Insulin Resistance in Egyptian Children and Adolescents with Prader Willi and Bardet Biedl Syndromes

Thesis Submitted for fulfillment of M.Sc. degree in Pediatrics

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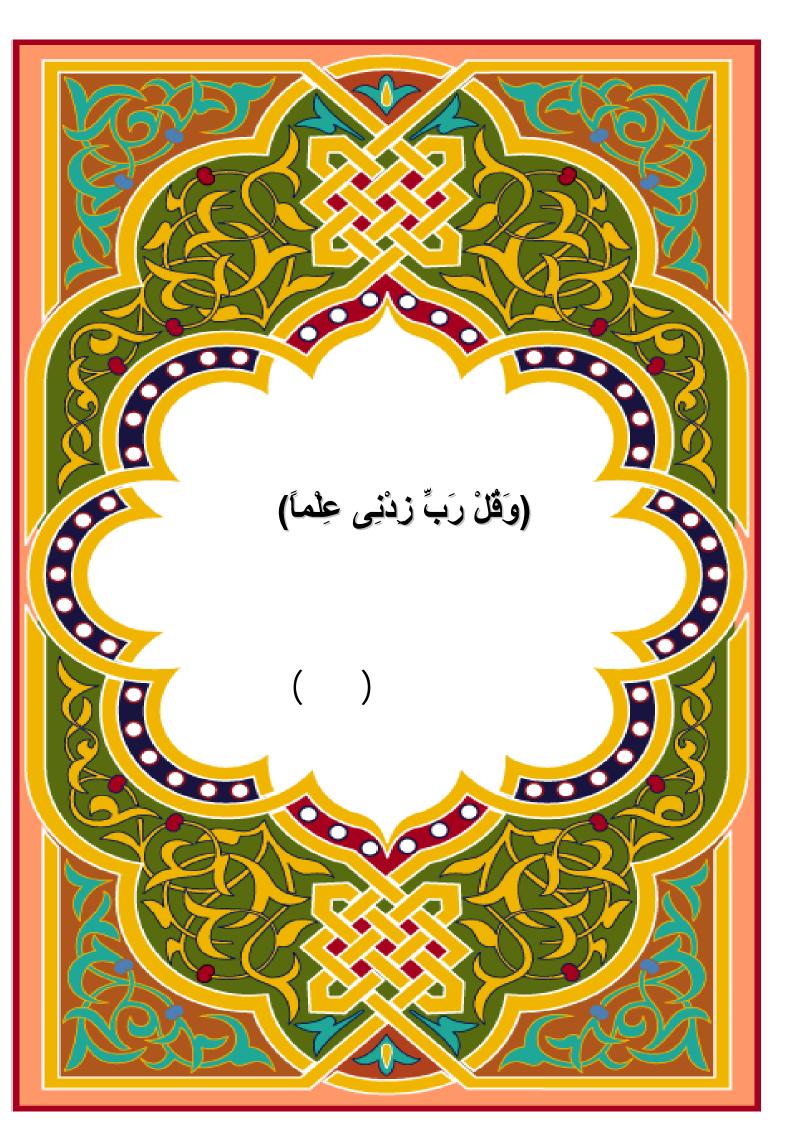
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Acknowledgement

First of all thanks to ALLAH, the source of all knowledge, who gave me the power by his abundant grace to produce this piece of work.

I wish to express my appreciation and sincere gratitude to **Prof. Dr. Mona Hassan Hafez**, Professor of Pediatrics, Faculty of Medicine, Cairo University, for her kind help, advice, constant guidance, effort and encouragement.

I would like to express my deep gratitude to **Prof. Dr. Fatma Ahmed F. Elmougy**, Professor of Chemical Pathology, Faculty of

Medicine, Cairo University, for her supervision, kind advice and
support.

I am very grateful to **Dr. Adel M. Ashour**, Assist. Prof. of Clinical Genetics National Research Centre not only for his kind assistance, support, but also for his patience with constant guidance and effort.

Also I'd like to thank **Dr. Maha Abd El Hamid Eid** for her valuable help and guidance in this research work.

I always feel grateful to my professors and colleagues in the clinical genetics department for their help and cooperation.

Also I wish to thank my father, my family, and my friends for their continuous support in life and in work.

