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Research Article

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Diabetic Nephropathy Screening for Microalbuminuria at the Paediatric Endocrine Department -Tripoli Medical Center, Libya

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ABSTRACT

Diabetic nephropathy is a clinical syndrome characterized by an increased urinary albumin excretion rate of 30-300 mg/day (20-200ug/min). The risk of nephropathy increases with increased duration of diabetes and poor glycemic control. There are five histopathology stages in the development of diabetic nephropathy from early renal hyperfilitration to end-stage renal disease (ESRD). This study was conducted at the Paediatric Endocrine department, Tripoli Medical Center. 1209 patients with type I diabetes mellitus (DM) were screened by 24-hour urine collections to detect microalbumne in 2 successive occasions 6 months apart. It was considered positive, if it is more than 30 mg/day.

374 patients (31%) were positive for microalbuminuria; 194 (52%) females and 180(48%) males. Microalbuminuria was seen maximally after 8 years of the onset of diabetes. Their mean hemoglobin A1c (HbA1c) over the last 3 years prior to microalbuminuria development was 10%. All patients with microalbuminuria were put on angiotensin-converting enzyme inhibitor (ACEI) drugs even in the absence of hypertension and all being followed up by annual icroalbuminuria assessment after diagnosis. 52 patients with overt proteinuria were put on a combination of ACEI and ARB (angiotensin receptor blocker) drugs to slow the progress to ESRD. Diabetic nephropathy is also a sign of worsening blood vessel throughout the body. Good glycemic control can prevent the development and slow the progress of diabetic nephropathy as well as other diabetic complications.

Keywords- *Antibacterial, Honey, Salmonella.*

INTRODUCTION

Type 1 diabetes mellitus is the most common endocrine metabolic disorder of childhood and adolescence. Long-term complications result from metabolic derangements usually in adulthood that affect small and large vessels resulting in retinopathy, nephropathy, neuropathy ischemic heart disease of arterial obstruction with gangrene of the extremities.[1-6] Diabetic nephropathy is a clinical syndrome characterized by an increased urinary albumin excretion rate (AER) of 30-300 mg / 24h (20-200 ug / min), so called microalbuminuria. That is confirmed on at least 2 occasions 3-6 months apart, with decline in the glomerular filtration rate (GFR) and elevated arterial blood pressure.[1-6,7]

Proteinuria history

Proteinuria was first recognized in diabetes mellitus in the late 18th century. In the 1930s, Kimmelstiel and Wilson described the classical lesions of nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension. By the 1950s, kidney disease was clearly recognized as a common complication of diabetes.[7,8] The presence of nephropathy appears to be the most important prognostic feature for morbidity and mortality in patients with type 1 DM. This is related to death due to renal failure as well as coronary artery disease.[1,2,9] Diabetes has become the most common cause of end-stage renal disease [ESRD] in the United States and Europe; this is due to the facts that; 1) diabetes is increasing in prevalence; 2) diabetic patients now live longer; and 3) patients with diabetic ESRD are now being accepted for the treatment in ESRD programs.

In the United States, diabetic nephropathy accounts for about 40% of new cases of ESRD. In 1997, the cost of treatment of diabetic[1,4-7,12] patients with ESRD was in excess of 15.6 billion dollars.[1,3-6,10,11] Diabetic-nephropathy is defined by leakage of a large amount of albumin in the urine. Only 30-40% of patients with type 1 diabetes mellitus develop clinical nephropathy despite detectable morphogical renal change. The risk of nephropathy increases with duration of diabetes up to 25-30 years. The duration after which this complication rarely begins.[1-5,10,11,17]

Natural history of diabetic nephropathy (5-stages)

Stage 1: Early renal hypefilteration with hypertrophy; very early diabetic increased demand upon the kidney is indicated by an above normal GFR.

Stage 2: Development of renal lesions without changes in function (GFR) remains elevated or returned to normal.

Stage 3: Incipient diabetic nephropathy with an albumin

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excretion rates of 20-200 µg/min; hypertension typically develops during stage 3.

Stage 4: Overt diabetic nephropathy with an albumin excretion rate of greater than 200 µg / min; the GFR has begun to decline steadily by 10% annually; blood urea and creatinine have started to increase; almost all patients have hypertension at stage 4.

