Islet Amyloid Polypeptide Plasma Concentration in NIDDM. Relatives.

Thesis

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HESHAM MOHAMMED RAFEE
M.B.B.CH.

Supervisors

Prof. Dr. Moghazy Aly Mahgoub.
Prof. of internal medicine and endocrinology.
Faculty of medicine. Ain Shams University.

Dr. SALAH SHELBAIA.
Assist. Prof. of internal medicine and endocrinology.
Faculty of medicine. Ain Shams University.

Ain Shams University.
Faculty of medicine
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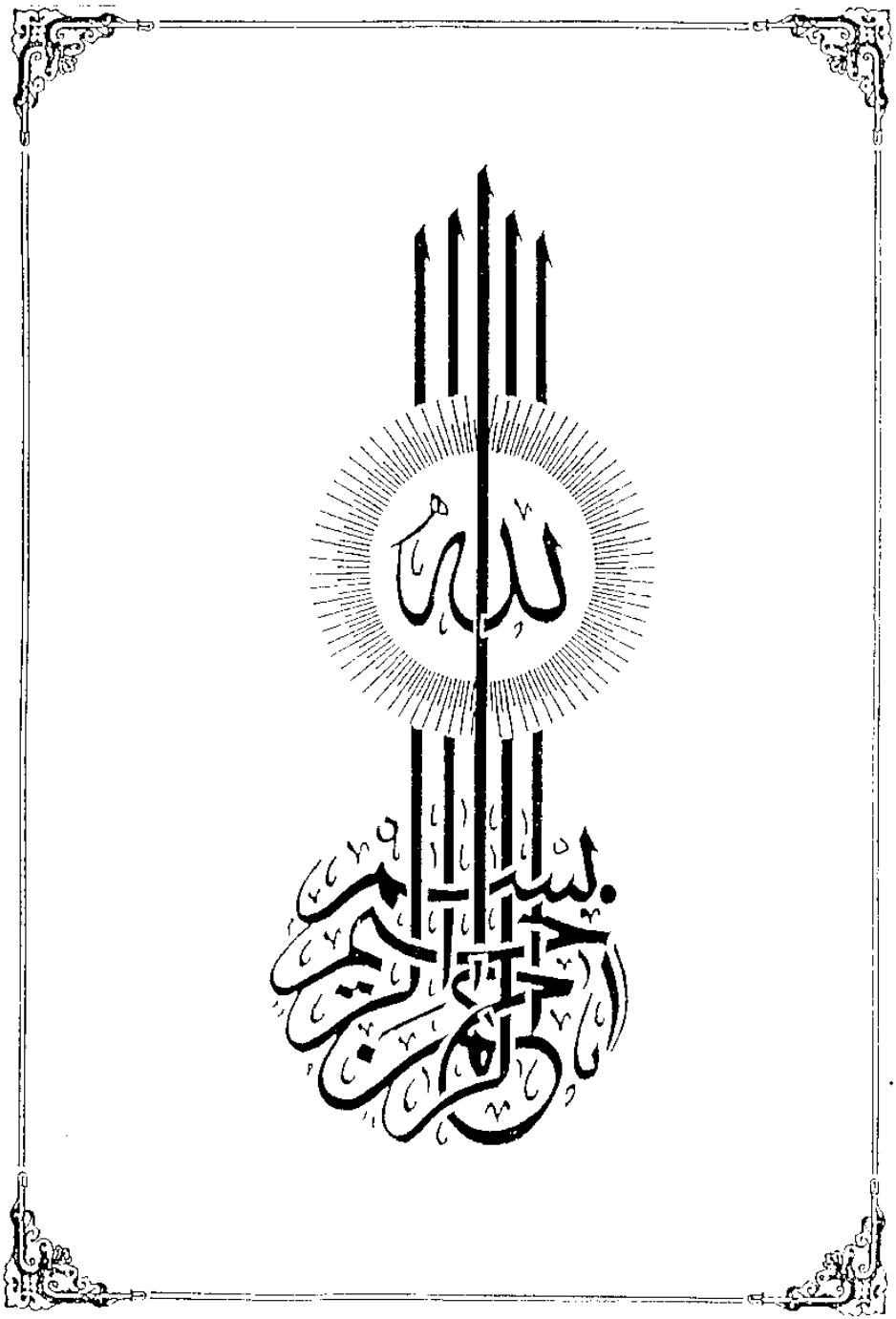

