GLYCATED HEMOGLOBIN (HbA_{1C}) AND FRUCTOSAMINE AS MARKERS OF DIABETIC CONTROL

Thesis

submitted by

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TO MY

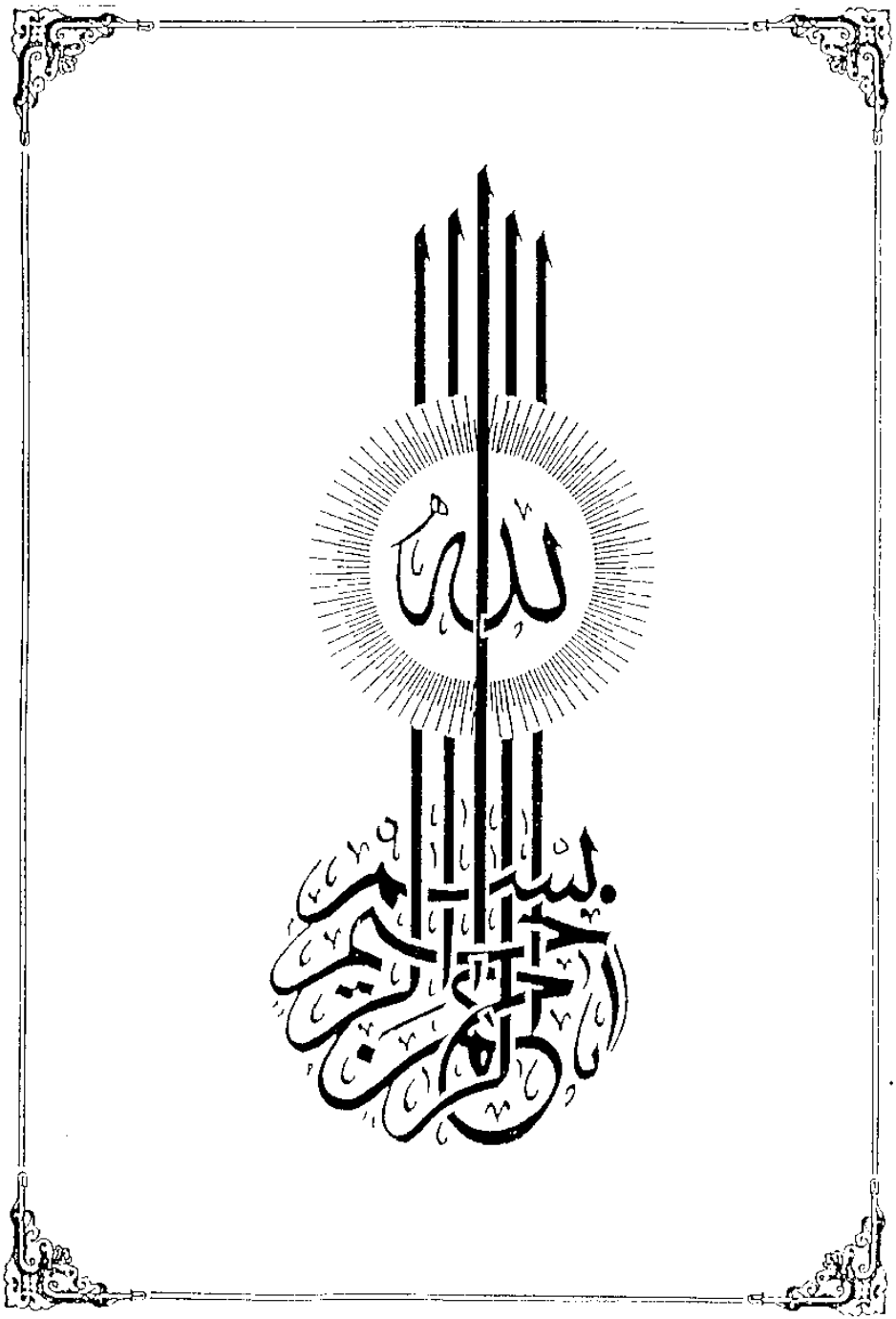
DEAREST FATHER

MOTHER AND BROTHERS

FOR THEIR LOVE

AND

ENCOURAGEMENT



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INTRODUCTION

AND

AIM OF THE WORK

The aim of our work is to evaluate the clinical usefulness of combination assay of serum fructosamine and HbA_{1c} in diabetes mellitus as markers of glycaemic control and to determine whether fructosamine might be a suitable alternative or a useful adjunct to Hb A_{1c} in the routine management.