Stage 5: End-stage renal failure with elevated serum creatinine levels or decreased GFR [fallen to approximately 10 ml /min] renal replacement therapy (haemodialysis, kidney transplant is needed).[1-7,10,11]

Pathophysiology

The earliest morphologic abnormality in diabetic nephropathy is the thickening of the glomerular basement membrane with expansion of the mesangium due to accumulation of the extracellular matrix.

There are three major histologic changes occur in the glomerulus of a person with diabetic nephropathy. First, mesangial expansion is directly induced by hyperglycemia. Second, thickening of the glomerular basement membrane [GBM] takes place. Third, glomerular sclerosis is caused by intra-glomerular hypertension (induced by renal vasodilatation or from ischemic injury induced by hyaline narrowing of the vessels providing the glomeruli). The exact cause of diabetic nephropathy is unknown, but one of the postulated mechanisms is the hyperglycemia causing hyperfilteration and renal injury. Advanced glycosylation products and activation of cytokines.

Hyperglycemia increases the expression of transforming growth factor- beta (TGF-Beta) in the glomeruli and of matrix proteins, specifically stimulated by this cytokines. TGF-beta may contribute to both the cellular hypertrophy and enhanced collagen synthesis observed in a person with diabetic nephropathy. Hyperglycemia may also activate protein kinase C, which may cause renal disease and other vascular complications of diabetes.[3,7,8,13]

The overall risk of developing diabetic nephropathy varies from 10% in Type II to about 30% in type I.[4-6]

Microalbuminuria [albumin excretion rate greater than 20 µg/min or 30 mg/day] is a marker of the silent phase of diabetic nephropathy. Without specific interventions, 80 % of subjects with type I diabetes who develop sustained micro-albuminuria have their urinary albumin excretion increases at a rate of 10-20% per year to the stage of overt nephropathy or clinical albuminuria [≥ 300 mg/24h or ≥200 µg/min] over a period of 10 -15 years with hypertension also developing along the way.[1-5,10,11,16]

Screening for microalbuminuria

Can be performed by three different methods:

1. Measurement of the albumin to creatinine ratio in a random spot of urine collection. This method is often found to be the easiest to carry out in an office setting. Morning collection of urine is the best because of the known-diurnal variation in albumin excretion.

2. 24-hour collection of urine with creatinine, allowing the simultaneous measurement of creatinine clearance, and a timed (e.g. 4-hours) overnight urine collection for protein.

3. Specific assays are needed to detect micro-albumiuria because standard hospital laboratory assays for urinary protein are not sufficiently sensitive to measure such levels.[1,4,5,7,10,11,16] Transient elevation of urinary albumin excretion: short-term hyperglycemia, exercise, urinary tract infection, marked hypertension, heart failure, and acute febrile illness.[1,5,10,16]

Does diabetic nephropathy have any other effects?

- Diabetic nephropathy is also a sign of worsening blood vessel disease throughout the body.

- Diabetic eye disease is usually present by this stage indicating damage to smaller blood vessels.[1-6,14,15]

- Larger blood vessels (arteries) are almost always affected leading to heart attacks, strokes and circulatory disease occurring more often and at a younger age than usual.

- Commonly diabetes will have also resulted in damage to small nerves causing "diabetic peripheral neuropathy" and "autonomic neuropathy".[1-6,12,14,15] What can be done to reduce the risk of problems?

The risk effect of diabetic nephropathy can be reduced by controlling blood sugar (HbA1c < 7 %), blood pressure (the recommended target is 110/70 mmHg), and cholesterol level (a target total cholesterol of < 3.5 mmol/l).[4,5,10,11]

MATERIALS AND MEETHODS

Study design: A retrospective study

Study place: Paediatric Endocrine department Tripoli Medical Center, Tripoli- Libya.

Study period: from 1990 to 2000 (10 years of research)

Study population: The patients presented during the study period were those with type I diabetes mellitus. The mean duration of diabetes was 12 years (8-18 years).

