Reliability of plasma fructosamine and Glycosylated hemoglobin assays for assessing the glycemic status of ureamic patients under conservative treatment and under hemodialysis

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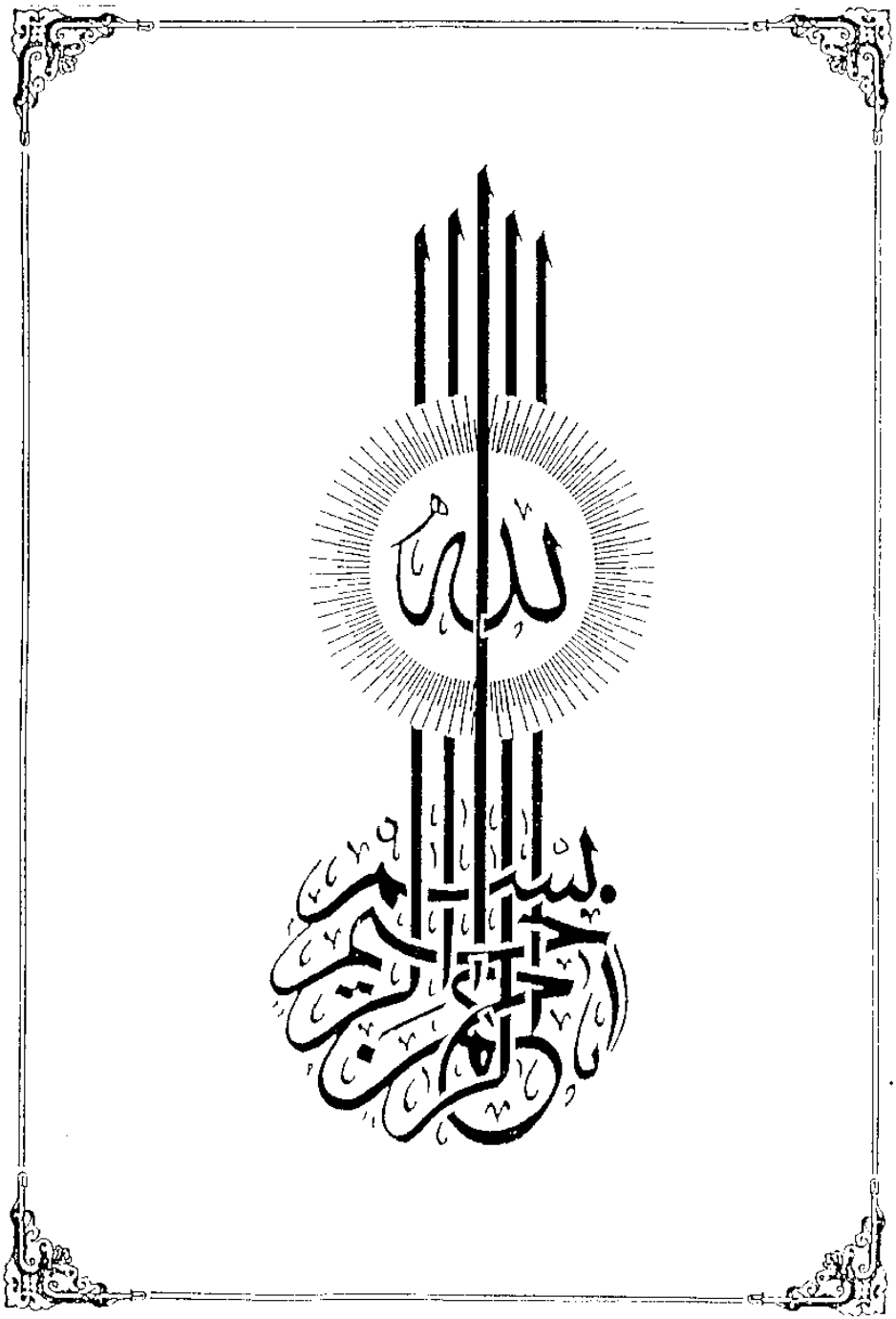

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INTERODUCTION AND AIM OF THE WORK

Diabetic nephropathy is a comman complication of diabetes mellitus leading to renal failure in about 93.9 percent of insulin dependent diabetes mellitus (Type I) and about 36.8 percent of non insulin dependent diabetes mellitus (Type II) patients . Also it is clear that the risk of renal disease is related to the degree of glycemic control . In diabetic patients with renal failure and under hemodialysis glycemic control is associated with decrease in the progression of the other complications as retinopathy, neuropathy and thickening of the muscle capillary basement membrane. Also the hemodialysis procedure can affect the glycemic condition of these patients . So medium and long assessment of glycemic status of this patients is very important ,(Cordonnier et al., 1993)

The aim of the work is to compare between the plasma fructosamine and glycosylated hemoglobin in the assessment of glycemic status in patients with diabetic nephropathy in various stages of the disease either patients on conservative treatment or under hemodialysis .

