INTRODUCTION

Diabetic nephropathy is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is believed to be the most important cause of chronic renal failure worldwide and may cause death two to three years after the initial lesion ***(Kalinina et al., 2009)***.

The earliest detectable change in the course of diabetic nephropathy is a thickening in the glomerulus which is detected by microalbuminuria. As diabetic nephropathy progresses, the number of glomeruli are destroyed by nodular glomerulosclerosis are increased. This leads to increase of albumin being excreted in the urine (frank proteinuria) ***(Chow et al., 2006)***.

Monocyte chemoattractant protein-1(MCP-1) is a potent chemokine produced by monocyte, fibroblast, macrophage, endothelial cell, and smooth muscle cells. It plays a vital role in inflammation by recruitment of monocytes to sites of injury ***(Sell and Eckel, 2007)*.**

Morri et al. (2005) discovered that (MCP-1) mediates renal interstitial inflammation, tubular atrophy and interstitial fibrosis by attraction of mononuclear cell. They demonstrated that protein overload in tubular cell up- regulate MCP-1 gene and its protein expression.

MCP-1 is a major promoter of inflammation, renal injury, and fibrosis in diabetic nephropathy. It was found that diabetes mellitus is associated with increase MCP-1 production from renal cells, so its urinary level can be used to assess renal inflammation in this disease ***(Tesh, 2008)***.

Genetic deletion and molecular studies in rodents have identified (MCP-1) as an important therapeutic target for treating diabetic nephropathy. This finding may provide a strong rational to develop specific therapies against MCP-1 and inflammation in diabetic nephropathy in order to delay its complication ***(Tam et al., 2004 and Frederick et al., 2009)*.**

AIM OF THE WORK

The aim of the present study was to evaluate the clinical utility of urinary Monocyte chemoattractant protein (MCP-1) as a prognostic marker in diabetic nephropathy and its relation to the severity of the disease.

I- DIABETIC NEPHROPATHY

Diabetic nephropathy is a serious complication of diabetes mellitus that often leads to end stage renal failure or stage 5 chronic kidney disease. It is a major cause of morbidity and mortality in diabetic patients ***(Rabkin , 2003)***.

A- Definition:

Diabetic nephropathy is a progressive kidney disease caused by angiopathy of the capillaries in the kidney glomeruli due to long standing diabetes. It is also known as (**Kimmelstiel-Wilson syndrome)** as the syndrome was discovered by British physician **Clifford Wilson** and German physician **Paul Kimmelstiel** and was published for first time at 1936 **(*Kimmelstiel and Wilson, 1936).***

It is also defined as a clinical syndrome characterized by persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart, with declined glomerular filtration rate (GFR), and elevated arterial blood pressure ***(Kostadaras, 2009).***

B- Epidemiology and Risk Factors:

The cumulative incidence of microalbuminuria in patients with type 1 diabetes was 12.6% over 7.3 years according to the European diabetes (EURODIAB). ***(Chaturvedi***

et al., 2001), While in patients with type 2 diabetes, the incidence of microalbuminuria was 2% per year and the prevalence 10 years after diagnosis was 25% in the U.K. Prospective Diabetes Study (UKPDS) ***(Adler et al., 2003).***

Proteinuria occurs in 15-40% of patients with type 1 diabetes, with a peak incidence around 15-20 years of diabetes ***(Wong et al., 2004),*** While in patients with type 2 diabetes, the prevalence is highly variable, ranging from 5 to 20% ***(Adler et al., 2003).***

Diabetic nephropathy is more prevalent among African Americans, Asians, American Indian origin, family history of kidney disease or high blood pressure, poor control of blood pressure, poor control of blood sugars, type 1 diabetes before age 20 and smoking ***(Young et al., 2003 and Wahren et al., 2007).***

Finally, consistent with the fact that diabetes is the leading cause of ESRD (End stage renal disease), It was found that 45% of deaths due to ESRD are among individuals with a primary diagnosis of diabetes ***(American Diabetes Association, 2004).***

C- Stages of diabetic nephropathy:

1- Stage I: Glomerular hyperfiltration and renal enlargement:

Stage I is the early hyperfunction hypertrophy stage found at diagnosis. Increased glomerular and kidney size are the prominent findings. In very early diabetes increased demand upon the kidneys is indicated by above normal glomerular infiltration rate (GFR). Approximately one third of patients have an elevated glomerular filtration rate (GFR) that is 20% to 40% higher than that of age-matched normal subjects ***(Lee et al., 2007).***

