GENETIC STUDY OF DIABETIC NEPHROPATHY

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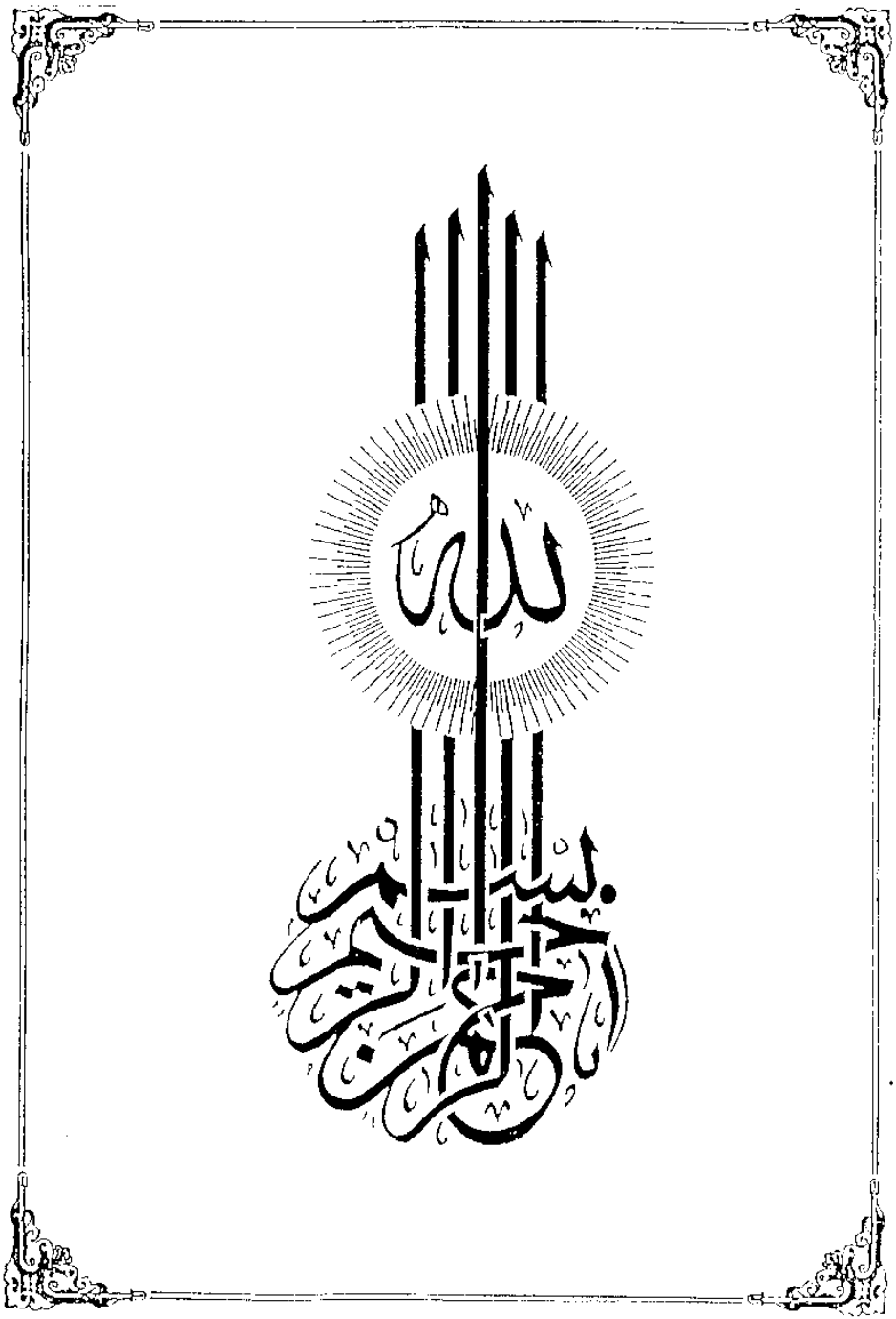

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CONTENTS

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ABREVIATION

* IDDM = Insulin - dependent diabetes mellitus
* NIDDM = Non insulin-dependent diabetes mellitus.
* DN = Diabetic Nephropathy.
* FBG = Fasting blood glucose.
* CRF = Chronic renal failure.
* ESRF = End stage renal failure .

