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Original Article

Cardiovascular Risk Profile and Prevalence of Microalbuminuria in Patients With Type 2 Diabetes Mellitus: The Campaign Disease Registry Results

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Abstract

Background: **To assess the cardiovascular risk profile of patients with type 2 diabetes mellitus (T2DM), the prevalence of microalbuminuria, and the prescription pattern in management of overall cardiovascular/renal risk in out patient practice.**

Methods: **In this cross sectional study consecutive adult patients with T2DM signed the informed consent and were interviewed by the investigator to establish the cardiovascular risk profile. Presence of microalbuminuria (20–200mg/l) was diagnosed using Micral-Test® strips. Analysis was done by descriptive statistics, and multivariate logistic regression was performed to identify the independent risk-factors for the development of microalbuminuria.**

Results: **Of the 1763 patients enrolled, data was analyzed on 1596 patients. Major cardiovascular risk-factors included hypertension (55.4%), sedentary lifestyle (49.8%), and metabolic syndrome (30.5%). Microalbuminuria was prevalent in 55.6% (95% CI 53.1-58.0) patients. On multivariate analysis, significant association was observed with total cholesterol (p = 0.029, OR: 2.26, 95% CI: 1.09 – 4.71) and diastolic BP (p = 0.015, OR: 2.67, 95% CI: 1.21 – 5.91). The most commonly prescribed antihypertensive drugs were angiotensin-converting enzyme inhibitors (41.7%), calcium channel blockers (13.2%) and beta blockers (10%), while most commonly prescribed antidiabetic drugs were sulfonylureas (61.9%), biguanides (56.1%) and thiazolidinediones (17.4%).**

Conclusions: **Patients with T2DM are at increased cardiovascular risk specifically with uncontrolled diastolic blood pressure and high total cholesterol levels. There is also a high prevalence of microalbuminuria in patient with T2DM.**

Key Words: **Type 2 diabetes mellitus, Cardiovascular risk, Microalbuminuria.**

Introduction

Diabetes mellitus (DM) is the commonest endocrine disorder .[1,2] Patients with type 2 diabetes mellitus (T2DM) often experience a long asymptomatic period of hyperglycemia leading to numerous complications at the time of diagnosis.[3] Diabetic nephropathy (DN), a common consequence of long-standing T2DM, has become the most common cause of end-stage renal disease.[4,5] About one third of patients with T2DM develop progressive deterioration of renal function.[6,7]Microalbuminuria (MAU) is defined as "a urinary albumin excretion rate of 30 to 300 mg in 24 hour urine collection or of 20 to 200 mg/min in a timed overnight urine collection" and is most often the primary manifestation of nephropathy in patients with DM.[8-13] MAU significantly impacts the risk of related vascular events like cardiac abnormalities, cerebrovascular disease, and, possibly, peripheral arterial disease (PAD). [14-18,20,21] The implicit associations between the troika of MAU, CV disease and progressive renal impairment are being unraveled.The hypothesis that "the kidney is a window of the vasculature" suggests that albumin leakage into the urine is a manifestation of widespread vascular damage, it is unclear whether MAU is a cause or a consequence of vascular disease. In light of these observations, endothelial function and chronic inflammation have been advanced as factors underlying the association.[22, 23]

The risk factors associated with MAU are poor glycemic control, insulin resistance , uncontrolled hypertension, smoking and central obesity.[13,24] In patients with T2DM, the risk of MAU is impacted by factors including age, gender, body mass index (BMI), duration of diabetes, and dyslipidemia [24]. Apart from old age and weight gain, hypertension and diabetes are reported as the two important physiological risk factors for MAU.[25] Arterial hypertension is known to significantly increase the risk of cardio-renal disease when present along with T2DM.[26] Conversely, a higher rate of prevalence of

hypertension is seen in patients with T2DM and elevated urinary albumin excretion.[27] CV damage like left ventricular hypertrophy, carotid artery thickening, and other end-organ damage are common presentations in hypertensive patients with MAU.[28-30]

In addition to the periodic measurement of albuminuria in all patients with T2DM and hypertension, preventive steps against albuminuria to prevent future renal and CV adverse events are warranted.[9,31,32] Treatment targeting urinary albumin levels demonstrably reduce the risk for CV events as well as kidney disease progression.[31,14] MAU can be reversed and the future development of overt DN, and consequently, CV risk can be significantly reduced.[15,33-36]

There is a lack of standardized nationwide data from Pakistan to define the prevalence of MAU and understand its association with adverse CV risk factors in patients with T2DM. In view of this, the CArdiovascular Risk Profile and Microalbuminuria Prevalence in Type 2 DiAbetes Mellitus Patients In the Out Patient SettinG In PakistaN (CAMPAIGN) study was conducted.

