Prevalence Of Insulin Dependent Diabetes Mellitus In School Children With A Study Of Microproteinuria In Diabetic Children

Thesis

Submitted In Fulfillment For

The Ph.D. Degree In Childhood Studie

 $\mathbf{B}\mathbf{y}$

Adel Naguib Hanna Guirqu

M.Sc. Pediatrics

National Research Center

Supervised

By

53161

Prof. Dr. Ramzy El-Baroudy

Prof. of Pediatrics

Cairo University

Prof. Dr. Samia Nour Prof. of Clinical Pathology Cairo University

Prof. Dr. Wasef Guirguis Assist. Prof. of Endocrinology National Research Center

> Ain Shams University 1995



DISCUSSION AND JUDGMENT COMMITTEE

The vice-president for higher studies and research of Ain-Shams University has approved to form the following committee for the discussion of

Mr. Adel Naguib Hanna Guirgis

1. Professor Dr. Ramzy El-Baroudy
Professor of Pediatrics Cairo University

Chairman

2. Professor Dr. Bahia Mostafa

Professor of Pediatrics Cairo University

Member

3. Professor Dr. Hamed El-Khiat

Professor of Pediatrics Ain-Shams University

3 Lie Moshald

Member



To my wife
whom I owe her the motive to finish this work
To my parents
who instilled in me a passion for knowledge

Acknowledgment

Words cannot express how deep I am grateful to *Professor Dr. Ramzy El-Baroudy*, Professor of Pediatrics, Faculty of Medicine, Cairo University, for his generous supervision, indispensable guidance and helpful advice which made me accomplish this work in its present form. Working under his supervision has been a source of constant delight and indeed a great privilege.

I wish also to express my sincere gratitude to *Professor Dr.*Samia Nour, Professor of Clinical Pathology, Faculty of Medicine,
Cairo University, for her honest supervision, kind assistance, the
great effort she did and the time she devoted to help me in the
laboratory part of this work.

I feel deeply thankful to *Professor Dr. Wasef Guirguis*, Professor of Endocrinology, National Research Center, for his never failing aid and guidance, as he was keen to offer advice and help that were of great importance to me. His valuable assistance and encouragement were indeed main support to me and to put this work to its best.

Finally, I cannot forget the efforts and great help of *Dr. Kamal Sharobeem*, in finishing the statistical part of this work.

Adel Naguib

Contents

Introduction and Aim of Work	1
Review of Literature	
Classification of Diabetes Mellitus	3
Incidence and Prevalence	9
Complications of IDDM	20
The Normal Kidney	35
The Diabetic Kidney	42
β ₂ Microglobulin	48
Proteinuria	53
Glycation of Proteins	57
Diabetic Proteinuria	60
Diabetes Mellitus and Psychiatry	76
Psychiatric Features of Diabetes Mellitus	87
Subjects and Methods	92
Results	106
Discussion	136
Summary	149
Conclusion	151
Recommendations	152
References	153
Arabic Summary	208

List of Tables

Table 1	Summary of Classification of Diabetes Mellitus in Children	
	and Adolescents.	8
Table 2	Concordance and Discordance for Diabetes in Identical Twin	s 18
Table 3	Relative Risk of Developing Type I Diabetes in Siblings	
	by HLA Genotype.	34
Table 4	Response Rate in The Study.	109
Table 5	Glycosuria in The Study.	109
Table 6	Prevalence of IDDM.	111
Table 7	IDDM in Primary School (Age 6-12 yr.).	111
Table 8	IDDM in Preparatory School (Age 11-14 yr.).	112
Table 9	IDDM in All Schools.	112
Table 10	Descriptive Statistics of All cases.	118
Table 11	Descriptive Statistics of Cases With Normal β_2MG .	119
Table 12	Descriptive Statistics of Cases With Abnormal β ₂ MG.	120
Table 13	Descriptive Statistics of Normal Control Cases.	121
Table 14	Values of β ₂ MG and HbA _{1c} in Control Group.	121
Table 15	Comparison Between Diabetics and Normal Controls as	
	Regards β ₂ MG and HbA _{1c} .	122
Table 16	Frequency Distribution of Family History in Diabetic	
	Patients.	125
Table 17	Frequency Distribution of Sex in Diabetics With Normal	
	β₂MG.	125
Table 18	Frequency Distribution of Sex in Diabetics With Abnormal	
	β_2 MG.	125
Table 19	Sex in IDDM Children With & Without β_2 -Microproteinuria	128
Table 20	Correlation Between Insulin Dose and β ₂ -Microglobulin.	129
Table 21	Correlation Between Insulin Dose & Duration of Diabetes	130

Table 22	HbA _{1c} in Comparison Between Diabetics With Normal	
	and Abnormal β ₂ -Microproteinuria.	131
Table 23	Duration in Comparison Between Diabetics With Normal	
	and Abnormal β ₂ -Microproteinuria.	132
Table 24	β ₂ -Microglobulin in Comparison Between Controlled and	
	Uncontrolled Diabetics.	134
Table 25	Cross Tab Between HbA ₁ and β ₂ MG.	135

.

