DEFECTS OF CARBOHYDRATE METABOLISM IN INFANTS OF DIABETIC MOTHERS

THESIS

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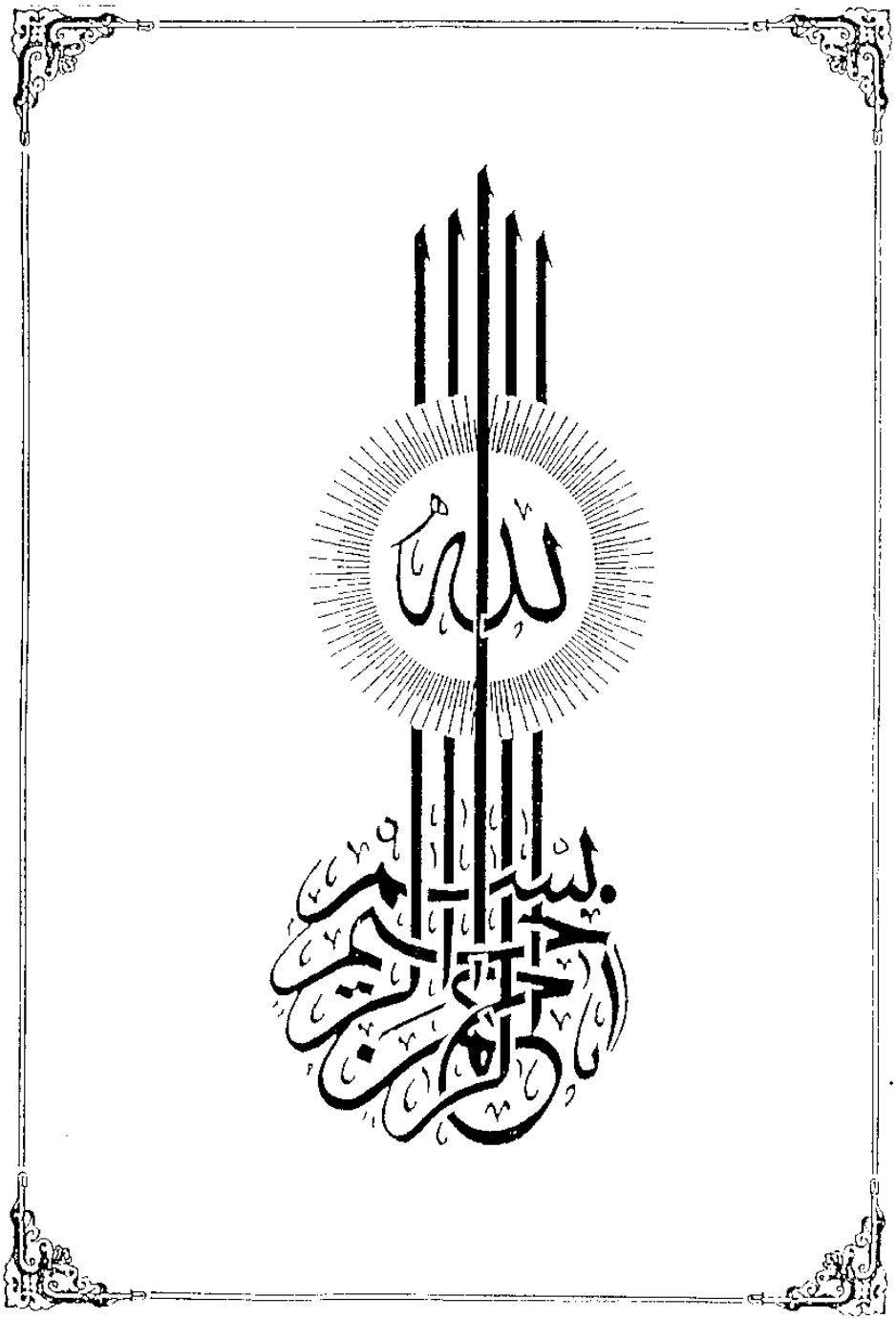

