Study of the Serum Amylin (Islet Amyloid Polypeptide) Level in Obese Subjects

Thesis submitted for partial fulfillment of the M.D. Degree in Endocrinology

Presented by

MOHAMED FATHALLA EL-KHOLY

M.Sc. Endocrinology - Ain Shams University

Under the supervision of

PROF. DR.
MOGHAZY ALY MAHGOUB
Professor of Internal Medicine and Endocrinology
Faculty of Medicine-
Ain Shams University

PROF. DR.
SALAH SHELBAIA
Professor of Internal Medicine and Endocrinology
Faculty of Medicine-
Ain Shams University

DR.
HALA MAHFOUZ
Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine-
Ain Shams University

DR.
MOHAMED REDA HALAWA
Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine-
Ain Shams University

DR. AFAF ABDEL-WAHAB
Fellow of Endocrinology
Faculty of Medicine-Ain Shams University

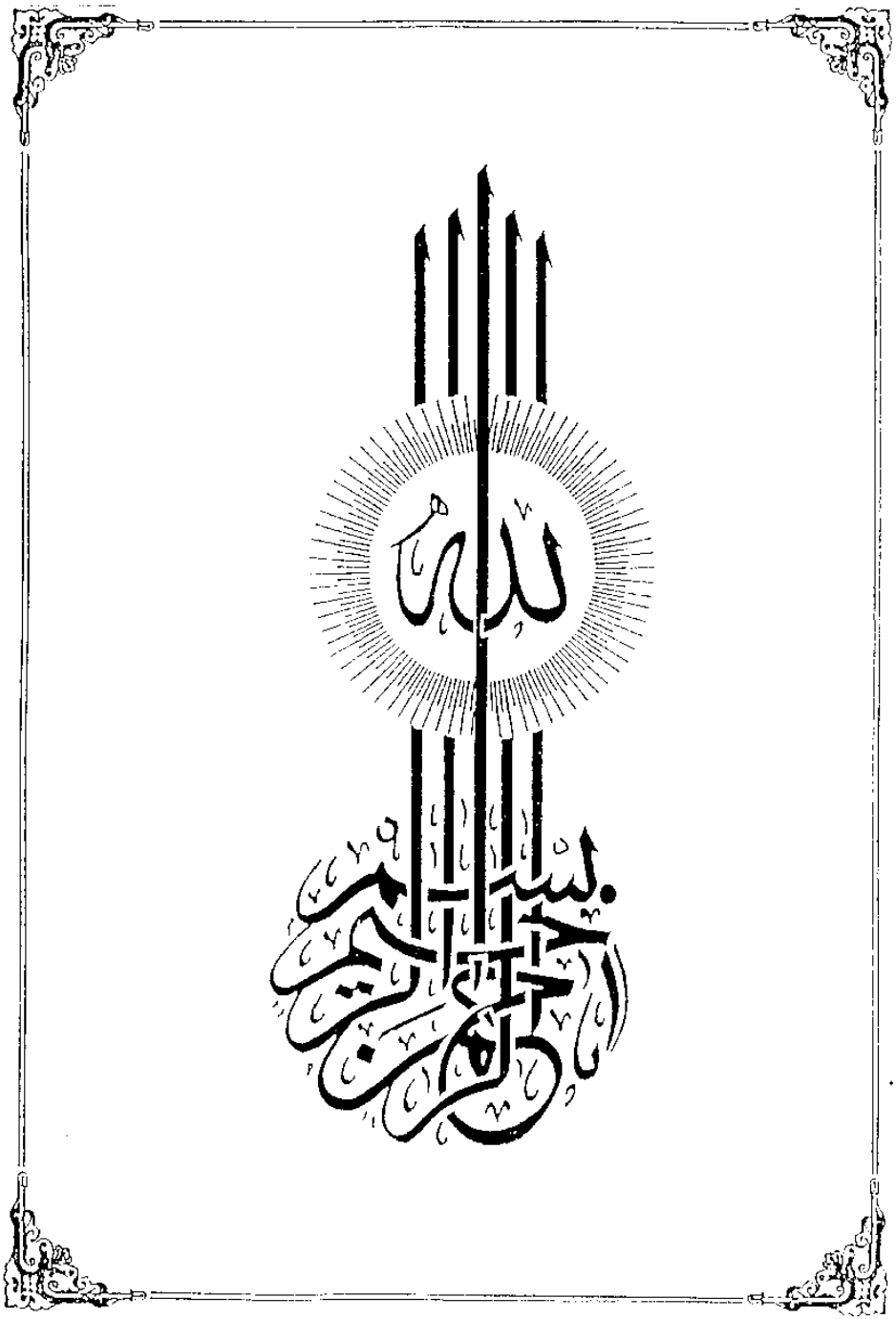
Faculty of Medicine
Ain Shams University
1998

بسم الله الرحمن الرحيم

" قالوا سبحانك لا علم لنا
إلا ما علمتنا أنك أنت
العليم الحكيم "

صدق الله العظيم

(سورة البقرة الاية ٣٢)



Acknowledgment

I wish to express my deep gratitude to Prof. Dr. ***Moghazy Aly Mahgoub****, Professor of Internal Medicine and Endocrinology, Ain Shams University, for his meticulous supervision, scientific support and judicious guidance despite many other demands on his time.*