2- Stage II: Early glomerular lesions or silent stage with normal albumin excretion:

Patients in this stage are by definition normoalbuminuric. In developing diabetes, glomerular infiltration rate remains elevated or has returned to normal but glomerular damage has progressed to significant microalbuminuria (small but above normal protein in urine).If glomerular filtration rate is more than 150 ml/min., the risk of late nephropathy is likely to be increased considerably. Glomerular lesion or structural changes appear within 18 to 36 months and may become prominent after 3.5 to 5 years after onset of diabetes ***(Maeda and Shiigai, 2007).***

3- Stage III: Microalbuminuric stage:

The third stage is characterized by persistent and usually increasing microalbuminuria and causes a high risk of developing overt diabetic nephropathy. About 30%-45% of type I diabetes with microalbuminuria would progress to overt proteinuria. Hypertension may also be a feature of the microalbuminuric stage. Hyperfiltration and renal enlargement persist. It is detected by urinary albumin excretion rate greater than 30 mg/24 hours or 20 µg/minute and less than 300 mg/24 hours or 200 µg/minute on three different occasions ***(Wahren et al., 2007).***

The prevalence of microalbuminuria varies from 25% to 40% in individuals with diabetes for 5 to 15 years and rarely occurs during the first 5 years of diabetes ***(Dubois and Bankauskaite, 2005).***

4- Stage IV: (Overt or Dipstick positive diabetes):

Glomerular damage has progressed to clinical albuminuria. The urine is dipstick positive containing more than 300 mg albumin in 24-hour period. Early in the course of overt diabetic nephropathy, glomerular filtration rate values may be normal or high normal and accompanied by a normal serum creatinine. Hypertension typically develops in this stage. This stage usually occurs 15 to 20 years after the onset of diabetes ***(Theodore et al., 2008).***

5- Stage V: (End stage renal disease- ESRD):

In late stage diabetes, glomerular damage continues with increasing amounts of protein in urine. The kidney's filtering ability begins to decline steadily and blood urea nitrogen (BUN) and creatinine (Cr) begin to increase. The (GFR) decreases about 10% annually. Almost all patients have hypertension in this stage. GFR falls to approximately (10mL/min) and renal replacement therapy is needed ***(Tonelli et al., 2006).***

D- Pathophysiology of Diabetic Nephropathy:

The key change in diabetic nephropathy and the earliest morphologic abnormality is the thickening of the glomerular basement membrane (GBM) and expansion of the mesangium due to accumulation of extracellular matrix ***(Sandeep, 2009).***

This changes detected as light microscopic findings, show an increase in the solid spaces of the tuft, most frequently observed as coarse branching of solid material (diffuse diabetic glomerulopathy). Large cellular accumulations also may be observed within these areas (*figures 1,2*). These are circular on section and are known as the Kimmelstiel-Wilson lesions/nodules. The glomeruli and kidneys are typically normal or increased in size initially, thus distinguishing diabetic nephropathy from most other forms of chronic renal insufficiency, where renal size is reduced (except renal

amyloidosis and polycystic kidney disease). ***(Chiarelli et al., 2009)***

Immunofluorescence microscopy may reveal deposition of immunoglobulin G along the GBM in a linear pattern (*figure 3*), but this is not immunopathogenetic or diagnostic. The renal vasculature typically displays evidence of atherosclerosis, usually due to concomitant hyperlipidemia and hypertensive arteriosclerosis ***(Shlipak, 2009)***.

Electron microscopy provides a more detailed definition of the structures involved. In advanced disease, the mesangial regions occupy a large proportion of the tuft, with prominent matrix content. Further more, the basement membrane in the capillary walls is thicker than normal (*figure 4*) ***(Shlipak, 2009)***.

