

PROGRESSION OF ALBUMINURIA AND RETINOPATHY WITH DURATION OF DIABETES MELLITUS

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ABSTRACT

Objective: To determine the progression of proteinuria with duration of type 2 diabetes mellitus, it also aimed at grading DR with duration of diabetes mellitus.

Study Design: Cross sectional study.

Place and Duration of Study: Duration of this study was 5 months, from Feb 2017 to Jun 2017.

Material and Methods: This study enrolled 53 patients with type 2 diabetes mellitus. Duration of this study was 5 months from February 2017 to June 2017. Urinary albumin was measured using the turbidometric method (Roche, Germany). A 3.5V Standard Ophthalmoscope (Welch Allyn) was used to examine the fundus. Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis.

Results: In this study, 52.8% (n=28) were males while 47.1% (n=25) were females. Average age was 56.2 ± 11.6 years. Patients were grouped according to duration of diabetes; group1: disease duration less than 5 years, group 2: disease duration between 5 to 10 years, group 3: disease duration more than 10 years. Average HbA1C was 8.53% in group 1, 9.51% in group 2 and 10% in group 3. In group 1, 22.6% (n=12) had urinary albumin less than 30 mg/dL. 16.9% (n=9) had urinary albumin equal to or more than 30 mg/dL and less than 300 mg/dL while no patient had urinary albumin equal to or more than 300 mg/dL. A *p*-value was 0.002. In group 2, 5.6% (n=3) had urinary albumin less than 30 mg/dL. Of 20.7% (n=11) had urinary albumin equal to or more than 30 mg/dL and less than 300 mg/dL while 1.8% (n=1) patient had urinary albumin equal to or more than 300 mg/dL. A *p*-value was 0.002. In group 3, No patient had urinary albumin less than 30 mg/dL. 18.8% (n=10) had urinary albumin equal to or more than 30 mg/dL and less than 300 mg/dL while 13.2% (n=7) patients had urinary albumin equal to or more than 300 mg/dL. A *p*-value was 0.001. In group 1, 1.8% (n=1) patient had DR. In group 2, 3.7% (n=2) patients had DR while in group 3, 20.1% (n=11) patients had DR. 45.3% of the patients were on oral hypoglycemic medications, 43.4% patients were on Insulin therapy while 9.4% patients were on Insulin and Oral Hypoglycemics both.

Conclusion: Patients had poor diabetic control despite being diagnosed for 5 to 10 years. Albuminuria progressed and grade of retinopathy increased with duration of diabetes. Relatively low rate of renal and retinal complications were found in this study.

Keywords: Diabetic nephropathy, Diabetic retinopathy, Diabetes Mellitus, HbA1C, Moderately increased albuminuria, Microalbuminuria, Severely increased albuminuria.

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INTRODUCTION

According to World Health Organization, it is estimated that number of patients with diabetes will rise to approximately 370 million by 2030 worldwide¹. Diabetic nephropathy (DR) is a major complication of diabetes mellitus and it has been reported that about 25-40% of type 1 or type 2 diabetic patients develop diabetic nephropathy within 20-25 years of the onset of

diabetes². Diabetic nephropathy is defined by the presence of severely increased albuminuria (formerly called macroalbuminuria) which is defined as urinary albumin excretion more than 300 mg/day. This common problem will occur in patients who have worse glycemic control, hypertension, glomerular hyperfiltration or a genetic predisposition³. Initial clinical manifestation of renal involvement in diabetes is an increase in albumin excretion which is called moderately increased albuminuria (formerly called microalbuminuria) which is defined as