INTRODUCTION

INTRODUCTION

As defined by the National Diabetic Data Group in 1979, diabetes occurs predominantly in two clinical varieties designated as type 1 and II. The type 1 diabetic, formerly called juvenile, or insulin-dependant, is characterized by onset before age 40, lean or normal body weight, insulin dependence, and a propensity for ketosis. Type II diabetes, previously termed maturity onset, often but not always is discovered in obese individuals older than 40, and is responsive to dietary therapy or oral hypoglycemic agents *(National diabetic Data Group, 1979) (Albert and Hockaday, 1983)*.

It is now apparent that diabetes and glucose intolerance are not diagnostic terms, but -like anemia- are simply symptom complexes or laboratory abnormalities which can result from a number of distinct etiologic factors. *[Rotter, JM and Rimoin, DL, 1981]*.

Diabetes mellitus is currently classified into "idiopathic" type and "diabetes associated with genetic syndromes and other conditions" *"National Diabetic Data Group, 1979)*.

The majority of the cases are placed into the idiopathic type which is further Subdivided into 2 major

groups: an insulin-dependent type (often referred to as jurenile onset diabetes) and a non insulin-dependent type (often referred to as maturity onset diabetes), this separation is based on family, twin, metabolic, immunologic and HLA association studies, regardless of the age of onset *Rotter, JM and Rimoir, DL, 1981).*

The kidney as atarget organ for secondarymicrovascular complications of diabetes mellitus represents a health problem of enormous social cost. *(Mauer, S.M., et al., 1981).*

Nephropathy in the 30-50% of type 1 diabetics who progress torenal insufficiencyhas been well described. After a mean of 17.3 years of hyperglycemia, proteinuria in excess of 1 gm dailydevelops, followed within 1-3 years by azotemia which worsers to uremia within the next 2-3 years *(Rutherford, W.E. et al., 1977 and Dectert, T., et al., 1978).*

The onset of proteinuria, although related to the level of exposure to hyperglycemia, appears to be influenced by genetic and/or environmental factors *(KrolewsKi, A.S. et al., 1985).*

In this respect, considerable argument has occured in the literature in relation to the possible influence of the HLA system *(Cove D.H., et al., 1980)*.

It would be of great interest to know early in the course of diabetes whether or not a patient was prone to the development of renal disease over the next decade. This would be of considerable importance in selecting patients for trials with intensified insulin treatment e.g., continuous subcutaneous insulin infusion *(Mogensen C.E., and Christensen C.K., 1984)*.

Since it has been demonstrated that antihypertensive treatment considerably retards the progression of nephropathy *(Mogensen C.E., 1982 & Parving H.H., et al., 1983)*, early identification with respect to the possible intiation of antihypertensive treatment also appears important *(Mogensen, C.E. and Christensen, C.K., 1984)*.

This study is to find out a correlation between HLA-DR type and the development of DN, this might be-if confirmed-a prediction parameter for the development of nephropathy in IDDM.