Three major histologic changes occur in the glomeruli of persons with diabetic nephropathy. First, mesangial expansion is directly induced by hyperglycemia, perhaps via increased matrix production or glycosylation of matrix proteins. Second, GBM thickening occurs. Third, glomerular sclerosis which is caused by intraglomerular hypertension resulting from renal vasodilatation or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli). The exact cause of diabetic nephropathy pathophysiological changes is unknown, but it may be due to various postulated mechanisms

like hyperglycemia (causing hyperfiltration and renal injury), advanced glycosylation products, and activation of cytokines. (*figure 5*). ***(Sandeep, 2009)*.**

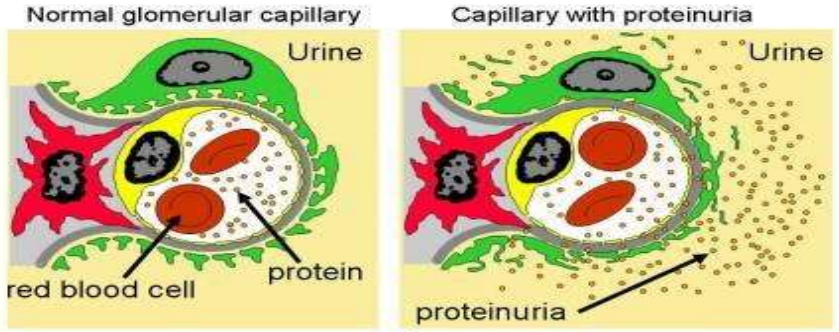

Figure (1): Changes in glomeruli in diabetic nephropathy ***(Chiarelli et al., 2009)***.

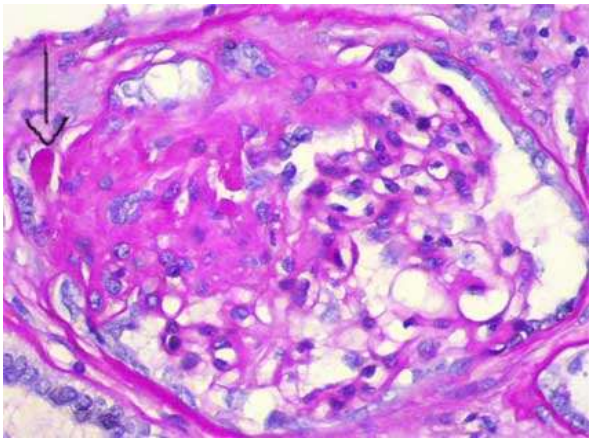

Figure (2): Glomerulus with segmental sclerosis (left superior corner). There are segments with preserved architecture. Notice small hyaline segments; they are proteins and other components ***(Chiarelli et al., 2009)***.

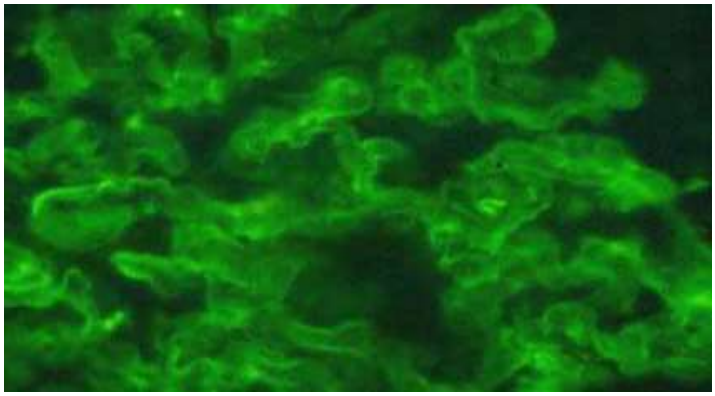

Figure (3): Linear positivity of IgG demonstrated by immunofluorescence ***(Shlipak, 2009)***.

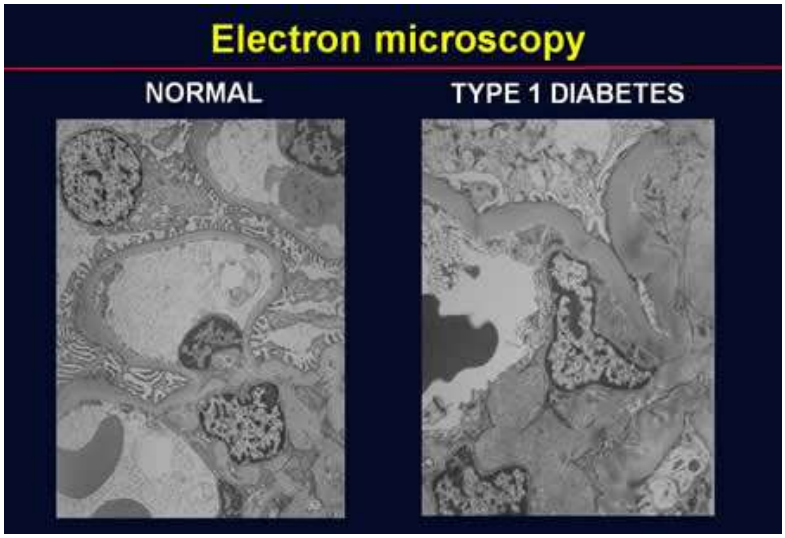

Figure (4): Normal subject and patient with diabetic nephropathy where you can appreciate thickening of the glomerular basement membrane and mesangial matrix expansion ***(Shlipak, 2009).***

