ORIGINAL ARTICLE

Frequency of Retinopathy in Type II Diabetic Patients with or Without Microalbuminuria

SAJID NISAR, FAZL-E-MATEEN, FAISAL MASUD

ABSTRACT

Background: Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus is associated with microvascular (i.e. retinal, renal, possibly neuropathic) and macrovascular (i.e. coronary, peripheral vascular). Diabetic retinopathy is the most dreadful complication of all and is the leading cause of blindness worldwide. Diabetic Nephropathy is heralded by the presence of microalbuminuria. Its relation with retinopathy in type I diabetics is well established, however, in type 2 diabetes it's still not clear. This study was designed to determine the frequency of retinopathy in patients with and without microalbuminuria.
Objectives: To determine the frequency of micoalbuminuria in type 2 diabetes mellitus and frequency of diabetic retinopathy among type 2 diabetics, with and without microalbuminuria
Setting: Diabetes Management Centre, Services Hospital, Lahore
Study Design: Cross-sectional survey
Study Duration: 6 months from 3rd Jan 09 to 2nd July 09
Methods: 300 type 2 diabetics were selected from Diabetes Management Centre. Their spot urine microalbuminuria was done and the patients were divided into two groups depending upon the presence or absence of microalbuminuria. Patients with macroalbuminuria and hypertension had already been excluded from the study. Retinoscopy of all patients was done and the frequency of microalbuminuria and retinopathy was determined.
Results: The age range was 35-70 years. 43% were male and 57% were female. Out of 300 diabetics 86 were found to have microalbuminuria i.e., 28.7%. Frequency of retinopathy was higher in patients with microalbuminuria (45.4%) whereas in patients without microalbuminuria it was 24.3%.
Conclusion: Frequency of retinopathy increases with the presence of microalbuminuria. In this study the statistical significant correlation was not determined. If this correlation is established in further studies then microalbuminuria can be used as a predictor of diabetic retinopathy.
Key words: Diabetes mellitus, Microalbuminuria, Diabetic nephropathy, Diabetic retinopathy.

INTRODUCTION

Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or combination of insulin resistance and inadequate secretion to compensate.[1] Diabetes is a leading cause of morbidity & mortality worldwide, and is sixth leading cause of death in United States accounting for more than 71,000 deaths a year[2].

The vast majority of diabetic patients are classified into one of two broad categories: type 1 in which there is an absolute deficiency of insulin, and type 2 diabetes, which is characterized by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion. In addition to the main two types it can also develop during pregnancy and secondary to pancreatic disorders, endocrinopathies and drugs etc.[3] Long standing hyperglycemia promotes the reaction of glucose with components of the arterial wall to form advanced glycation end products.

These products cross-link with collagen, thereby increasing arterial stiffness which in the presence of increased levels of low-density lipoprotein (LDL) and cholesterol promotes atherogenesis. In this way high blood glucose levels lead to endothelial damage - manifesting as microvascular or macrovascular damage[4].

The diabetic patient is susceptible to series of complications that cause morbidity and premature mortality[5]. Diabetic complications impose a heavy burden on health services because poor glycaemic control in patients with diabetes also has been correlated directly with increased overall health care costs.[6,7] Micro vascular disease also has a noticeable impact on the life of type 2 diabetic patients[8].

Diabetic retinopathy is the most severe of the several ocular complications of diabetes. The

Department of Medicine, SIMS/Services Hospital, Lahore
Correspondence to Dr. Sajid Nisar, Associate Professor

prevalence of diabetic retinopathy varied from 21% to 60% in persons with diabetes for less than five years and 15 or more years, respectively. Proliferative retinopathy varied from 1.2% to 67% in persons with diabetes for less than ten years and 35 or more years, respectively. The prevalence of blindness among DM patients was 16%.[9] After ten years of diabetes, severity of retinopathy is related to longer duration, high levels of glycosylated hemoglobin, presence of proteinuria. higher diastolic BP, and male sex.

Nephropathy associated with type 2 diabetes is the most frequent cause of end-stage renal disease worldwide. In the United States, the incidence of diabetic nephropathy has increased by 150 percent in the past 10 years[10].

The first clinical sign of renal dysfunction in patients with diabetes is generally microalbuminuria,[11] which develops in 2 to 5 percent of patients per year.[12,13] In type 2 diabetes, microalbuminuria is seldom reversible[14] but, instead, progresses to overt proteinuria in 20 to 40 percent of patients.[10] In 10 to 50 percent of patients with proteinuria, chronic kidney disease develops that ultimately requires dialysis or transplantation.[15,16] Forty to 50 percent of patients with type 2 diabetes who have microalbuminuria eventually die of cardiovascular disease[17,18]; this is three times as high a rate of death from cardiac causes as among patients who have diabetes but have no evidence of renal disease[13].

