INTRODUCTION
INTRODUCTION

Diabetes mellitus is a common serious metabolic disorder. Its true frequency varies from 1-2% in general population. Disease is characterised by metabolic abnormalities in form of hyperglycemia, hyperlipidemia and glycosuria and clinical presentation is in form of polyuria, polydipsia and polyphagia.

Common complications are retinopathy, diabetic nephropathy, atherosclerosis and ischemic heart disease and neuropathy.

Renal disease is the commonest complication and leading cause of death in diabetes. Diabetes affect the structure and function of kidney in many ways. Diabetic nephropathy is presented with variety of clinical syndromes like mild asymtomatic proteinuria, nephrotic syndrome, hypertension and progressive failure.

Diabetic nephropathy represents the single most important cause of renal failure in adults in the western world causing 25% of all new cases of uremia. The peak incidence of development of clinical disease occurs after about 16 years insulin dependent diabetes mellitus (IDDM). Overall, approximately 35-45% of patients with long standing insulin dependent diabetes mellitus will ultimately develop diabetic nephropathy defined as dip stick positive proteinuria, hypertension and falling GFR. (Christiansen and Andersen et al, 1985).
In insulin dependent diabetic patients incidence of nephropathy is 40-50% (Witzel et al, 1986). While less in non insulin dependent diabetes mellitus (NIDDM) one in four end stage renal disease patients turns out to be diabetic (Mogensen, 1984). The mortality in patients suffering from diabetic nephropathy is upto 100 times, that of age and sex matched background population and this is mainly due to enormous death from end stage renal disease (Borch Johansen et al, 1985).

Several lines of evidence indicate that renal hypertrophy and hyperfiltration are characteristics and early manifestation of human and experimental diabetes, which may contribute to later development of diabetic nephropathy. It also suggest that there is contribution of IGF-1 at very early stage to sequence of events that may lead to late diabetic nephropathy. Strict insulin treatment abolish both kidney IGF-1 accumulation and kidney growth.

Much has been learned in last decade regarding the pathology of the kidney in insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM). The major pathologic changes of diabetes include thickening of all renal extracellular basement membranes and mesangial matrix and mesangial cell expansion. Although much less is known regarding renal pathology in NIDDM as compared to IDDM, most proteinuric patients with NIDDM have typical diabetic nephropathy while approximately 25% have
Other forms of renal disease. Two renal lesions appear critical in diabetic nephropathy. Mesangial expansion out of proportion to the size of glomerulus is closely and inversely related to measures of peripheral capillary wall filtration surface, this expansion is also related to clinical features of proteinuria, hypertension and declining glomerular filtration rate (GFR). Arteriolar hyalinosis is related to global glomerulosclerosis and both are correlated with the clinical features of nephropathy. Renal extracellular basement membrane and matrix expansion appears to be secondary to increased production or decreased turnover, or both of normal structural constituents of the kidney. Microalbuminuria in the "Predictive range" is frequently accompanied by rising blood pressure and/or falling GFR and is associated with well established structural lesions. Thus microalbuminuria is a marker of quite advanced diabetic nephropathy.

The glomerular filtration of macromolecules is determined by intrinsic properties of glomerular capillary wall including size and charge selectivity and also by haemodynamic factors which govern GFR. Thus proteinuria can be altered by haemodynamic events such as changes in volume status or blood pressure independent of any changes in capillary wall structure.

During first decade of diabetes values for urine albumin excretion (AUE) rate usually remains normal averaging ≤10 mg/24 hours. There are however at least two
circumstances in which transient increase in UAE may be observed. First during episode of poor metabolic control and second during exercise mechanisms have not been fully characterised. Albumin excretion rate are rapidly reduced following improvement in metabolic control and cessation of exercise.

In patients with diabetes of several years duration, transient increase in UAE may result from the combination of altered glomerular haemodynamic function with early changes in glomerular capillary wall structure. In such patients exercise may serve as provocative test to reveal abnormalities in glomerular barrier function which are not apparent at rest.

Recent studies have shown that proteinuria in diabetic renal disease can be attributed to glomerular basement membrane thickening per se, it may well be caused by associated changes in basement membrane composition. It has been suggested that glycosylation of basement membrane constituents increases the permeability of basement membrane to macromolecules. In addition to this proteinuria may be related to changes in epithelial cell structure. It is not known whether these changes in epithelial cell structure represent a cause or consequence of increased glomerular permeability to macromolecules.

Microalbuminuria usually defined as having albumin excretion rates in range of 30-300 mg/24 hours and rates in excess of 500 mg/24 hours in turn reliably predict ultimate loss of kidney function in diabetic patients. The small
defect in glomerular barrier function which causes microalbuminuria must therefore regarded as the first sign of pathological process which leads in exorable renal failure.

Diabetic nephropathy is classified in five stages by Mogensen et al (1976).

Stage I : Early renal hypertrophy and hyperfunction.
Stage II : Renal lesion without clinical signs.
Stage III : Incipient diabetic nephropathy.
Stage IV : Clinical overt.
Stage V : End stage renal failure.

The observations that proteinuria precedes loss of renal function in diabetic patients has led to the assumption that maneuvers which reduces proteinuria will also retard the progression of diabetic renal disease. Morphometric studies suggest that the reduction of GFR in diabetic nephropathy is caused by progressive expansion of the glomerular mesangium. It is not certain that all maneuvers which reduce proteinuria will prevent reduction of GFR in diabetic patient.

Several therapeutic interventions, such as glycemic control, antihypertensive treatment and low to moderate protein diet have been shown to be effective in reducing microalbuminuria (Brouhard and Lagrone, 1990; Cievere et al, 1987; Evanoff et al, 1987; Kupin et al, 1987; Rudberg et al, 1988 and Zeller et al, 1991).
The management of diabetic patients with advanced nephropathy is not easy because such patients tend to have the nephrotic syndrome and severe damage to many other organs consequently, it would be of great value to try and alleviate the massive proteinuria which is characteristic of this condition. In early stages of diabetic nephropathy several maneuvers and drugs have been tried to reduce the proteinuria and retardation of progression of nephropathy. Now-a-days ACE inhibitors are much in use specially Captopril, Enalapril for reduction of proteinuria and improvement of renal function in diabetic nephropathy cases.

ACE inhibitors are safe and effective antihypertensive agents that have unique beneficial intrarenal actions related to reduction of angiotensin II, intraglomerular pressures and glomerular permeability and possibly to normalization of mesangial function.

Recently Lisinopril which is being argued as a better ACE inhibitor as compared to Enalapril in the management of hypertension, has been utilized in diabetic nephropathy cases. One to the paucity of literature about the use of Lisinopril in diabetic nephropathy with or without hypertension, thus study has been designed to know the effect of Enalapril versus Lisinopril in cases of diabetic nephropathy.