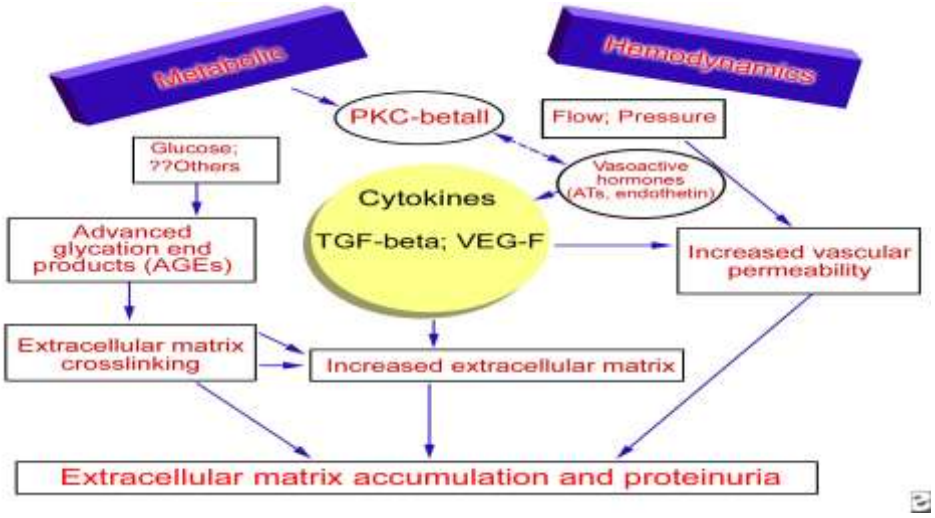

Figure (5): The pathogenesis of diabetic nephropathy ***(Sandeep, 2009)***.

E- Screening of diabetic nephropathy:

It is accepted by both the European and U.S. diabetes societies that regular screening of urinary albumin excretion is valuable in monitoring both type 1 and 2 DM. Screening for diabetic nephropathy must be initiated at the time of diagnosis in patients with type 2 DM, since 7% of them already have microalbuminuria at that time. For patients with type 1 DM, the first screening has been recommended at 5 years after diagnosis. However, the prevalence of microalbuminuria before 5 years in this group can reach 18%, especially in patients with poor glycemic and lipid control and high normal blood pressure levels ***(Emeka and Uchenna, 2006).***

The well established guidelines for microalbuminuria screening are shown in Figure (6).