REVIEW OF

LITERATURE

1) Metabolic defects:- beside hyperglycaemia there is accelerated fat and protein catabolism.

2) Structural damage triad (long-term sequelae):-

a) large vessel disease including accelerated atherosclerosis and medial calcification.

b) Microvascular disease characterized by thickening and abnormality of function of capillary basement membrane resulting in nephropathy and retinopathy.

c) Neuropathy: There are peripheral sensory and motor defects, autonomic nervous system dysfunction, segmental demyelination and abnormalities of Schwann cell (Porte and Halter, 1981).

Diabetes mellitus is also defined as a clinically and genetically heterogeneous group of disorders, that have one common feature -- hyperglycaemia due to deficient insulin level or effectiveness (Fajans et al., 1978).

Prevalence:-

Prevalance of diabetes is difficult to determine because numerous standards, many now no longer acceptable, have been used in diagnosis. The prevalence of non insulin dependent diabetes (NIDDM) is probably between 1 - 2 % using modern criteria for diagnosis (Genuth et al., 1976).

Estimates for insulin dependent diabetes are more reliable because most patients are diagnosed following the abrupt onset of symptoms. In England, the prevalence of type I illness is 0.22% by age 16 (Wadsworth, 1974), while in USA a study suggested a prevalence of 0.26% by age 20 (La Porte et al., 1981). The overall prevalence of diabetes is thought to be about 1% (Foster, 1987). If this is true, it follows that about one fourth of cases have insulin-dependent disease while three-fourths are non insulin dependent. The relative frequency of insulin dependent to non insulin dependent diabetes varies with age, being higher if a young population is studied and lower in the older age range.

Diagnosis of Diabetes Mellitus:

The National Diabetes Data Group of the National Institutes of Health (USA) in 1979 provided revised criteria for the diagnosis of diabetes following a challenge with oral glucose:-

1- Fasting (overnight): Venous plasma glucose concentration $\geq$ 140 mg/dl on at least two separate occasions.

[venous whole blood concentrations are 15% lower than plasma values. Capillary whole blood, utilized in patient self-monitoring, is equivalent to venous plasma.

2- Following ingestion of 75 gm. of glucose: Venous plasma glucose concentration $\geq$200 mg/dl at 2 h and on at least one other occasion during the 2h test (i.e two values $\geq$ 200 mg/dl must be obtained for diagnosis).

If the 2 h value is between 140 and 200 mg/dl and one other value during the 2 h test period is equal to or greater than 200 mg/dl, a diagnosis of impaired glucose tolerance is suggested. The interpretation would be that persons in this category are at increased risk for the development of fasting hyperglycaemia or symptomatic diabetes but that such progression is not predictable in an individual patient.

Most patients (75%) with impaired glucose tolerance never develop diabetes and subjects diagnosed as having diabetes by the second criterion may never manifest fasting hyperglycaemia or symptomatic deterioration. Consequently, the oral glucose tolerance test is rarely indicated in clinical practice although it is useful as a research tool (Foster, 1987).

Diabetes Mellitus is also classified into primary and secondary types. IDDM and NIDDM are considered primary or idiopathic which implies that no associated disease is present. In the secondary type another condition is responsible for the diabetic syndrome to develop (Foster, 1987).

In the classification recommended by NDDG (1979), insulin-dependent diabetes mellitus is not equivalent to insulin therapy.Rather, the term means that the patient is at risk for ketoacidosis in the absence of insulin as many patients classified as non insulin-dependent require insulin for control of hyperglycaemia although they do not become ketoacidotic if insulin is withdrawn (Foster, 1987).

The term type 1 has often been used as a synonym for insulin-dependent diabetes (IDDM) and type 2 diabetes has often been considered equivalent to non insulin dependent diabetes (NIDDM), (Bennett, 1983). This probably is not ideal (Keen, 1982 and Foster, 1987) since some patients with apparently non-insulin dependent diabetes may in fact be destined to become fully insulin-dependent and prone to ketoacidosis (Irvine, 1980).

The subset of patients in type 1 diabetes are non-obese subjects carrying the HLA-DR3/DR4 phenotype and exhibiting islet cell antibodies in the blood (Foster, 1987).

