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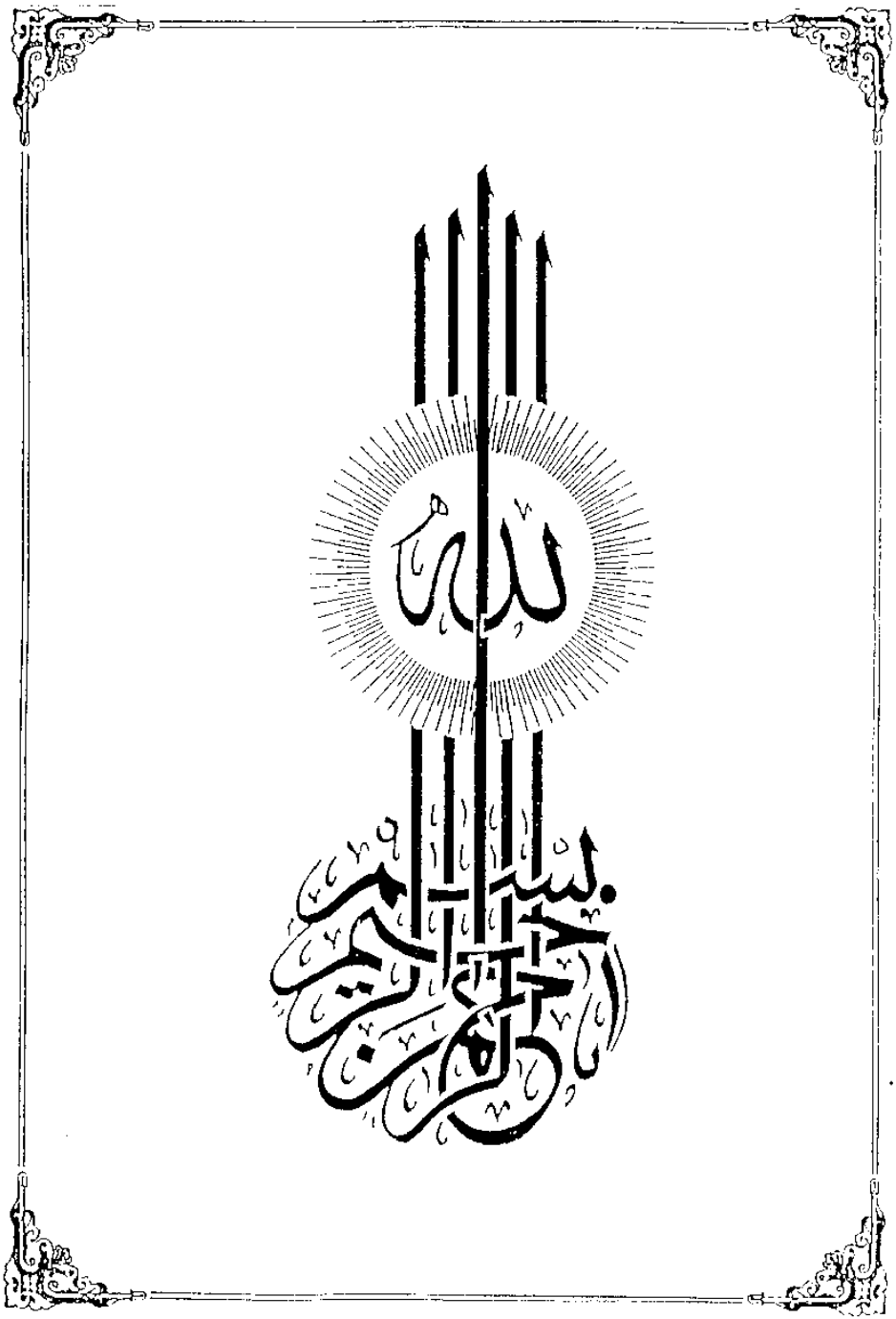
CONTENTS



INTRODUCTION

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AND AIM OF WORK

Recently, it has been shown that the level of glycosylated hemoglobin in a single blood specimen is an accurate and reliable measure of the glycemic status in diabetic patients over a 1-2 month period. The clinical evaluation of glycosylated hemoglobin determinations as an index of long-term control in the diabetic patient has been paralleled by the development of numerous methods for measuring HbAIC and total glycosylated hemoglobin. Several studies confirmed the relation between glycosylated hemoglobin and diabetic complications. However, a study on the interrelation between diabetic complications and erythrocytes metabolic disorder is still obscure.

Methemoglobinemia, sulfhemoglobinemia and carboxyhemoglobinemia have always been considered in the differential diagnosis of cyanosis when the latter is not due to hypoxia or abnormal right to left shunting. A threshold for cyanosis due to reduced Hb is known to be 5G/dL in mixed capillary blood, while this figure is 1.5-2 G/dL (about 10-20% of total Hb) and 0.5 G/dL (about 3% of total Hb) for Met-Hb and S-Hb respectively. At these concentrations, however, little symptoms (apart from cyanosis) are present. A contribution to tissue hypoxia cannot be, however, overlooked.