Data management and analysis: The data which was collected from medical records included: current age of the patients, their age at diagnosis, sex, duration of diabetes, family history of diabetes mellitus, hypertension, renal disease or any associated autoimmune diseases. Data was packaged and analyzed using the software program, SPSS. Mean HbA1c over the last 3 years, 24-hour urine collection for microalbuminuria, 5 years post-diagnosis and yearly thereafter were conducted. If urine albumin was more than 30 mg/day, patient was considered positive. When microalbuminuria was found in 2 successive occasions 6 months apart, blood pressure and progress of nephropathy were monitored.

RESULTS

The data collected for this study was analyzed by the SPSS software program. During this study period 1209 patients (out of 1339) with type I DM were screened for microalbuminuria. Microalbuminuria was detected in 374 (30.9%) patients; 194 (52%) females and 180 (48%) males. The most common age affected was ranging from 23 to28 years old, and microalbuminuria (Figure 1) was the highest at 8 years post diagnosis (Figure 2). Mean HBA1C was 10% over the last 3 years preceding

the assessment of renal status (Figure 3). 214 patients (57.2%) had no family history of diabetes, hypertension or renal disease, while 78 patients (20.9%) had a history of type II diabetes. 38 patients (10.2%) had a history of type I diabetes, 26 patients (7%) had a history of types I and II DM. The study also revealed that 6 patients (1.6 %) had a history of hypertension, whereas 4 patients (1.1%) had a history of renal disease. According to the findings of the present research, 225 patients (60%) were positive and had normal blood pressure, while 149 patients (39.8%) had a high blood pressure. All patients with positive microalbuminuria were on ACEI drugs even in absence of hypertension (to slow the progress for overt proteinuria). 52 patients (out of 374) had overt proteinuria (protein > 300mg /day), and they were on a combination therapy of ACEI and ARB drugs to slow progress to ESRD.

One patient with advanced kidney disease as well as GFR of (20-30%) was referred to nephrologists (Table1). Other complications associated with diabetic nephropathy, such as retinopathy was found in 122 patients (32.6%), peripheral neuropathy in 7 patients (1.8%), and limited joint mobility was presented in other 7 patients (1.8%). In this study, there was no correlation between incidences of autoimmune disease and diabetic nephropathy.

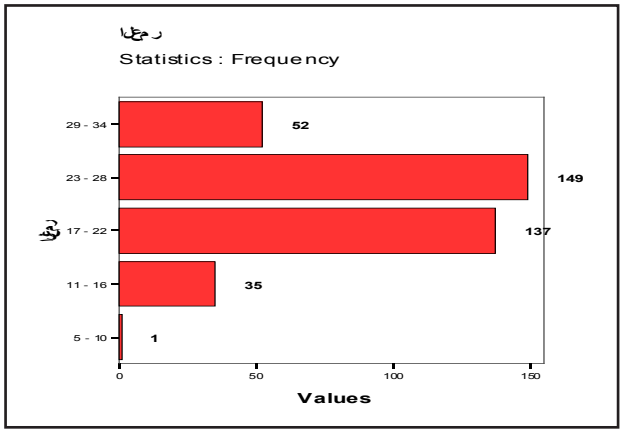

Figure 1: Age group distribution and + ve microalbuminuria.

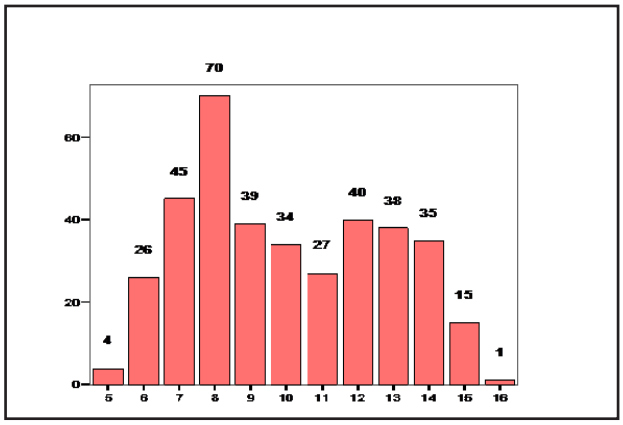

Figure 2: Duration in years from onset of DM to development microalbuminuria.