For this reason, it has been suggested that the classification recommended by NDDG (1979) can be modified such that the terms insulin-dependent and non-insulin-dependent describe physiologic states (ketoacidosis-prone and ketoacidosis-resistant respectively) while the terms type 1 and type 2 refer to pathogenetic mechanisms (immune mediated and non-immune mediated, respectively) (Unger and Foster, 1985).

Using such a new classification three major forms of primary diabetes would be recognized:-

1) type 1 insulin-dependent diabetes.
2) type 1 non-insulin dependent diabetes.
3) Type 2 non-insulin dependent diabetes.

Category 2) can be considered as type 1 IDDM in evolution i.e autoimmune beta cell destruction occur slowly with the result that there is delay in reaching ketoacidotic threshold (Foster, 1987).

Subclassification of idiopathic or primary diabetes:

Recent genetic studies (Fajans et al., 1978; Irvine, 1977; Pyke, 1977) coupled with new data from tissue typing

(Pyke, 1977 & Rosenberg et al., 1977) and serum autoantibody measurements (Lendrum et al., 1976) have provided strong evidence that idiopathic type 1 IDDM and idiopathic type 2 NIDDM are almost certainly not individually homogenous disorders (Rolter and Rimoin, 1978).

Although further subdivision of idiopathic type 1 IDDM and type 2 NIDDM is currently of little clinical usefulness, practitioners should be aware of these evolving concepts as they may soon aid in providing better prognostic information and more assured genetic counseling (Genuth, 1982).

IDDM and an increased risk for its development is associated with several human leukocyte antigens coded by different loci on chromosome 6. These include HLA-B8, B15, DW3, DW4 , CW3, B18, DR3, and DR4. It is thought that these HLA determinants are linked to but are not themselves diabetogenic genes.

One group of patients with IDDM is characterized by the presence of B8 combination with DR3, while B7 is likely to be absent. In this group, identical twins show high degree of concordance for diabetes, suggesting a genetically conferred inevitability to the disease. These patients as well as their relatives are more likely to have other autoimmune disorders, such as Hashimoto's thyroiditis, Graves' disease, idiopathic Addison's disease, primary

ovarian failure, pernicious anaemia and hypogamma globulinemia. Autoantibodies to islet cell antigens (ICA), which are transiently present in 80 to 90 per cent of all patients with IDDM at the time of diagnosis, are more likely to persist in the serum of these patients. ICA may even be present in relatives before diabetes can be diagnosed and may presage its early appearance. There is suggestive although not conclusive evidence that retinopathy and renal microangiopathy may be more common and more severe in this subtype of IDDM (Genuth, 1982).

In a second group of patients with IDDM, the HLA haplotype contains B15, often linked with CW3 and DR4, while B7 occurs with a normal frequency. In this subtype, identical twins may not be concordant for the disease, suggesting a genetic vulnerability to an environmental agent. Other autoimmune disturbances are not seen with increased frequency, serum autoantibodies to islet cell antigens tend to disappear after the first year of disease, and the pattern of microvascular complications does not stand out. On the other hand, these patients are reported to produce somewhat higher titres of antibody to the exogenous insulin that is administered therapeutically.

There is good evidence that HLA-B8 and HLA-B15 are linked to different diabetogenic genes. The relative risk of being diabetic is much greater if individuals have both B8

and B15 in their haplotypes. than if they have only one or the other antigen. Furthermore, the relatives of B8- B15 positive diabetics are also at greater risk for developing the disease than are those of B8-positive or B15 positive diabetic patients (Genuth, 1982).

Other forms of IDDM may well exist, linked to different HLA markers or to none. For example, several pedigrees with multiply affected siblings have B18 in their haplotype. In contrast, several families have been reported in which multiply affected siblings did not share any common haplotype.

To summarize, islet cell antibodies (ICA) are frequently present at diagnosis of the type (IDDM), other organ specific autoantibodies and abnormal immune responses may be present (Spielman et al., 1980). The presence of these autoantibodies have been used to sub-divide type 1 IDDM into:-

* Subclass "a" with persistent ICA and associated with other autoimmune phenomena.
* Subclass "b" with transient ICA and absent autoimmune phenomena
* Subclass "c" without ICA or autoimmune phenomena (NDDG, 1979).