Patients and Methods

Present study was a national, multicenter, observational, cross-sectional, and epidemiological study conducted between April 2009 and July 2009. This study aimed to recruit 1800 patients from 100 centers across 13 cities of Pakistan. The study was conducted in the ambulatory care setting, at individual outpatient clinics. Exclusion criteria included presence of type 1 diabetes, no diabetes, presence of primary renal pathology, concomitant urinary tract infection (diagnosed either on patient's history or available investigations or both), menstruation, pregnancy and refusal of consent. Of the 100 investigators who participated in the study, 70 were Physicians and 30 were specialists such as medical internists, diabetologists, and cardiologists.

This study entailed a single visit. The patients were recruited within a period of one month from the date of 'First Patient In' in the given center. Patients had to undergo a Micral-Test® (by Roche Diagnostics) on the day of the consultation at the investigator's clinic. The test was performed using test strips for the immunological, semi-quantitative *in vitro* determination of urinary albumin from morning urine sample. A value of 20-200 mg/l of albumin was judged as pathological. Our objective was to identify the proportion of T2DM suffering from Microalbuminuria (Micral test strips) in outpatient practice and not Clinical (Macroalbuminuria (> 200 mg/l)). Patients with > 200 mg/l were not specifically identified on 24 hours urinary/albumin test as the patient was diagnosed on Micral test.

Information on lipid profile including total cholesterol, high density lipoprotein (HDL), low density lipoprotein, very low density lipoprotein, triglycerides and other investigations such as serum creatinine, fasting blood glucose, random blood glucose, and abnormal glucose metabolism (HbA1c) was recorded

Pakistan has a diabetic population of 5.2 million.[37] In the DAP-WHO study , non-insulin dependent diabetes was reported as 98.0%. [38] This makes the population with non-insulin dependent diabetes mellitus equivalent to 5,096,000 patients with T2DM. As there were no local statistics available on CV risk profile (primary objective of this study), the best estimate was assumed to be 50.0%. Estimates show the prevalence of MAU as 34.0% in a study conducted in Karachi, Pakistan [39]. In order to capture the lower estimated prevalence between MAU and CV risk profile, 34% was plugged in as the expected frequency of MAU in the universal population of patients with T2DM with an assumption of a worst acceptable prevalence of 37%. Aiming for 99% confidence level and 3% precision, a sample size of 1,654 was required. Accounting for incomplete forms, ineligible patients etc., a sample size of 1800 patients was proposed. Estimations were done at country level.

Analysis population included only those who met inclusion and exclusion criteria and on whom all responses were documented and Micral-Test® was performed. CV risk variables were assessed as categorical and continuous variables depending on variable type. Continuous variables were reported as means with standard deviations. No comparisons were envisaged as this was a descriptive exploratory study. Bivariate analysis was performed to identify the associations between MAU and CV risk factors. Factors that showed a significant association with MAU in bivariate analysis were entered into a logistic regression to identify the independent risk factors for the development of MAU. In both the analyses, a p value <0.05 was considered significant.

Results

Of 1763 patients enrolled , 1596 (90.5%) patients were evaluable in this study. Remaining patients (167) were excluded because they did not meet the inclusion criteria. The mean age of the patients was 52.7 (±10.4) years and 83.5% of patients were between 4th to 6th decades of life. An equal gender distribution was observed among patients (49.9% men vs. 51.1% women). The mean duration of T2DM was 6.8 (±5.5)

years with a mean age at diagnosis of 43.8 (±12.6) years. About 65% of the patients had a BMI ≥25 kg/m2. Mean waist circumference was 99.4 (±13.2) cm. Mean height and mean weight was 161.6 (±10.9) cm and 73.7 (±13.6) kg respectively. Uncontrolled hypertension was observed in 58.0% of patients at the time of visit(Table 1). Patients with a known case of hypertension were 55.4% (884/1596) in which 19.1% (169/884) had a controlled BP. Patients with a history of antihypertensive intake was 50.3% (802/ 1596) in which 20.7% (166/802) had a controlled BP.

