD in Bangladesh[5,6]. Chronic dialysis treatment obviously decreases the quality of life and creates tremendous financial responsibility for the patient and society. So, much more attention should be paid to the measures which can detect renal involvement at an early stage and we can prevent, or at least retard the progression of renal insufficiency.

Microalbuminuria predicts the development of diabetic nephropathy, elevated GFR and increase blood pressure may also contribute to the progression in type 1 diabetes[7]. Also in type 2 diabetes it is predictive of clinical proteinuria and increase mortality[8]. Nevertheless, progressively increasing albuminuria, or albuminuria accompanied by hypertension, is most likely to be due to early diabetic nephropathy. So, detection of microalbuminuria is a suitable laboratory tool to be carried out routinely for the diagnosis of early diabetic nephropathy.

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Diabetic nephropathy occurs only in a subset of diabetic patients who are genetically predisposed, approximately 30 to 40 percent in type 1 diabetes and 30 percent in type 2 diabetes of more than 10 years of duration[9,10]. Why only one third of diabetic patients develop nephropathy cannot be explained solely by differences of glycemic control[11]. Familial clustering of diabetic nephropathy has been reported in type 1 diabetes[12]. A genetic influence of the development of nephropathy has similarly been described in Pima Indians with type 2 diabetes[13].

These observations suggest that genetic factors are involved in the susceptibility to develop diabetic nephropathy. Aim of this study in type 2 diabetic patients with family history of hypertension was to evaluate the possible genetic influence of familial predisposition to hypertension on microalbuminuria irrespective of presence or absence of hypertension.

Materials and Methods:

This cross sectional case-control study was carried out in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka in collaboration with Biomedical Research Group, Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and metabolic Disorders (BIRDEM) and Analytical Division, Bangladesh Council for Scientific and Industrial Research (BCSIR), Dhaka during the period of 2004-2006. Eighty-three subjects were included in this study of which 20 were healthy controls (16 men and 4 women) and 63 were newly detected untreated type 2 diabetic subjects (42 men and 21 women). Controls were selected from hospital staff, patients' friends and voluntary participants. They were free from any disease, not taking any drugs and had no family history of diabetes or hypertension. Diabetic subjects were selected from Outpatient Department of BIRDEM General Hospital. They were considered diabetic according to WHO criteria[26].

The diabetic subjects were studied by dividing them into several groups in the following way:

Based on family history of hypertension: a) Diabetes with family history of hypertension, FH (+) ve group. b) Diabetes without family history of hypertension, FH (-) ve group.

Based on presence or absence of hypertension: a) Diabetes with hypertension, hypertensive group. b) Diabetes without hypertension, normotensive group.

Based on presence or absence of microalbuminuria: a) Diabetes with microalbuminuria, microalbuminuric group. b) Diabetes without microalbuminuria, normomicroalbuminuric group.

Medical history of the patients was taken carefully. Clinical parameters (age, sex, body mass index (BMI), blood pressure and family history of hypertension) were recorded in a predesigned data sheet for the study. A positive family history of hypertension was recorded if one or both parents had been diagnosed hypertensive or were undergoing treatment for hypertension.

Specific laboratory investigations (blood glucose fasting and 2 hours post glucose load, serum urea, serum creatinine, albumin creatinine ratio (ACR) were done in each patient. Biochemical parameters were recorded in a predesigned data for the study.

Serum glucose was measured by glucose-oxidase method. Serum urea, serum creatinine, and urinary creatinine were measured by enzymatic colorimetric methods. Urinary albumin (microalbuminuria) was measured by immunoturbidimetry method.

First voided morning urine samples were collected in a clean test tube and centrifuged at a rate of 3000 rpm for 10 minutes. 1.5 ml of clear urine sample was transferred into a micro-centrifuge tube preserved at 70^0C in the freezer for analysis of urinary creatinine by alkaline picrate method and urinary albumin was estimated by immunoturbidimetry method. Another test tube containing urine was used for routine microscopic examination immediately.

Albumin creatinine ratio (ACR) was calculated from urinary creatinine and urinary albumin. Microalbuminuria (MA) was labeled in a patients when in first morning urine sample, albumin-creatinine ratio (ACR) was greater than mean±2SD (two standard deviation) ACR of Control subjects. An ACR of 2.0-2.5 mg/mmol to 20-35 mg/mmol corresponds to albumin excretion of 20-200 mg/min or 30-300 mg/day[27,28,29]. In this study control subjects' mean±2SD of urinary albumin creatinine ratio (ACR) was 2.77 mg/mmol. ACR 2.77 mg/mmol was taken as a cut-off value. Diabetic subjects with ACR <2.77 mg/mmol was designated as normoalbuminuric and subject with ACR >2.77 mg/mmol was designated as microalbuminuric.