ABBREVIATIONS USED

- IDM's : Infants of diabetic mothers.
- RDS : Respiratory Distress Syndrome.
- CNS : Central Nervous System.
- LDH : Lactate Dehydrogenase Enzyme.
- HLA : Histocompatability Leucocyte Antigen.
- OGTT : Oral Glucose Tolerance Test.
- IDDM : Insulin-Dependent Diabetes.
- NIDDM : Non-Insulin-Dependent Diabetes.
- HPL : Human Placental Lactogen.
- HCS : Human Chorionic Somatomammotropin.
- G-1-P : Glucose -1- Phosphate.
- G-6-P : Glucose -6- Phosphate.
- FFA : Free Fatty Acid.
- COA : Coenzyme A.
- IV : Intravenous.

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INTRODUCTION

Infants of diabetic mothers (IDM's) are considered high-risky infants, they have greater morbidity than infants of non diabetic women. The combination of diabetes mellitus and pregnancy represents a high-risk situation in caring for both mother and fetus (Ayromlooi, 1980).

Diabetes is a disease of particular interest as far as fetal development is concerned for it results in a naturally occurring disturbance of homeostasis that is variable but persistent throughout the whole of pregnancy, resulting in high incidence of toxaemia and polyhydramnios. The exact cause of the fetal complications associated with the disease is not fully understood. Any disturbance of maternal metabolic homeostasis is liable to interfere with fetal development, which may well explain why untreated diabetes is associated in pregnancy with an increased incidence of abortion, fetal abnormality and perinatal mortality. Likewise, until shown otherwise, it is reasonable to assume that it is the disturbance of maternal carbohydrate metabolism that is most likely to be responsible for the tendency to fetal macrosomia, hypoglycaemia in the newborn and even some instances of fetal death in diabetic pregnancy. (Beard and Oakley, 1976). Also these infants are more likely to be affected by hyperbilirubinemia, hypocalcaemia and respiratory distress syndrome (RDS), immediately after delivery.

Carbohydrate tolerance and insulin requirements seem to differ greatly during pregnancy, and despite careful treatment, the pregnancy may result in the birth of a newborn infant that either will be stillborn or eventually dies in the neonatal period from congenital anomalies or postnatal complications (Ayromlooi, 1980).

Carbohydrate metabolism occupies an essential role in energy production in the CNS. The metabolism of glucose is not merely a preferred pathway but an obligate path for the maintenance of physiologic function. Glucose and oxygen are important for the production of energy, and without an adequate supply of each, brain can neither develop nor survive (O'Neill, 1974).

Glycolysis "Embden-Meyrhof pathway" is the oxidation of glycogen or glucose to pyruvate or lactate. The activity of glycolytic enzymes is sensitive to induction by insulin. (Harper et al, 1977). So, it is important to study some of the enzymatic activity of glycolytic pathway in case of infants of diabetic mothers (IDM's).

AIM OF THE WORK

This study is a trial to put light on the status of carbohydrate metabolism in infants of diabetic mothers. As we will estimate the level of certain enzymes mainly aldolase and lactate dehydrogenase (LDH), as well as the level of serum glucose and lactic acid in cord blood of these infants.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus is a complex disease that can no longer be considered a single disease entity (Alford and Best, 1986). But it is considered as a syndrome of chronic hyperglycaemia of various aetiologies. It may present with acute symptoms that include thirst, polyuria and unexplained weight loss (classic onset) and these can progress to life threatening Ketoacidosis or hyperosmolar coma. Subacute symptoms include the above, together with pruritis vulvae, balanitis and other skin infections (Welborn, 1984).

A wide variety of derangements in carbohydrate, fat and protein metabolism is found without a clear causal relationship to the vascular and neurologic manifestations. In view of importance of the latter, it has been postulated by some that vascular disease is the primary defect; others consider it a complex disease of glucose metabolism. Although insulin deficiency is perhaps the most frequent feature, not all diabetics lack insulin (Kellen, 1980).