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INTRODUCTION TO THE WORK

Amylin or islet amyloid polypeptide (IAPP), is an amidated thirty-seven amino acid peptide which was initially isolated from insulinoma tissue (**Westermark et al 1987**). Amylin is secreted by similar stimuli to those secrete insulin from the beta cell of pancreas (**Edward et al 1992**).

Amylin aggregate to form amyloid deposits in the beta cell (**Hiramatsu et al 1994**). This amyloid deposits impair the beta cell function by damaging and covering beta cell (**Koopmans et al 1992**). Furthermore, amylin reduce insulin secretion and induce insulin resistance **(Lutz et al 1994)**. which may be significant in the pathogenesis of non-insulin-dependent diabetes mellitus **(Inoue et al 1992)**.

Amylin is present in normal human pancreatic islets **(Hartter et al 1990),** while its plasma level are elevated in insulin resistance conditions such as obesity and impaired glucose tolerance. In contrast, amylin is deficient in insulin-dependent diabetes mellitus (**Rink et al 1993**).

AIM OF THE WORK

The aim of this work is to study the plasma amylin level of the first degree relatives of non-insulin-dependent diabetes mellitus patients and correlate its value with glucose tolerance.

CHAPTER I

DIABETES MELLITUS

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1- Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia due to relative insulin deficiency, or resistance or both. It is common and affects approximately 30 million people worldwide. With approximately 5000 new cases per year. Diabetes usually irreversible and although patients can have a reasonably normal life-style, its late complications result in reduced life expectancy and considerable uptake of health resources. Macrovascular disease lead to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, while microvascular damage result in diabetic retinopathy and contributes to nephropathy **(John V Andersan et al 1994.).**

Insulin is the key hormone involved in the storage and controlled release within the body of the chemical energy available from food. It is synthesized in the beta cell of the pancreatic islets in the form of proinsulin, which is stored in secretory granules close to cell membrane. A biochemically inert peptide fragmet known as connecting (C) peptide breaks from proinsulin in the secretory process, so that equimolar quantities of insulin and C-peptide are released into the circulation. Insulin enters the portal circulation and is carried to the liver, its prime target organ. About 50% of secreted insulin is extracted and degraded in the liver ; the residue is broken down by the kidney. C-peptide is only partially extracted by the liver (and hence provides a useful index of the

rate of insulin secretion), but is mainly degraded by the kidney (**Kumar et al 1994).**

Blood glucose levels are closely regulated in health, despite the varying demands of food, fasting and exercise. The principal organ of glucose homeostasis is the liver, which absorbs and stores glucose (as glycogen) in the postaborptive state and releases it into the circulation between meals to match the rate of glucose utilization by peripheral tissues. The liver also manufactures glucose from breakdown of fat and protein by the process of gluconeogenesis. About 200 gm of glucose is produced and utilized each day. More than 90% is derived from the liver, three quarters from the glycogen and one quarter from gluconeogenesis. The remaining 10% derives from renal gluconeogenesis. The brain is the major consumer of glucose. Its requirement is 100 gm daily. Glucose uptake by the brain is obligatory and is not dependent on insulin. But, other tissues as fat and muscle are facultative glucose consumers. Insulin is the major regulator of glucose metabolism. At low insulin level, glucose production is maximal and utilization is minimal; at high level the situation is reversed **(Edwin A.M. et al 1993).**

2- Classification of Diabetes Mellitus

Diabetes may be primary or secondary. Although insulin-dependent diabetes mellitus (IDDM, type I diabetes) and non-insulin-dependent diabetes mellitus (NIDDM, type II diabetes) represent two distinct disease from the epidemiological point of view, clinical distinction may sometimes be difficult. The two disease processes should, in clinical terms, be visualized as opposite end of a continuous spectrum (**Kumar et al 1992).**

A classification of diabetes is given in table (1-1). The basis categories are those recommended by the National Diabetes Data Group except for division into primary and secondary types. Primary implies that no associated disease is present, while in the secondary category some other identifiable condition causes or allows a diabetic syndrome to develop. Insulin dependence in this classification is not equivalent to insulin therapy. Rather, the term means that the patient is at risk for ketoacidosis in the absence of insulin. Many patients classified as non-insulin-dependent require insulin for control of hyperglycemia, although they do not become ketoacidotic if insulin is withdrawn.