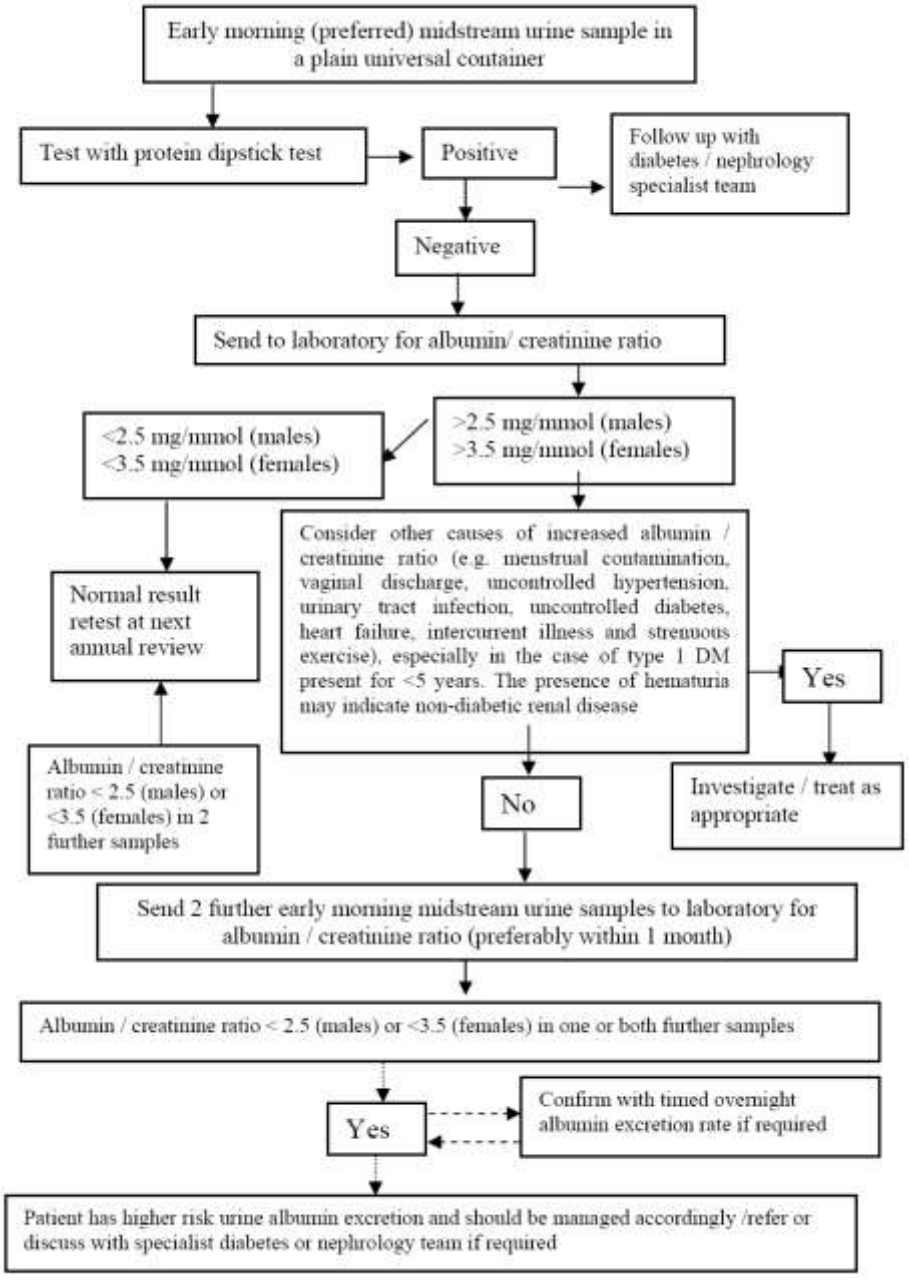

Figure (6): Screening of microalbuminuria ***(Sacks, 2006)***

F- Diagnosis of Diabetic Nephropathy:

1-Clinical Examination:

a- History:

Through history taking with stress on history of diabetes prompted by recent onset symptoms of polyuria, polydepsia and weight loss, passing of foamy urine, symptoms of diabetic retinopathy, fatigue and foot edema, other associated disorders such as symptoms of peripheral vascular occlusive diseases (cyanosis and ischemic pain) and symptoms of hypertension (headache and visual disturbance **(*(Sacks and McDonald, 2006).***

b- Physical examination:

Generally, diabetic nephropathy is considered after a routine urine analysis and screening for microalbuminuria but clinical examination also is important as patients usually have physical findings associated with long standing diabetes mellitus such as: hypertension, peripheral vascular occlusive disease (decreased peripheral pulse, carotid bruits), evidence of diabetic neuropathy in the form of decreased fine sensations and diminished tendon reflexes, evidence of fourth heart sound during heart auscultation and non healing skin ulcers ***(Shlipak, 2009).***

2- Laboratory diagnosis:

a. Monitoring of renal function.

b. Early predicators of diabetic nephropathy.

a- Monitoring of renal function:

i- Urine tests:

***- Urine analysis*:**

There are a variety of urine tests that assess kidney function. A simple, inexpensive screening test is routine urine anlaysis is often the first test administered if kidney problems are suspected. A small, randomly collected urine sample is examined physically for color, odor, appearance and specific gravity; chemically for substance such as protein, glucose and pH; and microscopically for the presence of cellular elements as red blood cell, white blood cell and epithelial cells, bacteria, crystals and casts. If results indicate a possibility of disease or impaired kidney function, one or more of the following additional tests is usually performed to more specifically diagnose the cause and the level of decline in the kidney function. Special finding associated with diabetic nephropathy is proteinuria, hematuria, and casts ***(Brenner and Flody, 1999 and Henry, 2001).***