Statistical Analysis:

All variables are expressed as mean±SD unless otherwise stated. Albumin creatinine ratio (ACR), Serum triglyceride are expressed as median (range). The comparison between the groups was made either by unpaired Student's t-test or Mann-Whitney U test as required by using SPSS windows

package 12.0 version and *p* value below 0.05 was considered significant.

Results:

Sixty three diabetic subjects was matched for age, BMI, blood pressure and renal function tests with twenty healthy controls. These two groups were studied for microalbuminuria. Table I shows the comparison between healthy controls and diabetic subjects. The incidence of microalbuminuria is significantly higher in diabetic subjects than controls [median (range), 1.03 (0.00-3.09) vs 1.80 (0.28-9.43) mg/mmol, $p<0.001$].

Fourty six diabetic normotensive subjects were match for age, BMI, glycaemic status and renal function tests with seventeen diabetic hypertensive subjects and were studied for microalbuminuria. Comparison of microalbuminuria was found no significant difference in diabetic normotensive and diabetic hypertensive subjects [median (range) 1.67 (0.17-8.62) vs 1.70 (.28-9.43) mg/mmol p = NS] (Table II).

Out of 63 diabetic subjects studied, 19 (30%) were microalbuminuric and 44 (70%) subjects were normoalbuminuric. Fourty four diabetic normoalbuminuric subjects were match with nineteen diabetic microalbuminuric subjects. Comparison of blood pressure was found no significant difference between diabetic normoalbuminuric and diabetic microalbuminuric subjects [systolic blood pressure (117±17 vs 125±17) mmHg p= NS; diastolic blood pressure (76±11 vs 82±10) mmHg p= NS] (Table III).

Thirty seven diabetic subjects with family history of hypertension FH (+) ve group were matched with twenty six diabetic subjects without family history of hypertension FH (-) ve group and were studied for systolic blood pressure, diastolic blood pressure and microalbuminuria. Table IV shows the systolic blood pressure, diastolic blood pressure and microalbuminuria were significantly higher in FH (+) ve group than FH (-) ve group. (Table IV)

Table I: Comparison in healthy controls and diabetic subjects.

Base line characteristics	**Control (n=20) (mean±SD)**	**DM (n=63) (mean±SD)**	**p-value**
Age (Years)	47±9	45±4	NS
BMI (Kg/m^2)	22.4±3.8	24±3.4	NS
Systolic BP (mmHg)	113±13	120±17	NS
Diastolic BP (mmHg)	74±8	78±11	NS
FPG (mmol/L)	5.2±.97	12.1±5.0	0.001
2h PG (mmol/L)	6.5±1.3	21.1±6.0	0.001
Blood urea (mg/dl)	26±7	27±7	NS
S creatinine (mg/dl)	1.1±.18	1.2±0.20	NS
ACR (mg/mmol)	1.03 (0.00-3.09)	1.80 (.28-9.43)	0.001

NS= Not significant.

Table II: Comparison in diabetic normotensive and diabetic hypertensive subjects.

Features	**Diabetic Normotensive (n=46) (mean±SD)**	**Diabetic Hypertensive (n=17) (mean±SD)**	**p-value**
Age (Years)	45±4	45±4	NS
BMI (Kg/m^2)	23.7±3.5	26±3.6	NS
FPG (mmol/L)	12.2±5.7	9.9±2.7	NS
2h PG (mmol/L)	20.2±7.7	19.8±4.4	NS
Blood urea (mg/dl)	27±7	29±8	NS
Serum creatinine (mg/dl)	1.25±0.16	1.0±0.36	NS
ACR (mg/mmol)	1.67 (0.17-8.62)	1.70 (.28-9.43)	NS

NS= Not significant.

Table III: Comparison between diabetic normoalbuminuric and diabetic microalbuminuric subjects.

Features	Diabetic normoalbuminuric (mean±SD)	Diabetic microalbuminuric (mean±SD)	p-value
Age (Years)	45±4	46±4	NS
BMI (Kg/m^2)	24.5±3.6	24.5±2.9	NS
Systolic BP (mmHg)	117±17	125±17	NS
Diastolic BP (mmHg)	76±11	82±10	NS
FPG (mmol/L)	11.4±3.9	13.6±7.0	NS
2h PG (mmol/L)	20.3±5.2	23.0±7.5	NS
Blood urea (mg/dl)	27±7	27±8	NS
S creatinine (mg/dl)	1.25±0.26	1.23±0.14	NS

NS= Not significant.