Abdel-Baset et al. (1983), reported high Met-Hb levels (20-30%) in patients with severe diabetic keto-acidosis in coma or precoma and reported a return to normal with efficient treatment of cases. Yano (1982), reported cases of infantile diarrhea with acidosis presenting with methemoglobinemia. He speculated a relation between acidosis and Met-Hb level (among other etiologies for this state). The common factor in either study is the presence of acidemia and methemoglobinemia. Kono et al. (1981), could prove inhibition of glycolysis in the RBC in states of acidemia. Inhibition of red cell glycolysis would reduce the yield of NADH, the main co-factor for Met-Hb reductase enzyme. This is why Met-Hb reduction is impaired with a resultant methemoglobinemia. If no acidemia is present would the diabetic state itself affect Met-Hb?

Sulfhemoglobin, produced by oxidant action of some drugs [Finch, 1948] might be expected to be affected by sulfonylurea drugs given in NIDDM patients.

Carboxyhemoglobin is not far from the normal red blood cell metabolism. It is endogenously produced during Heme degradation [Caburn et al., 1967].

Therefore, this work is dealt with to study the possibility of a metabolic disorder of erythrocytes and the possible contribution of hemoglobin derivatives to the development of diabetic complications.

REVIEW OF LITERATURE

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Diabetes

The definition of diabetes:

Diabetes mellitus is a disease syndrome best characterised as a state of chronic hyperglycemia of various etiologies. It may present with acute symptoms that include thrist, polyuria and unexplained weight loss (classical onset) and these can progress to life threatening ketoacidosis or hyperosmolar coma. Subacute symptoms include the above together with pruritus vulvae, balanitis, other skin infections, unusual fatigue or visual impairment. Chronic hyperglycemia may be asymptomatic, but is generally recognized as a predisposing risk for specific microvascular complications, namely retinopathy and nephropathy. The clinical suspicion of diabetes is strongly enhanced by finding glycosuria with or without ketonuria, but biochemical confirmation of the diagnosis is required by accurate measurement of blood glucose using a specific enzymatic glucose assay.

Revised criteria for the diagnosis of diabetes mellitus and other categories of glucose intolerance have been developed recently [National Diabetes Data Group, 1979] and these have been endorsed [World Health Organization "WHO", 1980] and supoorted by other national groups [Welborn, 1984].

Diagnosis of diabetes mellitus in non-pregnant adults:

1) Single blood glucose measurement:

With acute symptoms, gross and unequivocal elevation of blood glucose confirms the diagnosis, namely fasting venous plasma glucose level of 7.8 mmol/L or more (140 mg/dL or more) or post-absorptive venous plasma glucose levels of 11.1 mmol/L or more (200 mg/dL or more).

2) Two blood glucose measurements:

In the absence of symptoms of diabetes at least two abnormal values; fasting or post-absorptive as defined above, are required to establish diagnosis.

3) Oral glucose tolerance test (OGTT):

This should be reserved for specific indications since in florid diabetes, the test is unnecessary, wasteful, and can sometimes precipitate hyperosmolar coma. The indications are (a) equivocal fasting or random blood glucose values, (b) suspicion of gestational diabetes, (c) for clinical or epidemiological research, and (d) to exclude diabetes mellitus. The standard OGTT should be conducted with specific pre-requisites that include ambulatory status, unrestricted diet and cognizance of diabetogenic drugs. The test must be conducted in the morning after an unrestricted diet (more than 150 g carbohydrate for 3 days) and a 10-16 hour overnight fast. The OGTT is contraindicated if there is gross

elevation of post-absorptive blood glucose levels. At zero time a fasting blood sample should be obtained and 300 ml solution of 75 g glucose administered orally over 5 minutes. It is recommended that blood samples are collected at 30 minute intervals for two hours. For venous plasma glucose measured by a specific enzymatic assay both the two hour sample and one other sample should meet following criteria $\geq$ 11.1 mmol/L (i.e. $\geq$ 200 mg/dL) [Welborn, 1984].

Biochemical definition of impaired glucose tolerance (IGT):

This was called previously chemical diabetes as it is an OGTT diagnosis based on a fasting plasma glucose level of $<$ 7.8 mmol/L, plus a two hour plasma glucose level of between 7.8 and 11.1 mmol/L, and an intervening plasma glucose level of 11.1 mmol/L. Individuals with IGT are not diabetic but have an increased risk of progression to diabetes estimated to be at the rate of 1% to 5% per year. Increased susceptibility to atherosclerosic disease is implied, but this is due to association with known risk factors for arterial disease including hypertension, hyperlipemia, adiposity and aging. Risk of retinal or renal complications of diabetes in this group is low or absent [Welborn, 1984].