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urinary albumin excretion between 30 and 300 mg/day³. At this stage renal histology may be relatively normal or may reveal glomerulosclerosis⁴. Moderately increased albuminuria precedes the development of severely increased albuminuria and is considered to be a finding that predicts high risk for future nephropathy. The onset of severely increased albuminuria is, in the absence of effective therapy, often followed by a slowly progressive decline in glomerular filtration rate (GFR) and, given enough time, end-stage renal disease⁵. Pathologic abnormalities are noted in patients with long-standing diabetes mellitus before the onset of moderately increased albuminuria. There are four major histologic changes in the glomeruli in diabetic nephropathy: mesangial expansion; glomerular basement membrane thickening; podocyte injury; and glomerular sclerosis⁶. Strongest data relating to development of diabetic nephropathy in type 2 diabetic patients, was reported by the United Kingdom Prospective Diabetes Study (UKPDS). It was designed to compare the efficacy of different treatment regimens including diet, oral hypoglycemic, insulin, antihypertensives, varying blood pressure goals and other interventions on glycemic control and complications of diabetes in newly diagnosed type 2 diabetic patients. UKPDS enrolled 5100 type 2 diabetic patients and with respect to the development and progression of nephropathy reported that following 10 years of diagnosis, prevalence of moderately increased albuminuria, severely increased albuminuria and elevated plasma creatinine (more than 2 mg/dL) was 25, 05 and 0.8% respectively⁷. Yearly rate of progression from diagnosis to moderately increased albuminuria, from moderately increased albuminuria to severely increased albuminuria and from severely increased albuminuria to elevated plasma creatinine concentration was 02, 2.8 and 2.3% respectively⁷. Diabetic retinopathy (DR) is one of the most important causes of visual loss worldwide. Visual loss from DR may be secondary to macular edema (ME; retinal thickening and edema involving the macula), hemorrhage

from new vessels, retinal detachment, or neovascular glaucoma⁸. Data from the third National Health and Nutrition Examination Survey suggest that 30 percent of type 2 diabetics with renal insufficiency have nondiabetic renal disease, as inferred by the absence of albuminuria and retinopathy in this population⁹. In people with type 1 diabetes, DR is usually not evident until five or more years after onset, but after 20 years of type 1 diabetes 99% have some form of DR. In people with type 2 diabetes, diabetic retinopathy can be present directly at diabetes diagnosis; this may be due to years of undiagnosed diabetes. By 20 years of type 2 diabetes, about 60% of people have some level of diabetic retinopathy¹⁰. As far as treatment is concerned; Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARB) both are equally effective in the treatment of diabetic nephropathy in patients with type 1 or type 2 diabetes mellitus. Nevertheless, ACE inhibitors are preferred in type 1 while ARBs are preferred in type 2 diabetic patients with nephropathy¹¹. The aim of this study was to determine the association of proteinuria with duration of type 2 diabetes, it also aimed at relating diabetes with retinopathy.

MATERIAL AND METHODS

This was a cross sectional study. Duration of this study was 5 months from February 2017 to June 2017. It was done after approval from ethical review board of Khan Research Laboratory (KRL) Hospital. We use convenience sampling technique and selected all type 2 diabetes patients coming to our outdoor department and after applying exclusion criteria we selected 53 patients.

Laboratory Tests

Blood samples were collected by trained nurses. Drawn samples were adequately prepared and transported to the laboratory where these samples were analyzed within 24 hours. Plasma glucose, blood urea nitrogen (BUN) and creatinine were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan).

The level of HbA1c was measured using high performance liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan), which is the method that is certified by the National Glycohemoglobin Standardization Program.

A random 20-30 mL of midstream voided urine was collected in the morning, and then used to determine its level of urinary albumin. Urinary albumin was measured using the

Data Analysis

Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis. The clinical data of the study patients were stated as percentages. The difference between two groups were examined by Chi-Square test (Freeman Halton extension of Fisher's exact test was used). A *p*-value of ≤ 0.05 was considered statistically significant.

Table-I: HbA1C in different groups.

| Groups | HbA1C (%) | | |
|------------------|-------------------------------------|------------------------------|--------------------------------------|
| | 1 | 2 | 3 |
| Disease duration | Diabetes duration less than 5 years | Diabetes duration 5-10 years | Diabetes duration more than 10 years |
| HbA1C | 8.533 \pm 1.9966 | 9.5142 \pm 2.0932 | 10 \pm 2.1706 |
| No of patients | 21 | 15 | 17 |

Table-II: Progression of albuminuria with duration of diabetes mellitus.

