METABOLIC CHANGES IN DIABETES MELLITUS

Assay
Submitted for partial fulfilment of the degree of M.S.
(Medicine)

BY
MOAWIAH ALI AMIN RIZIK EL MASRI.

Ain Shams University
Faculty of Medicine

Supervised by :

Prof. Dr. Kamal El-Shawarbi

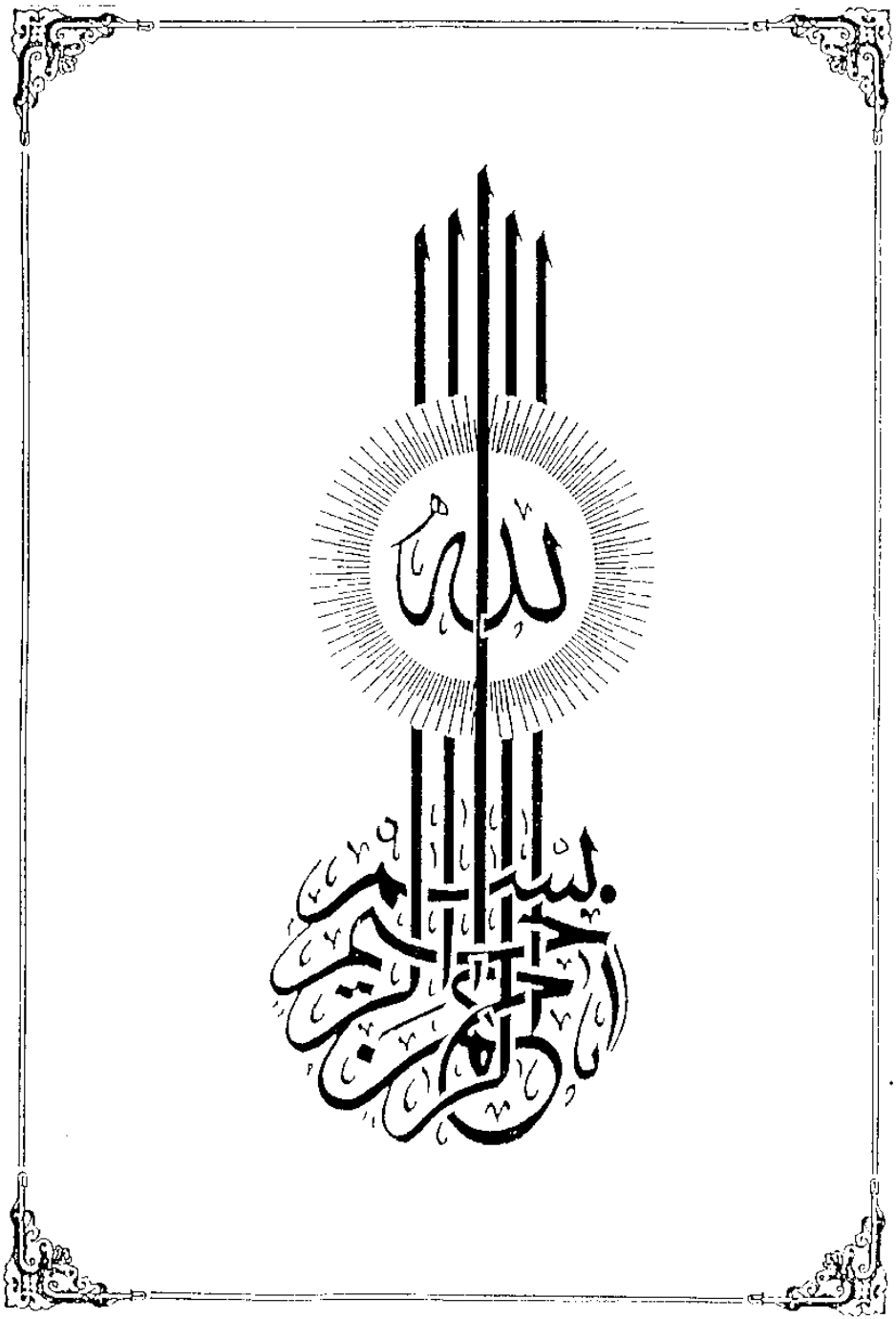
1977

ACKNOWLEDGEMENT

I would like to express my deepest gratitude to professor Dr. Kamal El-Shawarbi head of medicine for his suggestions, guidance and supervision.

I would like also thank all the staff of the department for their kind, and encouragement.

Dr. MOAWIA. ALI.



INDEX

------oOo------

METABOLIC CHANGES IN DIABETES MELLITUS

Diabetes mellitus is a common disorder of energy metabolism which results from an absolute or functional deficiency of insulin - Insulin deficiency leads to impairement of glucose transport, to a decrease in storage and synthesis of lipids, and to a decrease in synthesis of protein. These biochemical alterations lead to specific acute and chronic clinical features.

