# PANCREATIC INSULIN RESERVE IN CHRONIC RENAL FAILURE

**A THESIS**

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*The M.D. Degree in Internal Medicine*



**By**

**HOWAYDA ABDELHAMID ELSHINNAWY**
***M.B.,B.Ch., M.Sc.***





**Supervisors**

**PROF. DR. Badawy Labib Mahmoud**
*Professor of Internal Medicine & Nephrology,*
*Faculty of Medicine, Ain Shams University.*

**PROF. DR. HUSSEIN EL SAYED EL DAMASY**
*Professor of Internal Medicine & Endocrinology,*
*Faculty of Medicine, Ain Shams University.*

**DR. Hany Ali Refaat**
*Assistant Professor of Internal Medicine & Nephrology,*
*Faculty of Medicine, Ain Shams University.*

**DR. Mohamed Ali Ibrahim**
*Lecturer of Internal Medicine & Nephrology,*
*Faculty of Medicine, Ain Shams University.*

**Faculty of Medicine**
**Ain Shams University**
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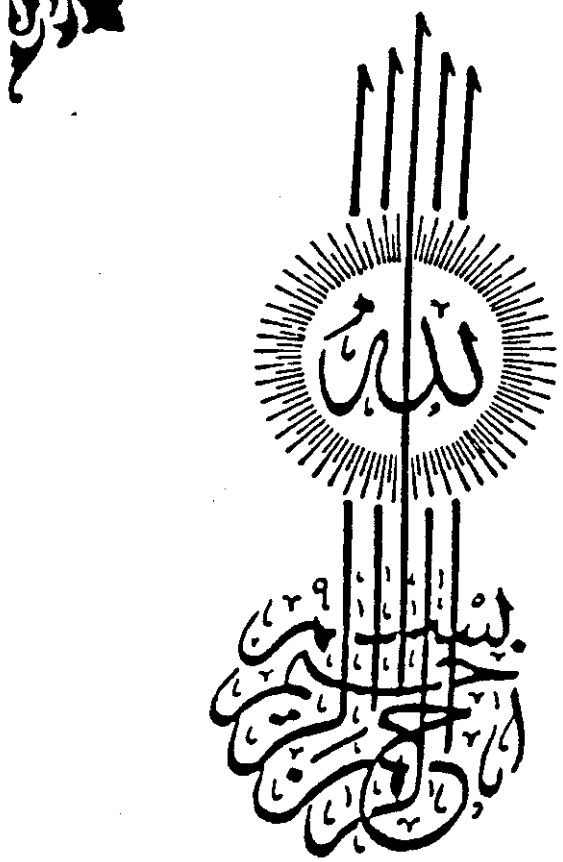

قالوا سبحانك لا علم لنا إلا ما
علمتنا إنك أنت العليم الحكيم.

صدق الله العظيم
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*Sometimes,*

*the truest feelings are those we keep inside,*

*and though not often mentioned,*

*they are the most sincere.*

*To My Family*

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# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| *ADCC* | : Antibody dependent cellular cytotoxicity. |
| *AER* | : Albumin excretion rate. |
| *APC* | : Antigen presenting cells. |
| *BSA* | : Bovine serum albumin. |
| *CF-ICA* | : Complement fixing islet cell antibodies. |
| *CGRP* | : Calcitonin gene-related peptide. |
| *CTL* | : Cytotoxic T-lymphocytes. |
| *ESRD* | : End stage renal disease. |
| *FFA* | : Free fatty acids. |
| *GAD* | : Glutamic acid decarboxylase. |
| *GBM* | : Glomerular basement membrane. |
| *HGP* | : Hepatic glucose production. |
| *IAA* | : Insulin autoantibody. |
| *ICA* | : Islet cell antibodies. |
| *ICSA* | : Islet cell surface antibody. |
| *IFN* | : Interferon. |
| *IL-1* | : Interleukin 1. |
| *MODY* | : Maturity onset diabetes of young. |
| *NK* | : Natural Killer cells. |
| *PAA* | : Proinsulin autoantibody. |
| *TNF* | : Tumour necrosis factor. |

# Introduction And Aim Of The Work

# INTRODUCTION

Chronic renal failure has been reported to contribute to insulin resistance, meanwhile the diabetic patients complicated with renal failure are commonly prone to hypoglycemia due to insulin therapy ***(Robert et al., 1992).***

This paradox makes difficult to adjust the dose of insulin required to control diabetes mellitus in patients developing chronic renal failure.