In patients with diabetes and renal disease, lowering blood pressure and the levels of urinary albumin is effective in reducing the risk of end-stage renal disease as well as that of myocardial infarction, heart failure, and stroke. Angiotensin-converting–enzyme (ACE) inhibitors or angiotensin II antagonists appear to be the most effective antihypertensive agents. Non-dihydropyridine calcium-channel blockers also lower levels of urinary albumin and the progression of renal disease and the combination of non-dihydropyridine calcium-channel blockers and ACE-inhibitor therapy is even more effective[10.]

Many studies have shown microalbuminuria is associated with the presence of retinopathy in persons with diabetes and with the presence of proliferative disease in younger-onset individuals. Individuals with microalbuminuria were more likely to have retinopathy than those without microalbuminuria. These data suggest that microalbuminuria may be a marker for the risk of proliferative retinopathy[19,20].

MATERIAL AND METHODS

This Cross-sectional study was completed in Diabetes Management centre, Services Hospital Lahore completed in six months after approval of synopsis. The calculated sample size was 300 cases, with 5% margin of error, 95% confidence level taking expected percentage of microalbuminuria in type 2 DM i.e., 25.9% (least frequency among the variables). All male and female patients between 25 to 70 years of age with type 2 diabetes mellitus diagnosed for more than 10 years and whose fasting blood sugar level is $\geq$126 mg/dl or random blood sugar level is $\geq$200 mg/dl at the time of diagnosis were included in the study. Patients who have had laser therapy of retina, taking ACE inhibitors, with blood pressure >140/90 determined clinically by manometer, with positive protein on dipstick (macroalbuminuria), with BUN > 20 mg/dl and creatinine > 1.20 mg/dl on labs and with RBC cast, WBC cast and tubular cast on urine microscopy were excluded from the study.

Data collection: Patients fulfilling inclusion criteria were selected from Diabetes Management Centre of Services Hospital, Lahore after taking informed consent. All their information was collected through a specially designed proforma. The proforma included demographic information like name, age and sex. Their spot urine microalbuminuria was checked (cut off value <28 mg/l). The patients were then divided into two groups depending upon presence or absence of microalbuminuria. Then their retinoscopy was done by retinal camera for any evidence of diabetic retinopathy (microaneurysm, dot and blot hemorrhages, hard exudates, soft exudates, venous looping and beading, new vessel formation and maculopathy). Effect modifiers like age, poor glycemic control in terms of HbA1c and treatment taken were controlled through stratification.

RESULTS

A total of 300 patients with type 2 diabetes mellitus diagnosed for more than 10 years were selected from the Diabetes Management Centre of Services Hospital Lahore.

Table 1 shows that amongst the 300 patients, 43% were male and 57% were females. Overall percentage of females was more than that of males.

Table 2 is showing age distribution of patients. According to it majority of diabetic patients were between age group 45-64 (68.7%). There were few patients at the extremes of age groups shown, with the minimum age of 35 and maximum age of 70. Mean age was 52.18 ± SD of 8.993.

Table 3 shows frequency of microalbuminuria among type 2 diabetics. Out of 300 patients 86 (28.7 %) patients were found to have microalbuminuria and 214 (71.3%) patients did not have microalbuminuria.

Table 4 shows frequency of retinopathy among type 2 diabetics. Out of 300 patients 91 (30.3 %) patients were found to have retinopathy and 209 (69.7%) patients did not have retinopathy.

Table 5 shows cross tabulation of microalbuminuria and retinopathy in a 2 x 2 table. It shows that out of 86 patients who had microalbuminuria 39 (45.4%) patients also had retinopathy, however, remaining 47 (54.6%) patients did not have retinopathy. Among the 214 patients who had no microalbuminuria, the frequency of retinopathy was 52 (24.3%). 162 (75.7%) patients had no retinopathy and microalbuminuria. It clearly shows that patients with microalbuminuria have more frequency of retinopathy (45.3%) as compared to the patients without microalbuminuria (24.3%).