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REVIEW

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PREVELANCE OF RENAL DISEASE IN A DIABETIC POPULATION

Diabetic patients less than 31 years old at the time of diagnosis have shown that about 20% of them develop uraemia, and the mortality rate in those with proteinuria was about three times more than in non proteinuria subjects, However patients who were free of nephropathy for more than 40 years of diabetes is unlikely to develop renal disease after this time, (Deckert et al., 1978) .

The mortality from renal disease with diabetes was 17 times more than in non diabetics, and renal failure caused 53% of deaths in diabetics diagnosed before the age of twenty, (Watkins and Moloney, 1982).

In a study of renal diseases in diabetics in Watford General Hospital, it was found that 16.8% of all diabetics have some evidence of renal disease as was judged by proteinuria or raised plasma creatinine, about 58% of those diabetics with renal disease were found to have intermittent proteinuria of less than 0.5 gm/24 hours; 27% were found to have persistent proteinuria in excess of 0.5 gm/24 hours. A further 11% were found to have evidence of renal failure without proteinuria. An additional 5% were found to have unrelated miscellaneous non-diabetic renal disease, (Nelstrop, 1983).

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The incidence of nephropathy in NIDDM patients as indicated by persistent proteinuria more than 300 mg per 24 hours has been reported to be approximately 16% in a study of European diabetic patients diagnosed after the age of 40 years. Other studies in slightly different selected population have reported lower prevalences of 12-14%, with males being affected more frequently (19%) than females (4%) . The prevalence of proteinuria increases steadily with the duration of diabetes from 7-10% in patients with diabetes diagnosed less than 5 years before, to about 20-30% in patients who have had diabetes diagnosed for more than 20-25 years , (Borch et al., 1985).

Glomerular disease is a common complication of diabetes mellitus leading to renal failure in 30 to 35% of insulin dependent (IDDM or Type 1) and about 6% of non-insulin dependent (NIDDM or Type 2), (Krowlewski et al., 1987) .

About 4000 cases of end stage renal disease due to diabetic nephropathy occur annually among diabetic patients in the USA. This represents about one fourth of all patients being treated from renal failure , (Donahue and Orchard, 1992) .

In 14- year follow-up study it was found that 80% of IDDM patients with an albumin excretion rate abone 30

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microgram/min developed clinical nephropathy, while only 4% of those with an Initial albumin excretion rate below 30 microgram/min developed clinical nephropathy, (Raskin and Tamborlane, 1996) .

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DIABETIC NEPHROPATHY

The kidney as a target organ for secondary microvascular complications of diabetes mellitus represents a major health problem. Recent studies in man and animal strongly support the concept that the primary responsibility for diabetic nephropathy rests on metabolic derangement of the diabetic state. However this metabolic derangement has complex biological effects ; it is unlikely that hyperglycemia produces all of the nephropathic influences of diabetes. Alterations in microvascular haemodynamics in diabetes probably contribute to glomerular pathology. These alterations may be based upon disturbed vasoactive control mechanisms regulating angiotensin and prostaglandin secretion and metabolism, (Mauer et al .,1981).

Hyperglycemic state is responsible for microvascular complications rather than separate inherited vascular abnormality. For example patients with secondary or acquired diabetes mellitus due to toxin exposure or pancreatic disease can develop the same vascular lesions , (Rose, 1987).

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AETIOLOGY OF DIABETIC NEPHROPATHY

Although the nature of the lesions of diabetic nephropathy are specific for diabetes , the rate of their development appears to be highly variable among insulin dependent diabetic patients. The factors that may influence the rate at which these lesions develop include the severity of the diabetic state and alterations in renal haemodynamics; in addition genetic factors could play an important role in determining the response of various renal structures to the diabetic state , (Mauer et al., 1983).

Evidence that the primary responsibility for diabetic nephropathy rests on the metabolic derangements of the diabetic state is derived from a number of studies in man and animal. The study of normal kidney transplants in diabetic patients showed that within two years most of these kidneys demonstrate hyaline lesions of the arterioles characteristic of diabetic nephropathy. Within four years all kidney transplants in diabetic patients showed these changes, in addition obvious mesangial thickening including nodular glomerular sclerosis was noted in many of these kidneys , (Mauer et al., 1976).