The term type I is often used as a synonym for insulin-dependent diabetes (IDDM), and type II diabetes has been considered equivalent to non-insulin-dependent disease (NIDDM). This probably is not ideal, since some patients with apparent non-insulin-dependent diabetes may in fact be destined to become fully insulin-dependent and prone to ketoacidosis. The subset of patients in this category are nonobese subjects who usually express HLA antigens associates with susceptibility to insulin-dependent diabetes and have evidence of an immune response to islet cell antigens. For this reason, it has been suggested that the classification shown in table (1-1) be modified such that the terms insulin-dependent and non-insulin-dependent describe physiologic states (ketoacidosis-prone and ketoacidosis- resistant, respectively), while the term type I and type II refere to pathogenetic mechanisms (immune-mediated and non-immune mediated, respectively). Using such a classification, three major forms of primary diabetes would be recognized:-

1-Type I insulin-dependent diabetes.

2-Type I non-insulin dependent diabetes.

3-Type II non-insulin dependent diabetes.

category 2 is an intermediate stage of autoimmun destruction in which sufficient insulin remains to prevent ketoacidosis but not to maintain normal blood glucose. The NIDDM stage of type I diabetes likely occur when the autoimmune process begins at an older age and progresses at a slower rate. It is infrequently seen when IDDM appears in childhood or early adolescence.

Secondary forms of diabetes encompass a host of conditions. Pancreatic disease, particularly chronic pancreatitis in alcoholics, is a common cause. Destruction of the beta cell mass is the etiologic mechanism. Hormonal causes include pheochromocytoma, acromegaly, cushing syndrome, and therapeutic administration of steroid hormones. "stress hyperglycemia," associated with severe burns, acute myocardial infarctions, and other life-threatening illnesses, is due to indogenous release of glucagon and catecholamines. Mechanisms of hormonal hyperglycemia include varying combinations of impairment of insulin release and induction of insulin resistance. A large number of drugs can lead to hyperglycemia, but most simply produce impaired glucose tolerance. Hyperglycemia and even ketoacidosis may occur as a result of abnormalities at the level of the insulin receptor. The dysfunction may be due to quantitative or qualitative defects in the receptor itself or to antibodies directed against it. The mechanism is essentially pure insulin resistance. A number of genetic syndromes are associated with impaired glucose tolerance or hyperglycemia. The three most common are the lipodystrophies, myotonic dystrophy, and ataxia-telangiectesia. The final

category, other, is poorly defined and is meant to include any condition which dose not fit elsewhere in the etiologic scheme. The appearance of abnormal carbohydrate metabolism in association with any of the secondary causes dose not necessarily indicate the presence of underlying diabetes, although in some cases a mild, asymptomatic primary diabetes may be made overt by the secondary illness.

Table (1-1) Classification of diabetes

PRIMARY

1- Insulin- dependent diabetes mellitus (IDDM, type 1)

2- Non- insulin- dependent diabetes mellitus (NIDDM, type 2)

a-Nonobese NIDDM.

b- Obese NIDDM.

c-Maturity- onset diabetes of the young (MODY)

SECONDARY

1-Pancreatic disease.

2-Hormonal abnormalities.

3- Drug or chemical induced.

4- Insulin receptor abnormalities.

5- Genetic syndromes.

6- Other.

(Unger-RH and Foster-DW 1992).

Non-insulin-dependent diabetes results from an imbalance between insulin sensitivity and insulin secretion. Both longitudinal and cross-