| | Average albuminuria (mg/dL) | Total Patients | <30 mg/dL | ≥ 30 mg/dL and <300 mg/dL | ≥ 300 mg/dL | <i>p</i> -value |
|---|-----------------------------|----------------|--------------------------------|-----------------------------------|----------------------------------|-----------------|
| Diabetes duration less than 5 Years | 49.7142 | 21 | 12 (57.2%) 15.2 \pm 5.436 | 9 (42.8%) 95.78 \pm 76.120 | 0 | 0.001 |
| Diabetes duration between 5 to 10 years | 104.2 | 15 | 03 (20%) 16.67 \pm 2.887 | 11 (73.3%) 108.45 \pm 90.390 | 01 (6.7%) 320 \pm 0.00 | |
| Diabetes duration greater than 10 years | 256 | 17 | 0 | 10 (59.8%) 196.20 \pm 96.781 | 7 (41.2%) 341.43 \pm 16.762 | |

Table-III: Retinopathy grades with duration of diabetes.

| | Patients with Retinopathy | | Grades of retinopathy |
|--------------------------------------|---------------------------|----------------|-----------------------|
| | Total patients | Percentage (%) | |
| Diabetes duration less than 5 years | 1 | 4.76 | NPDR (mild) |
| Diabetes duration 5-10 years | 2 | 13.33 | NPDR (mild) |
| Diabetes duration more than 10 years | 11 | 64.7 | NPDR (moderate) |

turbidometric method (Roche, Germany).

Retinopathy

A 3.5V Standard Ophthalmoscope (Welch Allyn) was used to examine the fundus. All patients underwent fundal evaluation after pupillary dilatation. DR was clinically graded following the norms of the international clinical diabetic retinopathy and diabetic macular oedema severity scales¹².

Exclusion Criteria

Patients with hypertension, known kidney disease, rheumatoid arthritis and on prolonged NSAID use were excluded.

RESULTS

Current study enrolled 53 patients with diabetes mellitus. 52.8% (n=28) were males while 47.1% (n=25) were females. Average age was 56.2 \pm 11.6 years. Minimum age was 32 years while maximum age was 83 years.

Patients were put in three groups according to duration of diabetes.

Average HbA1C was taken in each group. This is shown in table-I.

Table-II illustrates the association of albuminuria with duration of diabetes mellitus.

In patients having duration of diabetes less than 5 years, average albuminuria was 49.7 mg/dL. In patients having duration of diabetes between 5 and 10 years, average albuminuria was 104mg/dl. In patients having duration of diabetes more than 10 years, average albuminuria was 256 mg/dl. Details of sub-groups are shown below.

Out of 53 patients 1.8% (n=1) with diabetes duration less than 5 years, 3.7% (n=2) patients having diabetes duration between 5 and 10 years had mild nonproliferative diabetic retinopathy (NPDR) while 20.1% (n=11) patients with

our study, reasons for such high HbA1C levels can be multifactorial; non-compliance with medication, lack of proper follow ups, inappropriate HbA1C testing, low socio-economic status and cultural taboos being some of them.

In this study, patients having diabetes duration of less than 5 years, 16.9% had moderately increased albuminuria. Yearly rate of progression from diagnosis to moderately increased albuminuria was reported as 2% in UKPDS⁷. The rate of moderately increased albuminuria at the time of diagnosis of type 2

Table-IV: Patients on oral hypoglycemics.

| | Total Patients | <30 mg/dL | ≥30 mg/dL and <300 mg/dL | ≥300 mg/dL |
|--------------------------------------|----------------|-------------|--------------------------|------------|
| Diabetes duration less than 5 years | 18 | 10 (55.55%) | 8 (44.44%) | 0 |
| Diabetes duration 5-10 years | 4 | 0 | 4 (100%) | 0 |
| Diabetes duration more than 10 years | 2 | 0 | 2 (100%) | 0 |

Table-V: Diabetic patients on Insulin therapy.

| | Total Patients | <30 mg/dL | ≥30 mg/dL and <300 mg/dL | ≥300 mg/dL |
|--------------------------------------|----------------|-----------|--------------------------|------------|
| Diabetes duration less than 5 years | 2 | 01 (50%) | 01 (50%) | 00 |
| Diabetes duration 5-10 years | 10 | 02 (20%) | 07 (70%) | 01 (10%) |
| Diabetes duration more than 10 years | 11 | 00 | 06 (54.5%) | 05 (45.5%) |