I am very grateful to Prof. Dr., ***Salah Shelbaia****, Professor of Internal Medicine and Endocrinology, Ain Shams University, for his kind supervision, continuous encouragement, enthusiastic support and great help throughout the course of this thesis.*

My sincere thanks are due to Dr., ***Hala Mahfouz*** *and Dr.,* ***Mohamed Reda****, Lecturers in Internal Medicine and Endocrinology, Ain Shams University, for their helpful suggestions, while revising fully the manuscript.*

I would like to express my deep gratitude to Dr., ***Sadia Mohamed*** *and Dr.,* ***Nagwa Abdel Ghani,*** *for their advice and help in providing me with valuable material in the laboratory part of this thesis.*

Mohamed Fathalla

1998

List of Contents

List of Tables

List of Figures

Introduction and Aim of the Work

INTRODUCTION AND AIM OF THE WORK

Amylin (islet amyloid polypeptide) is 37 amino acid peptide hormone mainly produced by islet beta cells, co-secreted with insulin. Actions of amylin is mainly exerted on fuel metabolism as it antagonises actions of insulin on skeletal muscles but not on adipose tissue so it stimulates process of glycogenolysis and increase lactate turnover which acts as substrate for gluconeogensis in liver increasing hepatic glucose output. So amylin induces insulin resistance in skeletal muscles. Amylin inhibits insulin secretion.

Obesity is a very important risk factor in development of insulin resistance especially in patient with type II diabetes.

Aim of the Work

To study the serum amylin level in obese subjects (android and gynoid) and if it has any relation with abnormalities in glucose tolerance in these subjects.

Amylin

AMYLIN

STRUCTURE OF AMYLIN (ISLET AMYLOID POLYPEPTIDE):

Amylin also named islet amyloid polypeptide (IAPP) or diabetes associated peptide (DAP). 37 amino acid peptide first isolated, purified and characterised from the amyloid deposites in the pancreas of type II diabetics ***(Pittner et al, 1994)*** and it was subsequently identified as the principal constituent of amyloid deposits found in the pancreatic islets of 90% of patients with NIDDM ***(Amiel, 1993)***.

Amylin is present in normal human pancreatic islets where it is synthesized, copackaged and secreted primarily from pancreatic beta cells along with insulin and both under common regulation ***(Pittner et al, 1994)***. The amino acid sequence is depicted as follows:

Lys-Cys-Asn-Thr-Ala-Thr-Cys-Cys-Ala-Thr-Gln-Arg-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Ala-Ile-Leu-Ser-Ser-Thr-Asn-Asn-Val-Gly-Ser-Asn-Thr-Tyr ***(Betsholtz et al, 1990)***.

Amylin has structural and functional relationship to two other messenger proteins, calcitonin and calcitonin gene related peptide (CGRP). Amylin has relatively potent calcitonin like activity on bone metabolism and weaker calcitonin gene related peptide like activity on vasculature ***(Pittner et al, 1994)***. CGRP is a potent

vasodilator, while amylin is 100 times less potent than CGRP in reducing blood pressure ***(Cooper, 1995; Beaumont et al, 1994).*** CGRP is widely distributed in the nervous system and in the calcitonin producing thyroid C. cells ***(Westermark et al, 1996).***

CHEMICAL AND BIOLOGICAL ASPECTS OF AMYLIN

CGRP is encoded by a single copy gene located in the human being on chromosome 12. CGRP is expressed as a 93 a.a. (murine) and 98 a.a. (human) prepropeptide that is processed enzymatically resulting in removal of amino acid and carboxy terminal propeptide segments ***(O'Brien et al, 1993).***

The sequence of NH_2 and COOH terminal regions of IAPP are invariant suggesting that it is perhaps these regions that interact with IAPP receptors. Final IAPP molecule is represented by amino acids 31 to 70 of the precusrsor molecule ***(Steidsberg and Wilander, 1991; Nishi et al, 1990).***

Rat islet amyloid polypeptide differs from human islet amyloid polypeptide particularly in the region of amino acids 25-28 which is important for amyloid fibril formation. In rat and mouse, diabetes associated islet amyloid does not develop ***(Hoppener et al, 1994).***

IAPP is present in normal islets in significant amounts as judged by immunocytochemical staining and

has been localized by electron microscopy to the secretory granules of the beta cells ***(Johnson et al, 1988; Lukinius et al, 1989).*** The mRNA concentrations in secretory granules in rats are about 10% of these of insulin ***(Amiel, 1993).*** In humans, immunohistochemical and physiological evidence supports the notion that beta cells are heterogenous with respect to their relative content of insulin and IAPP. Therefore although IAPP is co-secreted with insulin in response to a variety of well known secretagogues, the molar ratio of these two proteins that is released from the islets may vary, depending upon the glucose concentration and prevailing metabolic milieu ***(O'Brien et al, 1993).***

As regards localization of IAPP inside the islet cells, examination of human pancreas from non-diabetic subjects showed that the greatest density of immunoreactivity for IAPP was found in the electron dense regions of some lysosomal or lipofuscin bodies, while to a lesser degree in secretory granules and in lamellar bodies. Occurrence of islet amyloid is paradoxically associated with loss of islet amyloid polypeptide immunoreactivity in beta cells ***(Westermark et al, 1993).***

Expression of human IAPP was localized to the islets of Langerhans, anterior pituitary and brain in transgenic animals ***(Fox et al, 1993).*** Concerning the metabolism of IAPP Ludvik et al ***(1994),*** suggested a