Micral-Test was performed on a random urine sample in 81% patients and on an early morning sample in 17% patients. More than half of the patients (55.6%; 95% CI: 54.2% - 59.1%) with T2DM in outpatient practice were detected to have urinary albumin excretion of 20-200 mg/L on the test. Only 10.7% had a similar test done prior to this study.

The major CV risk factors based on patients' history included hypertension in 55.4% patients, sedentary lifestyle in 49.8% patients and metabolic syndrome in 30.5% patients. Bivariate analysis was performed to study the correlation between CV risk factors and MAU . Compared to proportion of patients with negative Micral-Test results the analysis indicated a significant association between positive MAU and systolic BP ≥130 mm Hg (p <0.01), diastolic BP ≥85 mm Hg (p <0.01), fasting blood glucose >140 mg/dL (p = 0.008), total cholesterol ≥200 mg/dL (p = 0.003), triglycerides ≥200 mg/dL (p = 0.02), HbA1c >7 (p = 0.004), sedentary lifestyle (p = 0.02), family history of premature CV disease in first degree relative before 50 years of age (p = 0.002), hypertension (p <0.01), diabetic nephropathy (p <0.01), congestive heart failure (p <0.01), metabolic syndrome (p <0.01), CAD (p <0.01), PAD (p <0.01) and mean duration of diabetes (p <0.01). Out of 1596 patients enrolled in the study, HbA1c was available for 553 patients. Of the 553 patients, 412 patients had HbA1c > 7%. i.e 26% of all patients had an elevated HbA1c. Of the 412 patients, 253 (61.4%) MAU positive patients had an HbA1c >7 (Table 2). Significant association was observed with total cholesterol (p = 0.029, OR: 2.26, 95% CI: 1.09 – 4.71) and diastolic BP (p = 0.015, OR: 2.67, 95% CI: 1.21 – 5.91). Patients with MAU were 2.26 times more likely to have high total cholesterol levels and 2.67 times more likely to have high diastolic BP. High cholesterol and DBP does contribute to the model with higher average for the MAU positive after controlling other factors constant.

Table 1.Demographic and clinical characteristics of patients (n = 1596)

Parameters	**Values***
Mean age (years)	52.7 ± 10.4
Mean Age at diagnosis (years)	43.8 ± 12.6
Mean Duration of diabetes (years)	6.8 ± 5.5
Mean Weight (kg)	73.7 ± 13.6
Mean Height (cm)	161.6 ± 10.9
Proportion of Males	49.9
Mean BMI	28.3 ± 5.6
Proportion overweight (25 – 29.9 kg/m2)	36.0
Proportion Obese (≥ 30.0 kg/m2)	29.0
Mean Waist circumference (cm)	99.4 ± 13.2
Proportion (%) of males with WC ≥ 90 cm	34.9
Female ≥ 80 cm	39.6
Mean systolic blood pressure (mm Hg)	135.6 ± 19.8
Mean diastolic blood pressure(mm Hg)	85.9 ± 11.1
SBP ≥ 130 mm Hg / DBP ≥ 80(mm Hg)	925 (58.0)
HbA1c (%)	8.5 ± 4.3

*All values are mean ± SD except values expressed for gender, overweight, obesity, waist circumference for male and female, and SBP ≥ 130 / DBP ≥ 80, which are in n (%) ;BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin.

The most common antihypertensive drug classes prescribed to the patients with T2DM were angiotensin-converting enzyme (ACE) inhibitors (41.7%).Similarly, the most common oral antidiabetic drug pioglitazone (16.6%) being the most prescribed drugs in each category, respectively (Table 3).