REVIEW
OF
LITERATURE

DIABETIC NEPHROPATHY (DN)

Definition

Diabetic Nephropathy is a disease characterized by persistent proteinuria, decline in glomerular filtration rate (GFR), blood pressure elevation and progression to end-stage renal failure (ESRF). This disease should not be confused with the morphologic term diabetic nephropathy, which means light microscopic renal lesions showing acombination of glomerulopathy, arteriolar hyalinosis and tubular abnormalities. *(Hans-Henrik P., et al., 1983).*

Mauer, S.M., defined DN as a multifaceted pathologic entity which spans the continuum from early renal hypertrophic changes to late stages of advanced structural distortion of the gemeruli, renal vasculature, interstituim, and tubules *(Mauer, S.M., et al., 1981)*. The classical clinical manifestations of this pathologic entity, overt continuous proteinuria, hypertension and declining GFR. *Jones, R.H., et al., 1979*, represents non specific consequences of this continuium. *(Maurer, S.M., et al., 1981).*

Clinically manifest DN means the presence of a proteinuria detectable by routine laboratory methods. *(Castiglioni, A., and Savazzi, G.M., 1988).*

The stages in diabetic renal disease:

In comparison with other renal disorders, the natural history of renal involvement in insulin dependent diabetes follows a very characteristic and probably unique pattern. Thus a series of stages in the development of renal changes in diabetes is recognizable *(Mogensen, C.E., et al., 1983).*

1. Stage 1: Early hypertrophic-hyperfunction:

Changes are found at diagnosis before insulin treatment is started. They may persist for many years when diabetes control is poor. *(Viberti, G.C., et al., 1982)*

Renal size is markedly increased early in the course and concomitantly increased function also is found both in human and experimental aminal diabetes. *(Brown, D.M., et al., 1982).* It is possible that in the early course of diabetes mellitus increased size of the kidney and associated phenomena are linked to the development of at least some aspects of the late diabetic glomerulosclerosis *(Mogensen, C.E., et al., 1983; Castiglioni, A. and Savazzi, G.M., 1988).* Increased urinary albumin excretion, aggravated during physical exercise is also a characteristic finding *(Vittinghus, E., and Mogensen, C.E., 1982).*

Stage	Time since onset, years	Characteristics
1	0	renal hypertrophy, hyperfiltration, normal GBM thickness, high basal albuminuria, corrected by insulin therapy
2*	1–10	thickening of the GBM, increased mesangial matrix, hyperfiltration, increased albuminuria after exercise or when diabetes is suboptimally controlled
3 (incipient DN)	10–15	in 30–40% of the patients microalbuminuria (30–300 mg/day or 20–200 µg/min) and microhypertension; risk factors: microalbuminuria > 50 mg/day, GFR > 150 ml/min/1.73 m²
4 (overt DN)	10–20	in 30–40% of the patients diffuse or nodular glomerulosclerosis, macroproteinuria (> 500 mg/day), frequent hypertension, possible development of nephrotic syndrome, gradual lowering of GFR (mean 1.2 ml/min/month)
5 (uremia)	20–30	glomerular sclerosis and hyalinosis, GFR < 10 ml/min, sometimes early symptoms of uremia

* This stage appears at present still incompletely defined and of unknown prognostic significance.

* DN in Type 1 diabetes.

2. Stage 2. Glomerular Lesions without clinical disease:

For many years after the start of insulin treatment, during standard control, the characteristic feature is that all standard clinical parameters related to renal function are normal. However, numxerous studies have shown a very consistent elevation of GFR. This increase is on the order of 20-30%, whereas the increase in the untreated situation is on the order of 30-40% *(Christainsen, J.S. et al., 1982; Mogensen , C.E., 1982)*. The elevated renal function is most likely linked to the imperfect metabolic control obtained during standard insulin regimens. GFR was shown to be more increased than extracellular volume in the type 1 diabetes, suggesting what has been termed "a real renal hyperfunction". *(Brochner-Mortensen, J and Bitzel, J. 1982)*. The well preserved kidney function found in many patients is evidenced by the fact that normal albumin excretion persists, despite the fact that pronounced structural alterations may be found when renal biopsy specimens are examined. It is characteristic that a gradual increase in the thickness of the glomerular basement membrane is found with increase in duration of diabetes followed by changes in the volume of the glomerular mesangium. *Oesterby , R. 1983)*. The apparent paradox i.e structural abnormalities associated with normal