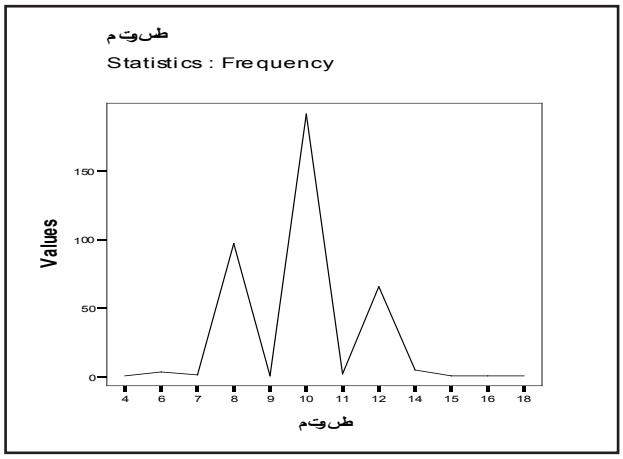

Figure 3: The effect of glycemic control in developing microalbuminuria, mean HBA1c 10%.

DISCUSSION

Diabetic nephropathy does not occur in all diabetics.[4,5] 1209 patients were screened for microalbuminuria; only 374 patients (31%) were positive. The risk of diabetic nephropathy is greater when the duration of diabetes was more than 8 years and associated with poor diabetic control. The mean HbA1C in our study group was 10%. Microalbuminuria usually starts after 5 years of diabetic duration, in 4 of our patients, it started at 5 years duration. The Diabetic Control and Complication Trial (DCCT), and U.K Prospective Diabetes Study (UK PDS) have definitively shown that intensive diabetic therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in people with diabetes.[4,5]

The glycemic control recommendation for all patients with diabetes in accordance with the American Diabetes Association: Standards of Medical Care for patients with diabetes mellitus should be followed in this regard.

All our patients with diabetic nephropathy even in early stages (albumin exaction rate was 30 -300 mg /day) were put on angiotensin-converting enzyme inhibitor (ACEI). In the absence of high blood pressure, this supposed to slow the progress to overt proteinuria and being followed up by annual microalbuminuria assessment after diagnosis of microalbuminuria in order to know the response to therapy; either resolving or progressing. These drugs do not only reduce blood pressure in the large vessels, but also directly affecting the filtering system of the kidneys in terms of protein leaks.[18,19,22]

Progress from one stage to the next can take many years, with 23 years being the average length of time to reach stage five. Only one patient in our study reached this stage.

Hypertension or high blood pressure is a complication of diabetes that is believed to contribute most directly to diabetic nephropathy. 225 patients (60.16%) who were positive for microalbuminuria had blood pressure within normal limit, but they were already on ACE inhibitor drugs. However, 149 patients (39.8%) had a high blood pressure were put on a combination therapy of both ACEI and ARB.[4,5,10,11,19,22]Hypertension is believed to be both

the cause of diabetic nephropathy, as well as the result of damage that is created by the disease. As kidney disease progresses, physical changes in the kidney often lead to increased blood pressure. Uncontrolled blood pressure can make the progress toward stage five diabetic nephropathy (kidney failure) occur more rapidly.

Patients with overt proteinuria were put on a combination therapy of ACEI and ARB drugs to slow the progress to end-stage renal disease, and being followed up closely to see the effectiveness of therapy on the disease progress.[18,19,22-24]

Many studies have documented the beneficial effects of these agents beyond simply blood pressure control to reducing kidney protein leak. Patients with advanced kidney disease are more at risk for low blood sugar because insulin is not being readily excreted from the kidney.[5,10,11]

The rate of deterioration of renal function can be markedly slowed by aggressive control of blood pressure and dietary protein restriction.[7,10,11]

As diabetic eye disease usually presents by the stage of microalbumiuria development indicating damage to smaller blood vessel retinopathy,[14,15,21] but in our study only 32% out of 374 patients who had microalbuminuria had retinopathy as well. This most likely was done in those patients by routine eye examination. We could have detected more retinopathy if immunflourecent study for early changes had been investigated

CONCLUSION

a) Screening for diabetic nephropathy in type I diabetes mellitus should start from 5 years post- diagnosis and annually thereafter.

b) In the presence of microalbuminuria, angiotensin converting enzyme inhibitor and/or angiotensin receptor blocking drugs even in the patient with absent hypertension.

c) Refer to nephrologists when ESRD develop.

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