Diabetes mellitus is probably the most common serious endocrine problem, it occurs in all races and in all geographic areas. Its geographic prevalence varies widely, in some measure in relation to differences in gene frequencies, but likely more in relation to nutritional and other enviromental factors. Epidemiologic studies are in general agreement that arout one per cent of adults in the united states are known to have diabetes, and that a comparable number, as may be determinal by screening procedures, have asymptomatic carbohydrate intolerance or "chemical diabetes".

The prevalence of diabetes increases with age and body weight. Diabetes occurs in approximately 1 of 2500

children under 15 years of age and 1 of 1000 school age children, with no sex preference. "Nelson,[20] 1975" . It is very uncommon in infancy. The prevalence of known diabetes increases from 8 per 1000 adults in the age range from 25 to 44 years to over 60 per 1000 in those over 60 years of age. About 4 per cent of persons known to have diabetes have had the onset of clinical features before they were 15 years of age. Screening of sibling with diabetes has disclosed that 12 to 25 per cent have asymptomatic carbohydrate intolerance. "Cooke[4], et al., 1966".

There is overwhelming evidence that most cases of diabetes mellitus are genitically determined. The mode of genetic transmission, however, is still uncertain, as there is no specific genetic marker. Autosomal recessive transmission has been most frequently proposed, in which case one would anticipate the eventual development of diabetes in 100 per cent of children of two diabetic parents and of identical twins of diabetics. "Cooke[4] et al., found overt diabetes in only 4.1 per cent of children of two diabetic parents, and felt that only 25 per cent would

eventually becomes, diabetic. Some have suggested that diabetes is best explained on a multifactorial or polygenic basis. Its proposed that there are several genes that may affect carbohydrate metabolism and that an accumulation or association of genetic defect would lead to increasing biochemical and clinical alterations. The expression of these genetic disturbances is proposed to be greatly influenced by a variety of enviromental factors, such as diet, body weight stress, and soforth.

Action of Insulin[31] :

Insulin is a powerful hormone with broad influences. Directly or indirectly, it affects the structure and function of every organ in the body - indeed, of every biochemical constituent.

The amount of insulin action depends at least on the :

a) amount of insulin secretion,
b) insulin distribution,
c) amount of insulin binding to its specific receptor,
e) types and amounts of nutrients inside and outside the cell,
f) types of ions and their concentrations , and
g) amounts and types of other hormones.

Some of the tissues that insulin has been shown to affect are : muscle (skeletal & heart), adipose tissue, liver, leucocytes, mammary glands, seminal vesicles, fibroblasts, smooth muscle cells, cartilage and bone, skin, lens, pituitary, peripheral nerves, aorta and thymocytes.

Insulin's main function are to stimulate anabolic reactions involving carbohydrate, fat, proteins and nucleic acids. It catalyzes the formation of macromolecules in cells which then are used in cell structure, energy stores and regulation of many cell function. Insulin stimulates the synthesis of protein from amino acids, nucleic acids from mononucleotides, polysaccarides from monosaccharides, and lipids from fatty acids.

The following are some of the specific actions of insulin.

Insulin increases :

a) Plasma membrane transfere of glucose and certain other monosaccharides, some amino acids, some fatty acids, potassium and magnesium;

b) Magnesium activated (Na + K) ATPase activity;

c) Glucose oxidation;

d) Glycogenesis;

e) Lipogenesis;

f) Proteogenesis, and;

g) Formation of ATP, DNA, and RNA.

Insulin decrease :

a) Glycogenolysis,

b) Lipolysis,

c) Proteolysis,

d) Gluconeogenesis,

e) Ureogenesis, and;

f) Ketogenesis.

Some of the activities of insulin results from it's inhibition of the supply of CAMP, causing less activity of protein kinase. This is associated with less phosphorylation of enzymes, but an increase in activity of some nonphosphorylated enzymes. The latter enzymes tend to promote anabolism : glycogenesis, proteogenesis, lipogenesis, increased levels of nucleic acids, and mitogenesis. Insulin does not stimulate glucose transport in red blood cells or in the brain, nor does it promote tubuler reabsorption of glucose by kidney

or glucose absorption by intestinal mucosa. "Wiliams,[26] 1974".

Pathogenesis of Diabetes Mellitus :

Diabetes mellitus occurs when there is a functional deficiency in circulating insulin. This may occur through several distinctly different mechanisms. The traditional view is that it results from a deficiency of synthesis and or release of insulin from the beta cells of the pancreas, in which case the concentration of insulin in the peripheral circulation would be zero or low, and the usual response to challenge with insulinogenic agents would be absent or grossly blunted. In adult diabetics, however, or in children with chemical diabetes, isulin levels may be higher and the responses to stimulation may be greater than normal. There are three possible explanations.