Immunofluorescent microscopic studies of these transplanted kidneys showed increased linear renal extracellular membrane staining for albumin and immunoglobulin G.

These pathologic changes in normal kidneys

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occurred whether the donor was related to the recipient or was a cadaver with no personal or family history of diabetes , (Mauer et al., 1976).

Exposure to increased glucose concentration alters the chemistry of glomerular and other basement membranes, since accumulation of basement membrane-like material characterizes several of the microangiopathic sequelae of diabetes. The role of increased non enzymatic glycosylation on structure, function and metabolism of basement membrane is very important. This non enzymatic glycosylation of the glomerular basement membrane will cause its thickening and will cause increased permeability of the filteration barrier ,(Cohen et al., 1981).

Poor diabetic control is probably the most important factor of diabetic nephropathy, glucose may be incorporated into the basement membrane altering its structure and increasing permeability and also there are abnormalities of platelet function and impaired red cell deformability which may also play a role. Attempts to identify risk factors for developing nephropathy have not been successful, neither blood pressure, poor diabetic control nor trace protienuria have proved useful indications of future renal disease. The condition is slightly more common in males, (Watkins and Moloney 1982) .

However in a more recent study it was found that

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subsequent renal failure can be predicted in diabetic patients with albumin excretion rates exceeding 30 microgram/min , also the increase in microalbuminuria correlates with hypertension and this may explain why increased proteinuria in those patients is associated with a high tendency of cardiovascular deaths even in the absence of renal failure . Careful glycemic control as well as a low-protein diet (0.6 gm/ kg/d) may reduce both the hyperfilteration and the elevated microalbuminuria in the early stage of diabetes and in those with incipient diabetic nephropathy , (Hostetter 1992) .

Three major pathways have been proposed to explain how hyperglycemia leads to glomerulosclerosis.

The first : Metabolic pathway is of primary importance, for example, glycosylation of mesangial and basement membrane proteins (similar to that which occurs with hemoglobin) leading to mesangial hyperplasia and enhanced production of basement membrane like material, (Rose & Black, 1994).

The second : Haemodynamic pathway proposes a primary role of hyperglycemia induced alteration in renal haemodynamics . There is often 25 to 50% elevation in the glomerular filteration rate (GFR) in both experimental animals and many patients early in the course of IDDM. This effect may be mediated by renal vasodilatation, (Rose & Black, 1994).

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The third :- Familial and genetic pathway which explain why there is only a proportion of diabetic patients who develop renal disease, (Seaquist et al., 1989).

The Metabolic Pathway :

Reaction between glucose and lysine amino acid terminal of circulating and structural proteins gives rise to glycation products by non enzymatic glycation.

Two types of glycated products are identified . The first is a relatively short lived protein which undergoes Amadori rearrangement with formation of stable but chemically reversible sugar-protein structure - and the second is a structural protein with slower turn over character such as collagen, mulin, elastin. Non enzymatic glycation is thus likely to affect the glomerular basement membrane and other matrix components in the glomerulus. This increased GBM glycation may lead to an increase in the degree of disulphide bridge crosslinking via increased oxidation of sulphydryl groups collagen components. Aminoguanidin blocks the advanced glycation end products and is shown to prevent the aortic collagen cross linking and the cross linking of collagen to lipoproteins as well as the thickening of GBM and glomerular trapping of IgG molecules, (Brownlee et al., 1988).

The reaction of glycation may enhance the binding of circulating plasma proteins to structural components

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in the GBM and mesangial matrix. By the presence of reactive carbonyl group on the glucose molecule, it may attached to these structures. Glycation of the structural proteins or circulating proteins may interfere with their degradation leading to reduction of degradation of glomerular components which may result in mesangial matrix and GBM accumulation and expansion, (Brownlee et al., 1983).

Also proteins or lipids when exposed to aldose sugars undergo to an irreversible modifications resulting in the formation of the so called advanced glycation end -products (AGES). These are especially important in the setting of diabetes mellitus due to hyperglycemia charactristic of this disorder.

The reaction of (AGES) with the vascular wall is by a cellular receptor called the receptor of advanced glycation end products (RAGE), which is present on the surface of endothelial cells, smooth muscle cells, mesangial cells, mononuclear phagocytes and certain neurons . This reaction may result in the induction of monocyte chemotaxsis as well as oxidant stress . One of the consequences of AGE-RAGE induced cellular oxidant stress is the enhanced experssion of vascular cell adhesion molecule -1 on the endothelial surface which may lead to attraction of mononuclear phagocytes into the vessel wall. Inhibition of RAGE may interfere with monocyte chemotaxis and also its attraction into the vessel wall where AGES is present

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