Table 2. Bivariate analysis of risk factors and microalbuminuria (n = 1596)

Risk Factors	+MAU, n (%)	-MAU, n (%)	p-value
BP systolic mmHg			
<130	214 (41.1)	307 (58.9)	<0.01
≥ 130	632 (64.6)	346 (35.4)	
BP diastolic mmHg			
< 85	335 (47.1)	376 (52.9)	<0.01
≥ 85	511 (64.8)	277 (35.2)	
FBG mg/dL			
≤ 140	260 (53.8)	223 (46.2)	.008
>140	243 (62.8)	144 (37.2)	
Total Cholesterol mg/dL			
< 200	178 (51.1)	170 (48.9)	.003
≥ 200	137 (64.0)	77 (36.0)	
Triglycerides mg/dL			
< 200	134 (51.1)	128 (48.9)	0.02
≥ 200	106 (62.7)	63 (37.3)	
HbA1c (%)			
≤ 7	67 (47.5)	74 (52.5)	0.004
>7	253 (61.4)	159 (38.6)	
Gender			
Male	437 (54.8)	360 (45.2)	0.14
Female	462 (58.5)	328 (41.5)	
Sedentary lifestyle			
Yes	479 (60.3)	316 (39.7)	0.02
No	316 (53.1)	279 (46.9)	
Unknown	53 (54.1)	45 (45.9)	
Family history of premature CVD in 1st degree relative < 50 years of age			
Yes	233 (62.3)	141 (37.7)	0.002
No	462 (53.5)	402 (46.5)	
Unknown	125 (64.1)	70 (35.9)	
Hypertension			
Yes	578 (65.4)	306 (34.6)	<0.01
No	259 (43.7)	334 (56.3)	
Unknown	24 (68.6)	11 (31.4)	
Diabetic Nephropathy			
Yes	286 (80.8)	68 (19.2)	<0.01
No	476 (47.1)	534 (52.9)	
Unknown	89 (68.5)	41 (31.5)	
Congestive Heart Failure			
Yes	76 (69.7)	33 (30.3)	<0.01
No	705 (55.0)	577 (45.0)	
Unknown	65 (67.7)	31 (32.3)	
Metabolic Syndrome			
Yes	304 (62.4)	183 (37.6)	<0.01
No	477 (53.8)	409 (46.2)	
Unknown	59 (62.8)	35 (37.2)	
Coronary Artery Disease			
Yes	115 (65.7)	60 (34.3)	<0.01
No	646 (54.4)	541 (45.6)	
Unknown	94 (67.6)	45 (32.4)	
Peripheral Artery Disease			
Yes	102 (69.9)	44 (30.1)	<0.01
No	664 (54.4)	557 (45.6)	
Unknown	83 (65.9)	43 (34.1)	
History of Stroke			
Yes	28 (56.0)	22 (44.0)	0.53
No	786 (56.7)	600 (43.3)	
Unknown	39 (63.9)	22 (36.1)	
History of MI			
Yes	44 (61.1)	28 (38.9)	0.08
No	760 (56.2)	593(43.8)	
Unknown	47 (69.1)	21 (30.9)	
Duration of diabetes (years)			
<1 yrs	48 (46.2)	56 (39.9)	<0.01
1-5 yrs	352 (50.3)	348 (49.7)	
6-8 yrs	165 (63.7)	94 (36.3)	
9-11 yrs	159 (65.7)	83 (34.3)	
>11	157 (61.1)	100 (38.9)	

MAU, microalbuminuria; BP, blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; CVD, cardiovascular disease; MI, myocardial infarction

Table 3.Distribution of patients based on prescription pattern (n = 1596)

Prescribed drugs	n (%)
Class of antihypertensive drugs	
ACE inhibitors	666 (41.7)
Calcium channel blockers	211 (13.2)
Beta blockers	162 (10.2)
Angiotensin receptor blockers	145 (9.1)
Diuretics	120 (7.5)
Nitrates	26 (1.6)
Others	113 (7.1)
Class of antidiabetic drugs	
Sulfonylureas	988 (61.9)
Biguanides	896 (56.1)
Thiazolidinediones	278 (17.4)
Insulin	167 (10.5)
Alpha glucosidase inhibitors	47 (2.9)

ACE, angiotensin-converting enzyme

Monotherapy was given to 36.6% and 39.3% of patients using antidiabetic and antihypertensive drugs, respectively; while remaining proportion of patients from both the classes were given treatment using combination of 2 drugs in 56.1% and 13.7%, 3 drugs in 8.6% and 3.6% and 4 drugs in 0.9% and 1.1%, respectively.