The kidney has been suggested as the main organ for degradation of C-peptide. This hypothesis was tested in subjects with varying degrees of renal failure. The basal steady state concentration of C-peptide and immune reactivity of insulin were determined. There was a significant inverse correlation between creatinine clearance and C-peptide with highest C-peptide level in nephrectomized patients, supporting the hypothesis of the kidney being the organ mainly responsible for the degradation of C-peptide ***(De Fronzo, 1978).***

On the other hand, peripheral conversion of proinsulin to insulin and C-peptide does not occur in terminal renal failure. Hyperinsulinism observed in renal failure can be explained by circulating proinsulin ***(Katz and Rubenstein, 1973).***

It was concluded that the increase in proinsulin, insulin and C-peptide are due to hypersecretion of B-cells, decreased renal degradation or excretion ***(Rabkin et al., 1984).***

In spite of hyperinsulinemic state observed in chronic renal failure, some diabetic patients may need to increase their insulin requirements once hemodialysis is started ***(Modan et al., 1985).***

## AIM OF THE WORK

The aim of this study is to assess the pancreatic insulin reserve in diabetic and non-diabetic chronic renal failure patients and to speculate from the therapeutic point of view any modification in insulin dosage in diabetic patients developing varying degrees of renal failure.

It will also evaluate the effect of hemodialysis on the pattern of insulin secretion and insulin level, as well as C-peptide level, in chronic renal failure patients.

# Review Of Literature

# REVIEW OF LITERATURE
# DIABETES MELLITUS

Glucose is the usual currency of metabolism, as it represents the most important sugar that travels in the blood to all the tissues of the body. It serves as a source of energy and as a promordial precursor for other carbon containing compounds ***(Lienhard et al., 1992).***

Diabetes mellitus is a genetically determined disorder of the metabolism of carbohydrate, fat and protein associated with a relative or absolute insufficiency of insulin secretion and with varying degrees of insulin resistance. In its fully developed clinical expression, it is characterized by fasting hyperglycemia and in the majority of long-standing patients by microangiopathic vascular complications, especially in the eye and kidney, and by an increased frequency of macrovascular disease such as coronary heart and peripheral vascular disease and by neuropathy ***(Ellenberg and Rifkin, 1990).***

The total prevalence of diabetes mellitus in Egypt is 4.3% with distinct geographical difference : 5.7% in urban areas, 4.1% in the rural agricultural parts and 1.5% in rural desert areas inhabited by Bedouins ***(Arab, 1992).***

**CLASSIFICATION** : According to ***Ellenberg and Rifkin (1990)***:

***I- Type I : Insulin-Dependent Diabetes Mellitus (IDDM) :***

It was formerly termed juvenile-onset diabetes. It occurs in approximately 10% of all patients with diabetes mellitus ***(Lesile et al., 1989).***

This type of diabetes is characterized by polyuria, polydypsia, weight loss, normal/increased appetite, fatigue and visual disturbances. Insulin deficiency leads to excessive accumulation of glucose and fatty acids, with consequent hyperosmolality and hyperketonuria ***(Jonathan et al., 1991).***

It is now clear that IDDM is the result of a long, latent, progressively damaging process to pancreatic Beta-cells. Clinically, this latency period is characterized by the loss of the first phase of insulin response to intravenous glucose and by the presence of islet cell antibodies (ICA) which can be detected months or even years before the clinical onset of diabetes mellitus by immunofluorescence ***(Jonathan et al., 1991).***

Type I (IDDM) is subclassified into :

**Type Ia :** where there is association with HLA types e.g. $DR_3$, $DR_4$, generally cytoplasmic and complement fixing

...

islet cell antibody positive at diagnosis but later become negative.

**Type Ib :** where there is close association with other auto-immune endocrinopathies and persistant islet cell antibodies ***(Ellenberg and Rifkin, 1990).***

***II- <u>Type II : Non-Insulin Dependent Diabetes Mellitus (NIDDM)</u> :***

It was formerly termed maturity-onset diabetes. It affects 3-7% of adults in most Western countries ***(Conner and Smith, 1991).*** This type comprises a group of milder forms, occurring predominantly in adults, of whom 85% are obese. Glucose tolerance of those obese patients often return normal after weight loss and they are usually hyperinsulinemic with some degree of insulin resistance. The remaining 15% have an absent or delayed early phase of insulin release in response to glucose, with tendency to familial aggregation and the involvement of environmental factors in its pathogenesis ***(Albert and Hockaday, 1983).***

NIDDM usually presents insidiously, with initial signs of chronic skin infections or generalized pruritus and vaginitis. A family history of mild diabetes is usually reported ***(Jonathan et al., 1991).***