Aetiology :

In primary diabetes there is no obvious cause but a number of factors have been implicated :

1. Genetic :

There is certainly some degree of hereditary disposition. Early-onset insulin dependent diabetes has a positive association with Histocompatability Leucocyte Antigen (HLA) Loci DR_3 and DR_4. There is no HLA association with late-onset diabetes but despite this the condition is more strongly familial. The children of diabetics have an increased incidence of the disease. (Fletcher, 1982).

2. Autoimmunity :

Some cases of insulin-dependent diabetes are clinically associated with autoimmune disease such as Addison's disease, autoimmune thyroiditis and pernicious anaemia, prompted a search for pancreatic islet cell autoimmunity in diabetic patients. Islet cell antibodies have been found in variable proportions with type I diabetes. (Rose et al., 1982).

3. Infections :

There are peaks of incidence of early-onset diabetes at ages 12 and 20 years, and during the autumn and spring. Perhaps this is related to an increased incidence of certain infections causing "isletitis". (Fletcher, 1982). Correlation between viral infections and development of type I diabetes has been reported in cases of mumps, rubella (Menser et al., 1978), and type 4 coxackie B virus. (Yoon et al., 1979; Rose et al., 1982).

4. Insulin Production :

In early-onset Ketotic diabetic there is undoubtedly a failure of insulin production and the plasma insulin is low or absent. In the obese Late-onset non-Ketotic diabetic, the plasma insulin is normal or even raised and responds to a carbohydrate load. Presumably there is some factor which prevents its effective action (Fletcher, 1982). The ineffectiveness of secreted insulin may be caused by many factors which have been classified according to their site of interference with insulin action in relation to insulin receptors. Prereceptor inhibitors consist of anti-insulin antibodies, while receptor inhibitors include insulin receptor antibodies and "down" regulation of receptors by hyperinsulinism, as in B-cell adenema. Secondary or postreceptor defects may result either from poor responsiveness of principal target organs as in obesity, hepatic cirrhosis or from hormonal excess of glucocorticoids, progesterone, thyroxine or growth hormone, which may be caused by endocrinal disease or drug intake (Karam, 1985).

5. Obesity :

Obese persons tend to have raised levels of plasma insulin and to be relatively insulin resistant. There is no doubt that the majority of Late-onset diabetics are overweight. In most such patients calorie restrictions will lower plasma glucose, even to normal (Fletcher, 1982).

6. Stress :

Physical stress may induce a diabetic state. Any major physical trauma such as severe accident, burns, surgery or myocardial infarction

impairs insulin release. Pregnancy (gestational diabetes) or the administration of corticosteroids can have a similar effect on the plasma glucose although the medication may be different. In most patients carbohydrate tolerance is restored as and when the stress passes off but occasionally the diabetes persists (Fletcher, 1982).

Chemical Pathology :

Whatever the aetiology, in all cases of diabetes hyperglycaemia results from deficiency of insulin. This is absolute in insulin-dependent diabetes (IDD) and relative in non-insulin-dependent diabetes (NIDD). When the glucose concentration in the blood exceeds the capacity of the renal tubules to reabsorb it from the glomerular filtrate, Glucosuria occurs. Glucose prevents reabsorption of water in the renal tubules due to its high osmolarity, so polyuria and nocturia occur. Polyuria leads to water and electrolyte loss, but so long as thirst mechanism is intact, it is compensated by polydipsia.

Impaired utilization of carbohydrate results in a sense of "fatigue", and causes two main compensatory mechanisms, under the influence of growth hormone and adrenocortical hormones, to operate in an attempt to provide alternative metabolic substrate.

The compensatory mechanisms are :

1. Increased glycogenolysis and gluconeogensis.
2. Increased lipolysis leading to raised fasting plasma concentration of non-esterified fatty acids. Fatty acids are degraded by the liver with the production of molecules of acetyl coenzyme-A which enter the citric acid cycle by condensation with oxaloacetic acid. In severe diabetes more is formed than can enter the citric acid cycle, instead acetyl Co A is converted to acetoacetic acid, beta-hydroxybutyric acid and acetone. These acids are called "Ketone bodies" which are oxidized and utilized as