Table IV: Comparison in diabetic subjects with family history of hypertension FH (+) ve group and diabetic subjects without family history of hypertension FH (-) ve group.

Features	FH (+) ve (n=37) (mean±SD)	FH (-) ve (n=26) (mean±SD)	p-value
Age (Years)	45±4	45±4	NS
BMI (Kg/m^2)	24.8±3.2	24.1±3.7	NS
Systolic BP (mmHg)	127±16	110±14	0.001
Diastolic BP (mmHg)	81±9	72±11	0.001
FPG (mmol/L)	11.3±4.2	13.1±5.9	NS
2h PG (mmol/L)	20.7±5.7	21.1±6.5	NS
Blood urea (mg/dl)	27±7	27±8	NS
S creatinine (mg/dl)	1.20±0.20	1.20±0.19	NS
ACR (mg/mmol)	2.23(0.28-9.43)	1.52(.29-3.91)	0.03

NS= Not significant.

Discussion:

In this study population, the prevalence of microalbuminuria is 30%. This finding is consistent with other studies in the Bangladeshi population. The incidence of microalbuminuria was 37% in a study with newly detected, untreated type 2 diabetic subjects by Iqbal in 2000 [14]. Three previous studies on young onset (under 30 years) type 2 diabetic subjects of Bangladeshi population also showed similar results[15,16,17]. When diabetic microalbuminuric subjects were matched for age, BMI, blood glucose, and renal function tests with diabetic normoalbuminuric subjects and studied for blood pressure. No significant difference in blood pressure was found between diabetic normoalbuminuric and diabetic microalbuminuric subjects. Hada and Iqbal also found similar results in type 2 diabetic subjects in the similar population[17,14]. Contrary to this, increased blood pressure has been reported in type 1 diabetic patients with microalbuminuria[18,19]. But there is some controversy as to whether the elevated arterial pressure precedes the development of microalbuminuria in type 1 diabetes or it occurs after its development[20]. Microalbuminuria is related with blood pressure and known duration of diabetes[21]. Systolic blood pressure has been found to be a determinant of microalbuminuria in type 2 diabetes[21]. Nevertheless, from the earliest phase of microalbuminuria, blood pressure tends to increase by an average of 3 to 4 mmHg per year compared with 1 mmHg per year in long term normoalbuminuria in type 1 diabetic patients and healthy controls[22]. But, the absolute level of blood pressure in patients with microalbuminuria often within the conventional normotension[23].

To see the relation of microalbuminuria with hypertension, the diabetic subjects were studied after dividing them into hypertensive and normotensive groups. Who were matched for age, BMI, blood glucose and renal function tests. Diabetic normotensive subjects showed similar albumin creatinine ratio with hypertensive group. So, in the absence of family history of hypertension, microalbuminuria was similar in diabetic subjects with or without hypertension. This result was similar with the other study in the Bangladeshi population[14].

To observe the possible genetic influence of family history of hypertension on the albumin creatinine ratio (ACR) or microalbuminuria, diabetic subjects with family history of hypertension (FH +ve group) was matched for age, BMI, glycaemic status and renal function tests with diabetic subjects without family history of hypertension (FH -ve group) and were studied for systolic blood pressure, diastolic blood pressure and microalbuminuria. The systolic blood pressure, diastolic blood pressure and

microalbuminuria were significantly higher in FH (+) ve group than FH (-) ve group. This result is supported by many of the literatures that the familial predisposition to increased arterial pressure contributing to the susceptibility to diabetic nephropathy[24,11]. The association of microalbuminuria with family history of hypertension raise the possibility that the genetics of essential hypertension and diabetic nephropathy may partially overlap. Thus any candidate gene proposed for essential hypertension can also be considered as a susceptibility gene for diabetic nephropathy[25]. In the present study, it is found that increased ACR in type 2 diabetic subjects with familial predisposition to hypertension have significantly higher systolic and diastolic blood pressure in comparison with diabetic patients without family history of hypertension.

Limitations:

This study had some limitations. It was a single center study, sample size was small and the observation was only on the newly diagnosed patients. A larger multi-center study including large number of patients is necessary to justify the results.

Conclusion:

Therefore familial predisposition to hypertension can identify a subgroup of type 2 diabetic subjects who are prone to develop microalbuminuria and increased arterial pressure in diabetic population irrespective of presence or absence of hypertension.

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