Table-VI: Diabetic patients on Insulin and oral hypoglycemics.

| | Total Patients | <30 mg/dL | ≥30 mg/dL and <300 mg/dL | ≥300 mg/dL |
|--------------------------------------|----------------|-----------|--------------------------|------------|
| Diabetes duration less than 5 years | 00 | 00 | 00 | 00 |
| Diabetes duration 5-10 years | 01 | 01 (100%) | 00 | 00 |
| Diabetes duration more than 10 years | 04 | 00 | 02 (50%) | 02 (50%) |

diabetes duration more than 10 years had moderate nonproliferative diabetic retinopathy. Table-III shows patient sub-groups with diabetic retinopathy.

Table-IV to VI illustrates sub-groups of diabetic patients on oral hypoglycemics, insulin therapy, and insulin & oral hypoglycemics combined respectively.

DISCUSSION

This study was conducted to study degree of albuminuria and grade of retinopathy with duration of diabetes mellitus. It was reported that HbA1c levels showed a significant increase with the duration of diabetes¹³. This is also revealed in

diabetes may be higher in older patients. This was illustrated in a cross-sectional population study of older adults in Finland. Sixty-nine out of 891 people developed diabetes at 3.5-year follow-up. Moderately increased albuminuria was present in 44 percent of these patients¹⁴. In our study only 1.8% patients having diabetes duration less than 5 years had retinopathy. This is in contrast to international literature where the prevalence of DR was reported to be 17% in a study done in 1984¹⁵. In a different study it was reported that up to 21% of patients with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes, and most develop some degree of retinopathy over time¹⁶.

In present study, patients having diabetes duration between 5 to 10 years, 20.7% had moderately increased albuminuria while 1.8% patients had severely increased albuminuria. According to UKPDS, almost 20% patients will develop moderately increased albuminuria by 10 years of disease duration⁷. In our study only 3.7% patients having diabetes duration between 5 to 10 years had retinopathy. In a study it was reported that the prevalence of any retinopathy was 8% at 3 years, 25% at 5 years, 60% at 10 years¹⁶.

In our study, patients having diabetes duration of more than 10 years, 18.8% had moderately increased albuminuria while 13.2% patients had severely increased albuminuria. In a study it was reported that cumulative prevalence of moderately increased albuminuria is about 25%-30% after 10 years of diabetes, and 40%-60% after 20 years of diabetes¹⁷. The reported prevalence of moderately increased albuminuria among patients with type 2 diabetes approximately 10 years after the diagnosis ranges from 25 to 40 percent^{18,19}. In a systematic review of 28 studies in type 2 diabetes (10,298 patients), the prevalence of moderately increased albuminuria was 26 percent at a mean diabetes duration of 10 years²⁰. The prevalence of severely increased albuminuria was 5.3 percent at 10 years after diagnosis in UKPDS⁷. Ethnicity may also be important as four- to five-year rates of progression to severely increased albuminuria as high as 37 to 42 percent have been described in Pima Indians and Israeli patients²¹. In our study 20.07% patients having diabetes duration more than 10 years had retinopathy while the prevalence of diabetic retinopathy was reported to be 60% at 10 years and 80% at 15 years in one study¹⁶. In another study it was reported that by 20 years of type 2 diabetes, about 60% of people have some level of DR¹⁰. In Type 1 diabetic patients, the severity of DR has decreased, with only 18 percent of retinopathy patients found to have vision-threatening levels of retinopathy at 20 years follow-up, compared with 43 percent at 20 years in the earlier Wisconsin study²². Similarly, in studies from the United States and United

Kingdom, rates of DR and the proportion of patients with type 2 diabetes requiring laser therapy have decreased over a six-year interval^{23,24}.

CONCLUSION

Patients had poor glycemic control despite being diagnosed for 5 to 10 years. Albuminuria progressed and grade of retinopathy increased with duration of diabetes. Relatively low rate of renal and retinal complications were found in this study.

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