Table 1: Gender of patient

Gender	Frequency	%age
Male	129`43.0	
Female	171	57.0

Table 2: Frequency and percentages of age groups

Age in years	Frequency	%age
35-44	61	20.3
45-55	119	39.7
56-64	87	29.0
65-70	33	11.0

Table 3: Frequency of microalbuminuria

Microalbuminuria	Frequency	%age
Yes	86	28.7
No	214	71.3

Table 4: Frequency of retinopathy

Retinopathy	Frequency	%age
Yes	91	30.3
No	209	69.7

Table 5: Frequency of 'Retinopathy' in patients with and without 'Microalbuminuria'

Microalbuminuria	Percentage retinopathy		Total
	Yes	No	
Yes	39(45.4 %)	47(54.6%)	86(100%)
No	52(24.3 %)	162(75.7 %)	214(100%)
Total	91	209	300

DISCUSSION

The incidence of diabetes mellitus is fast increasing in our part of the world.[21] Being a chronic disorder, much of its morbidity and mortality is related to the presence of associated long term complications[22]. According to the World Health Organization, diabetes affects more than 170 million people worldwide, and this number will rise to 370 million by 2030. About one third of those affected will eventually have progressive deterioration of renal function. The first clinical sign of renal dysfunction in patients with diabetes is generally microalbuminuria, which develops in 2 to 5 percent of patients per year. In type 2 diabetes**,** unlike type 1 diabetes, microalbuminuria is seldom reversible[7D] but, instead, progresses to overt proteinuria in 20 to 40 percent of patients.

Blindness is the most dreaded complication of diabetes. In 2002, 124 million people suffered from low vision and 37 million were blind. In western nations, diabetes mellitus is the first cause in loss of vision among younger patients.

The pathogenesis of diabetic retinopathy and nephropathy is same, that's why is has been postulated that microalbuminuria can be used as a predictor of retinopathy, and can be used as a marker to refer the patients for screening of retinopathy.[20]In this study an attempt has been made to determine the frequency of microalbuminuria in type 2 diabetes and to determine the frequency of retinopathy in patients with and without microalbuminuria.

Numerous studies were carried out to determine the prevalence of retinopathy and microalbuminuria in diabetes Type 2. These studies yielded different rates between 16 to 53.4% for retinopathy.[23,24,25] In a study the prevalence of diabetic retinopathy was 39.3%.[20] Our study showed the frequency of 30.3% which is somewhere in median range. The variation in rate could be as a result of different methods used in those studies, the population and or the races involved, or variation in controlling blood sugar level.

The prevalence of microalbuminuria in our study was 28.7%. Parving et al reported the incidence rate of 22% of microalbuminuria in diabetes type 2 [26]whereas Lunetta reported the incidence rate of 15%.[27] In another study the frequency of microalbuminuria was 153 (25.9%) out of 590 patients.[20] The above-mentioned studies show that there is a significant relationship between the degree of retinopathy and microalbuminuria.

However there are few studies opposing such relationship. Erasmus et al showed that in 113 patients suffering from TYPE 2, the incidence rate of microalbuminuria was as high as 54% among males and 59% among females. Prevalence of retinopathy was 16%. They concluded that microalbuminuria may not predict retinopathy and occurs independently from either glycaemic control or elevated blood pressure levels.[28]The population chosen for the study

influences the different incidences achieved in various studies.

The present study shows that patients having microalbuminuria had high frequency of retinopathy i.e., 45.4% and patients without microalbuminuria had low frequency i.e., 24.3%.

The method used to measure microalbuminuria has also significant influence on difference in frequency of microalbuminuria. In my study immunoturbiditic method was used and only one sample was sent for microalbuminuria but in a study done by Manaviat Clinitek 100 (made by Bayer Corporation-Elkhart, USA) was used to measure microalbuminuria. Three urine samples were taken during three to six months and if two samples were positive, microalbuminuria was affirmed.[20]

In this study the method to measure microalbuminuria is simple and economical and the results were not very different from the studies where microalbuminuria was measured three times.

This study shows the frequency of retinopathy in patients with and without microalbuminuria, which clearly showed that frequency of retinopathy increased with presence of microalbuminuria.

Further studies are required to better understand the relationship between microalbuminuria and retinopathy. Understanding this relationship will give us better insight into the pathophysiology of microvascular complications of diabetes. This will enable us to introduce new treatment and diagnostic modalities which can reduce morbidity and mortality related to diabetic microvascular complications.

CONCLUSION

This study shows that patients with microalbuminuria develop retinopathy more frequently than those who don't have microalbuminuria. However it is not clear that microalbuminuria can be used as a predictor of presence of diabetic retinopathy in type 2 diabetics. This predictor function needs further study in one or more prospective cohorts of patients with type 2 diabetes to validate its efficacy. If its efficacy is confirmed, it may permit referral to ophthalmologist at early stages of retinopathy.