Discussion

In this large prospective epidemiological study a high burden was found , of MAU ,in patients with T2DM in outpatient setting in Pakistan. Major CV risk factors observed among the patients were hypertension,

sedentary lifestyle and metabolic syndrome. More than half of the patients (55.6%) with T2DM in outpatient practice were detected to have urinary albumin excretion of 20-200mg/L on the Micral test. A value of 20-200 mg/L of albumin was judged as pathological. The well-established risk factors that showed high significance included fasting blood glucose, total cholesterol, poor glycemic control, family history, hypertension, metabolic syndrome, microvascular complications and duration of diabetes. The study also offers interesting hypothesis about the possible independent role of diastolic BP and total cholesterol levels as independent correlates of MAU. The prevalence of MAU in the study population was 55.6% (95% CI 53.1 – 58.0). It could also reflect a rapid rise in cases where kidneys are impacted because of uncontrolled and poor glycemic control. [40-42]

The association of MAU with hypertension has long been established and is known to be accompanied by left ventricular diastolic dysfunction and left ventricular hypertrophy.[43-45] MAU was found to be significantly associated with hypertension in the current study, in accordance with previous findings.[46] Similar findings were observed in previous studies that reported systolic BP and diastolic BP to be associated with MAU.[43-48] Multivariate logistic regression also reported diastolic BP to be significantly associated with MAU in the current study.

A higher incidence of silent myocardial infarction has been reported in T2DM patients with MAU compared to normoalbuminuria. [49] While the trends of association between specific CV events and MAU vary between these studies, they are in agreement about the overall relationship between CV risks with MAU. High triglyceride levels, a significant CV risk factor, could initiate endothelial damage and eventually induce renal disease in patients with T2DM. [50] High triglyceride levels were significantly associated with presence of MAU which confirms data from a study in Pakistan where 93.7% patients with MAU had triglyceride>150 mg/dL. [11] According to World Health Organization and other studies , MAU is one of the most important components of metabolic syndrome. [51,52]

A significant correlation was observed between increased HbA1c and MAU in our study population corroborating results from other studies [40,53]. Euglycaemia exerts a stronger influence on MAU than macroalbuminuria, implying that early glycaemic control must be considered to avoid the onset of nephropathy rather than initiating diabetes management post-onset.[54]

In the current study effects of life style on CV risk in T2DM patients with MAU was assessed. So far, only few studies indicate smoking as a risk factor for albuminuria among patients with T2DM.[55] A statistically non-significant difference was seen in the smoking status of patients in MAU positive and negative groups, though more patients in the MAU positive group were past or current smokers.

In present study, ACE inhibitors were the most commonly prescribed antihypertensive drugs, followed by calcium channel blockers, beta blockers, angiotensin-receptor blockers (ARBs), and diuretics. Recent guidelines advocate the use of ACE inhibitors as the first choice for diabetic hypertension and ARB+ACE inhibitors for DN.[56-58] Addition of beta blockers to ACE inhibitors improves endothelial function and reduces urinary albumin excretion in T2DM patients with MAU.[59] In patients with congestive heart failure, ARBs are recommended as a first-line drug by American Diabetes Association for their superiority over calcium channel blockers in reducing heart failure.[60,61] The prophylactic use of beta blockers is recommended for high risk patients, in view of its post-myocardial infarction protective effect on CV mortality. ACE inhibitor or ARBs result in significant CV and/or renal morbidity reductions in patients with albuminuria, with or without good glycaemic control.[62] The prescription pattern of antihypertensive drugs in the present study was found to be consistent with the evidence-based guidelines.

In this study, sulphonylureas were most commonly prescribed antidiabetic drugs followed by biguanides and thiazolidinediones. A similar pattern of prescription was observed in studies from Asia.[63,64] The prescription pattern of different classes of drugs in patients with T2DM in Pakistan was found to be rational and, to a great extent, compliant with evidence-based guidelines.

Conclusion

1. Prevalence of MAU in Pakistani patients with T2DM is high. These patients are also at an increased CV risk, specifically with uncontrolled diastolic BP and high total cholesterol levels.
2. Early screening strategies for DN, with better glycemic, hypertension and cholesterol control will aid in averting/reducing adverse cardiovascular consequences in these patients.

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