I- Defective insulin molecule concept :

O'Brien has proposed that certain forms of diabetes may results from the production of a biologically defective insulin molecule. Such a molecule would be detected by immunoassay as "Insulin" but have decreased biologic activity.

The discovery of pro-insulin, the naturally occuring immediate precursor of insulin, may fit into this concept. Pro-insulin, a single-stranded, cross-linked polypeptide, is found in the general circulation of normal subjects in very minimal concentration or not at all. It is found in increased concentration in obesity and in some cases of islet cell adenoma.

Studies to date do not suggest that the hyperinsulinism commonly seen in maturity - onset diabetes can be explained on the basis of large amounts of pro-insulin in the circulation.

II- Sluggish insulin release concept :

In the normal individual the ingestion or injection of insulinogenic compounds such as glucose, sulfonylurea compounds, aminoacids or glucagon leads very rapidly to release of insulin from the pancreas. There is evidence that in patients with maturity onset type of diabetes, a basic defect is an impairment in insulin release following glucose to rise more rapidly and to higher level than normal.

III- Insulin resistance concept :

In acromegaly, in cushing syndrome and in patients with pheochromocytoma, specific hormones, elaborated in excess,

effectively antagonize the action of insulin at one or several biochemical sites. Most patients with diabetes have no clinically apparent features that suggest excess of hormone antagonist to insulin. Growth hormone continues of hormone antagonist to insulin. Growth hormone continues to be of special interest in this regard. Growth hormone levels are frequently elevated in overt diabetes, particularly in juvenile diabetics under poor control.

Other factors that may effectively interfere with the action of insulin at the cell membrane include a material extracted by Vallance-Owen from serum of diabetics, which antagonizes insulin action in vitro and is known as synalbumin. It is considered by some as a specific marker for diabetes. A highly specialized form of insulin antagonism occurs in patients with lipoatrophic diabetes. The antagonist, the so-called lipid mobilizing factor, is probably either pituitary or hypothalmic in origin.

Diabetes is reported to be more common in children who have had congenital rubella - pancreatitis may rarely result in diabetes, specific examples occuring occasionally

in mumps. Diabetes may be a late complication of optic fibrosis. Levels of antibodies to coxackie virus B have been reported to be elevated in children with recently diagnosed diabetes.

Diabetes occurs in increased incidence with such autoimmune endocrine diseases as Hashimoto's thyroiditis and Addison's disease. Antibodies to thyroid, adrenal and gastric tissues are found in approximately 15 per cent of children with diabetes and are found in increased incidence and titers in families of such children.

Disturbances in the physiologic processes occur in proportion to the degree of insufficiency of insulin, the rate of utilization of sugar and the respiratory quotient decrease : hyperglycemia and glycosuria ensue. Norishment is thus lost. As the loss of sugar increases, protein is drawn upon in an attempt to replace sugar to supply energy and as a result, a negative nitrogen balance ensues, and wasting of the muscle becomes prominent. There is an increased output of sugar from the liver. synthesis of fat from carbohydrate is reduced or even stopped. Also, the catabolism of fat is speeded up in direct proportion to the

reduction of carbohydrate utilization. As lipolysis is accelerated, a point is reached when ketones are produced in quantities beyond the capacity of the tissues to utilize them, and the excretion of ketones in the urine follows.

Unless these processes are favourably influenced by treatment, they tend to progress until the capacity to excrete ketone bodies is reached. It is at this stage that the retention of ketone bodies in the blood becomes detectable in an increasing amount. Unchecked, these processes, with great latitude in the ranges of progressiveness, will lead to a fatal outcome.

Setten, in investigating biologic processes under normal conditions, a considerable portion of the body fat is broken down resynthesized daily and that insulin is quantitatively more involved in the synthesis of fat from carbohydrates than it is in the synthesis of glycogen. Indeed, about ten times as much as sugar goes into the formation of glycogen. In the diabetes, both of these processes fat and glycogen production are interfered with to a great degree, and sugar, normally used in fat and

glycogen production, is not utilized in normal amounts but accumulates in the blood and is excreted.

The disturbance in metabolism in diabetes are remarkedly accelerated and increased in degree by acute infections, and, toxeamias. Facilities now at hand have reduced almost to the disappearing point, the risk of which these complications formerly held.

Fifty-five years age, Joslin reports, 63.8 per cent of the patients died of diabetic coma, where as now a death due to this complication is unusual - 1.5 per cent in 1944-1956, and, no death in 1956.

Formerly, attention was focussed on the changes recorded above, and their immediate ramifications. The picture has changed.

Diabetes, by lending itself well to control with diet, insulin and oral hypoglycemic agents, has been subduced, and life has been remarkably prolonged. As the acute difficulties yielded to therapy and longevity was