REFERENCES

1. Umesh M. Diabetes mellitus and hypoglycemia. In: Lawrence M, Tierney Jr, Stephen J, Mc phee Maxine A, Papadakis. Current medical diagnosis and treatment. 43 er ed. New York: Mc Graw- Hill; 2004: 1146-7.
2. Arias E, Anderson RN, Hsiang-Ching K, Murphy SL, Kochanek KD. Deaths: final data for 2001. In National vital statistics reports. Vol 52. Hyattsville, MD, National Centre for Health Statistics 2003.
3. Gale EAM, Anderson JV. Diabetes mellitus and other disorders of metabolism. In: Kumar and Clark. Clinical medicine. 6th ed. Edinburgh, United Kingdom: WB Saunders 2005: 1101-51.
4. Cooper ME, Bonnet F, Oldfield M, Jandeleit-Dahm K. Mechanisms of diabetic vasculopathy: an overview. Am J Cooper ME, Bonnet F, Oldfield M, Jandeleit-Dahm K. Mechanisms of Hypertens 2001; 14: 475-84.
5. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8; 360:129-39
6. Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycaemic control. Diabetes Care 1997; 20: 1847-53.
7. MenzinJ,Langley-Hawthorne C, Friedman M, Boulanger L, Cavanaugh R. Potential short-term economic benefits of improved glycaemic control: A managed care perspective. Diabetes Care 2001; 24: 51-5.
8. Papadopoulos AA, Kontodimopoulos N, Frydas A, Ikonomakis E, Niakas D. Predictors of health-related quality of life in type II diabetic patients in Greece. BMC Public Health. 2007 Jul 30; 7:186.
9. Bamashmus MA, Gunaid AA, Khandekar RB. Diabetic retinopathy, visual impairment and ocular status among patients with diabetes mellitus in Yemen: A hospital-based study. Indian J Ophthalmol. 2009 July-August;57(4):293-298.
10. Remuzzi G, Schieppati A, and Ruggenenti P. Nephropathy in Patients with Type 2 Diabetes. N Engl J Med 2002 11;346:1145-51.
11. Ritz E. Albuminuria and vascular damage -- the vicious twins. N Engl J Med 2003; 348:2349-2352.
12. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. BMJ 1997;314:783-788.
13. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225-232.
14. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-878.
15. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-869.
16. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345:851-860.
17. Eurich DT, Majumdar SR, Tsuyuki RT, Johnson JA. Reduced mortality associated with the use of ACE inhibitors in patients with type 2 diabetes. Diabetes Care 2004;27:1330-1334.

18. Parving HH, Mauer M, Ritz E. Diabetic nephropathy. In: Brenner BM, ed. Brenner & Rector's The kidney. 7th ed. Vol. 2. Philadelphia: Saunders, 2004:1777-818.
19. Boelter MC, Gross JL, Canani LH, Costa LA, Lisboa HR, Três GS, Lavinsky J, Azevedo MJ. Proliferative diabetic retinopathy is associated with microalbuminuria in patients with type 2 diabetes. Braz J Med Biol Res. 2006 Aug;39(8):1033-9.
20. Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. BMC Ophthalmol. 2004 Jul 1; 4:9.
21. Shafique M, Rehman KU, Haider Z, Sidiqui AM, Shehzad A. Micro vascular complications in Pakistani NIDDM (non-insulin dependent diabetes mellitus. patients. Pak Postgraduate MJ 1998; 9: 1-4.
22. Powers AC. Diabetes mellitus. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's principles of internal Medicine.16th ed. New York: McGraw-Hill 2005: 2152-79.
23. Liu DP, Molyneaux L, Chua E, Wang YZ, Wu CR, Jing H et al: Retinopathy in a Chinese population with type 2 diabetes: factors affecting the presence of this complication at diagnosis of diabetes. Diabetes Res Clin Pract 2002; 56:125-131.
24. Wirta O, Pasternack A, Mustonen J, Laippala P, Lahde Y: Retinopathy is independently related to microalbuminuria in type 2 diabetes mellitus. Clin Nephrol 1999, 51:329-334.
25. Sobngwi E, Mbanya J, Moukouri EN, Ngu KB: Microalbuminuria and retinopathy in a diabetic population of Cameroon. Diabetes Res Clin Pract 1999; 44:191-196.
26. Parving HH, Hommel E, Mathiesen E, Skott P, Edsberg B, Bahnsen M et al: Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. BMJ 1988; 296:156-160.
27. Lunetta M, Infantone L, Calogero A, Infantone E: Increased urinary albumin excretion is a marker of risk for retinopathy and coronary heart disease in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 1998; 40:45-51.
28. Erasmus RT, Oyeyinka G, Arije A: Microalbuminuria in non-insulin-dependent (type 2) Nigerian diabetics: relation to glycaemic control, blood pressure and retinopathy. Postgrad Med J 1992; 68:638-42.