Classification of the diabetic syndrome:

1) Primary diabetes:

Whenever one is speaking of diabetes, usually the idiopathic type or primary diabetes is the one concerned. It is subdivided into insulin dependent diabetes (IDDM) or type I, which forms about 7-10% of the diabetic population in the U.S. [Olefsky, 1985] and into non-insulin dependent diabetes (NIDDM) or type II. NIDDM is further subdivided into "obese" - forming around 80% - and "non-obese" constituting about 20% [Olefsky, 1985]. The terms "juvenile" and "maturity" onset previously used for classifying diabetes are no longer considered adequate or appropriate. Some patients, mature in years, may develop diabetes that is insulin dependent. They are now classified as type I (IDDM) and need insulin always. There is also the presentation of maturity disease type in young subjects, called "maturity onset diabetes of the young" (MODY), where the youth patient can well be controlled without insulin treatment. Such a patient is a type II (NIDDM) occurring at a young age. It should be remembered that type I (IDDM) diabetics may not always require insulin from the outset - but, by definition, will inevitably need this treatment eventually. Similarly, type II (NIDDM) diabetics may require insulin on a temporary basis as, for instance during a severe infection or to

cover a surgical operation or during the course of pregnancy [Anderson, 1983].

Type I (IDDM) patients are mostly young (less than 30), underweight with a peak age onset 12-14 years. The disease onset is usually rapid with a peak incidence in autumn and winter. They are ketosis prone. They are deficient in insulin stores (beta cell mass less than 10%) and consequently need insulin treatment indefinitely. There is frequently an HLA association (especially B 8 and B 15). The presence of antibodies to islet cells is frequent at onset of diabetes in IDDM patients and hence the term type IA (with islet cell antibodies-ICA-positive) and type IB with ICA negative [Anderson, 1983].

Type II (NIDDM) is the commonest form of diabetes. There is no evidence of seasonal incidence or of any HLA association, and no correlation with islet cell antibodies. Patients with type II (NIDDM) syndrome can be divided clinically into those who are obese and who require and respond to dietary treatment alone, and those without significant obesity who fail to respond completely to dietary measures and who often require treatment with a sulfonylurea to achieve and maintain adequate control. The latter category are usually young relatively and often deteriorate, after a variable period of good

control, and require insulin meaning that pancreatic beta cell failure supervened. A study of the family history may help in determining the prognosis for these patients; a family history of type I (IDDM) will suggest that the patient is likely to become insulin dependent in due course, whereas a family history of type II (NIDDM) suggests that the patient also will fall into this group. The previously known MODY presentation is best regarded as type II diabetes (NIDDM) occurring at a particularly early age and showing a dominant mode of inheritance [Anderson, 1983].

2) Other forms of diabetes:

2.1. Impaired glucose tolerance "IGT", chemical diabetes, borderline or subclinical diabetes:

The oral GTT is abnormal as described above.

2.2. Latent diabetes (or previous abnormality):

Persons currently with normal glucose tolerance who have previously demonstrated diabetes mellitus or IGT.

2.3. Secondary diabetes:

Diabetes here is secondary to:

a) Pancreatic disease (pancreatectomy, pancreatic insufficiency, hemochromatosis, cystic fibrosis, pancreatic calcification, tropical diabetes mellitus, carcinoma of pancreas).

b) Hormonal (excess counterinsulin hormones e.g. Cushing's syndrome,acromegaly, phaeochromocytoma).

c) Drug induced (e.g. thiazide diuretics, steroids, phenytoin, contraceptive pills, frusemide and other loop diuretics, diazoxide).

d) Specific genetic syndromes (Friedreich's ataxia, muscular dystrophy, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, ataxia telangiectasia).

e) Insulin receptor abnormalities of types A and B.

f) Other types: Hyperlipoproteinemia (types III, VI and V), type I glycogenosis, chronic renal failure, hepatic cirrohosis.

2.4. Gestational diabetes:

Glucose intolerance with onset during pregnancy. Although the condition reverts to normal after delivery, it may recur during future pregnancies and there is a high risk of the subsequent development of diabetes later in life [Anderson, 1983].

2.5. Potential diabetes:

The word potential abnormality refers to those individuals who may eventually develop the overt syndrome, but in whom no abnormality of glucose tolerance is demonstrable. Situations in which the potential diabetic state may be suspected include:

1. The identical non-diabetic twin of a diabetic.

2. An individual, both of whose parents are diabetic.

3. A woman who has given birth to a live or still born child weighing 4.5 kg or more at birth.

4. Individuals with circulating pancreatic islet cell antibodies.

5. Individuals with histocompatibility haplotype identical to those of a diabetic sibling [Anderson, 1983].