List of Figures

: 1	Translation of Early Reversible Metabolic Imbalances	24
2	Polyol Pathway.	25
3	Gross Morphology of Renal Circulation.	36
4	Comparison of The Blood Supplies of Cortical and	
	Juxtamedullary Nephrons.	36
5	Schematic Depiction of The Glomerular & surrounding	
	Structures.	36
6	The Interaction Between Parental Stability, Adjustment	
	and The Child's Attitude to His Illness.	90
7	Factors Affecting Diabetes Control.	90
8	Distribution of Screened Students.	107
9	Frequency Distribution of Sex in Screened Students.	108
10	Number of Students Turned to be Diabetics.	110
11	β ₂ MG in Normal Controls and Diabetics.	123
12	HbA _{1c} in Normal Controls and Diabetics.	124
13	Distribution of Family History for Diabetics.	126
14	Distribution of Sex for Diabetics.	127
15	Duration of Diabetes in Normal & Abnormal Urine	
	$\beta_2 MG$.	133
	2 3 4 5 6 7 8 9 10 11 12 13 14	 5 Schematic Depiction of The Glomerular & surrounding Structures. 6 The Interaction Between Parental Stability, Adjustment and The Child's Attitude to His Illness. 7 Factors Affecting Diabetes Control. 8 Distribution of Screened Students. 9 Frequency Distribution of Sex in Screened Students. 10 Number of Students Turned to be Diabetics. 11 β₂MG in Normal Controls and Diabetics. 12 HbA_{1c} in Normal Controls and Diabetics. 13 Distribution of Family History for Diabetics. 14 Distribution of Sex for Diabetics. 15 Duration of Diabetes in Normal & Abnormal Urine

List of Abbreviations

ACE Angiotensin Converting Enzyme

BMG Beta-2-Microglobulin

DEMPU Diabetes Endocrine Metabolic Pediatric Unit

GBM Glomerular Basement Membrane

GDM Gestational Diabetes Mellitus

GFR Glomerular Filtration Rate

HbA₁ Glycated Hemoglobin

HLA Human Leukocyte Antigen

IDDM Insulin Dependent Diabetes Mellitus

LMW Low Molecular Weight

NAG N-Acetyl Beta glucosaminidase

NIDDM Non Insulin Dependent Diabetes Mellitus

RBP Retinol Binding Protein

UAER Urinary Albumin Excretion Rate

Introduction & Aim of Work

Introduction

Diabetes Mellitus is a syndrome of disturbed energy homeostasis caused by a deficiency of insulin or its action and resulting in abnormal metabolism of carbohydrate, protein, and fat. It is the most common endocrine-metabolic disorder of childhood and adolescence with important consequences on physical and emotional development. Individuals affected by insulin-dependent diabetes confront serious burdens that include an absolute daily requirement for exogenous insulin, the need to monitor their own metabolic control, and the need to pay constant attention to dietary intake. Morbidity and Mortality stem from the metabolic derangement and from long-term complications that affect small and large vessels and result in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities.

The acute clinical manifestations can be fully understood in the context of current knowledge about the secretion and action of insulin; considerations point to autoimmune genetic and other etiologic mechanisms as factors in the genesis of type I diabetes, and there is an emerging consensus that the long-term complications are related metabolic disturbances. These considerations form the basis of the therapeutic approaches to this disease (Behrman et al., 1992).

Diabetes Mellitus has been known since antiquity. Reference is made in a Papyrus Ebers (1550 B.C.) to "a medicine to drive away the passing of too much urine". The first accurate clinical description of the disease was made by Aretaeus of Cappadozia in the second century A.D., who stated, "Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine". The early references to diabetes most certainly were to the ketoacidotic form of the Thomas Willis described the sweet character of the urine in disease. diabetes in the latter part of the seventeenth century. He recognized that

diabetes was rare among the ancients, "But in our age given to good fellowship and guzzling down chiefly unalloyed wine; we meet with examples and instances enough". He undoubtedly was describing the increasing frequency of a non-ketotic form of the disease (Wrenshall et al., 1962).

Throughout the course of history, diabetes mellitus was thought to be a single entity. The concept that diabetes mellitus is not a single disease, but rather a clinical syndrome characterized by inappropriately elevated fasting and or postbrandial blood glucose and the development of long term microvascular, macrovascular, and neuropathic changes is of very recent origin and stems from numerous investigations into the epidemiology, genetics, etiology, and pathogenesis of clinical diabetic states.

Aim of Work

The aim of work is to determine the prevalence of insulin dependent diabetes mellitus among school age children in Egypt and to assess the role of β2-microglobulin as a tool to detect early renal affection in diabetic children and to study the effect of diabetes metabolic control and duration of the disease on the presence of microproteinuria.

Review of Literature

Classification of Diabetes Mellitus

Diabetes Mellitus is not a single entity but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance.

Before 1980, a variety of descriptive terms were used to classify diabetes, some based on the age of onset and others, the stage or the degree of severity of the disease. A welter of confusion hindered the assessment of data from studies of the natural history of the disease and its complications. The U.S. National Diabetes Data Group then created a new classification based on clinical or descriptive observations from epidemiologic studies of large populations to provide uniform designations and a framework for investigative and epidemiologic data on diabetes (National Diabetes Data Group, 1979).

A similar but more inclusive classification adopted by the world Health Organization Expert Committee on Diabetes Mellitus in 1980 has been accorded general acceptance (WHOEC, 1980).

Three major forms of diabetes and several forms of carbohydrate intolerance have been identified. The overall classification of diabetes mellitus and other categories of glucose intolerance is shown in table "I".

• Type I-Insulin Dependent Diabetes Mellitus (Juvenile-Onset Diabetes)

Type I diabetes is usually characterized by abrupt onset of symptoms, although present evidence suggests that its evolution may involve an antecedent period of slowly developing autoimmune damage to the pancreatic B-cells (Gorsuch et al., 1981; Harrison et al., 1992).