Last but not least I'd like to express many thanks to the patients who were involved in the study, and their parents. This work would've never been accomplished without them.

Abstract

Childhood obesity has become a pandemic. Obesity is the most important cause resulting in the development of insulin resistance and its complications. Obesity is a central feature of some genetic syndromes. This study included 18 patients with syndromic obesity (9 cases with Prader Willi syndrome (PWS) and 9 cases with Bardet Biedl syndrome (BBS)) and for comparison another 19 cases with simple obesity were included in the study. The aim of the work was to study differences in the degree of insulin resistance between patients with syndromic obesity and those with simple obesity. History, Clinical examination, detailed anthropometric measurements and laboratory investigations including Homeostatic Model Assessment (HOMA) for evaluation of insulin sensitivity were done for all patients. The results revealed that patients with PWS had lower mean HOMA values when compared to subjects with simple obesity; however the differences were statistically insignificant, while patients with BBS showed insignificant differences regarding HOMA values when compared to subjects with simple obesity.

Key words: obesity, insulin resistance, Prader-Willi syndrome, Bardet-Biedl syndrome, Homeostatic Model Assessment (HOMA).

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List of Abbreviations

AAP American Academy of Pediatrics
ACTH Adrenocorticotropic homone

AGRP agouti related protein

AHO Albright's hereditary osteodystrophy

ALMS1 Almstrom syndrome 1 gene

AN Acanthosis nigricans
ARC Arcuate nucleus

AT1 angiotensin II receptors type-1
ATPIII Adult Treatment Panel III
BBS Bardet-Biedl syndrome

BDNF brain-derived neurotropic factor BIA Bioelectric impedance assay

BMC bone mineral content bone mineral density
BMI body mass index

CAI central adrenal insufficiency

CART cocaine- and amphetamine-related transcript

CCDC28B Coiled –coil domain containing 28B

CCK Cholecystokinin

CDC Centers for Disease Control and Prevention

CEP Centrosomal protein

CIGMA continuous infusion of glucose with model assessment

CNS central nervous system

CRH Corticotropin Releasing Hormone

CRP C reactive proteinCT Computed tomography

DEMPU Diabetic, Endocrine and Metabolic Pediatric Unit

DEXA Dual-energy x-ray absorptiometry

ERG electroretinographic

ESHRE/ASRM Rotterdam European Society of Human

Reproduction/American Society for Reproductive

Medicine

ESRD end stage renal disease

FFAs free fatty acids FFM fat free mass

FGIR Fasting glucose/insulin ratio
FIRI Fasting Insulin Resistance Index
FISH fluorescence in situ hybridization
FMRP Fragile X Mental Retardation Protein

FSH follicle stimulating hormone

FSIVGTT frequently sampled IV glucose tolerance test

GDM gestational diabetes mellitus

GH growth hormone

GH axis Growth Hormone axis

GHS-R Growth Hormone Stimulating Hormone Receptor

GLP-1 Glucagon-like peptide 1 GLUT4 Glucose transporter 4

GNAS1 Guanine Nucleotide Binding Protein, Alpha

Stimulating

Gsα G protein

HDL high density lipoprotein

HIV human immunodeficiency virus HOMA Homeostatic model assessment

I0 Fasting insulin

IC the imprinting centre

IDF International Diabetes Federation

IFG impaired fasting glucoseIFT intraflagellar transportIGF insulin growth factor

IGF-BP insulin growth factor bound protein

IGT impaired glucose tolerance

IL interleukin

IR Insulin resistance
IST insulin sensitivity test
LDL low density lipoprotein

LEP leptin

LEPR Leptin receptor
LH luteinizing hormone
MC3R melanocortin 3 receptor
MC4R mlanocortin 4 receptor

MCH Melonocyte Concentrating Hormone MCP-1 monocyte chemo-attractant protein-1

MKKS Mckusick Kauffman syndrome

MKS Meckel syndrome

MRI magnetic resonance imaging
MSH melanocyte stimulating hormone

NIDDM non-insulin dependent diabetes mellitus type II

diabetes mellitus

NO nitric oxide NPY Neuropeptide Y

NRC Diabetic, Endocrine and Metabolic Pediatric Unit

Ob Obese gene

Ob-R Ob receptor (Leptin receptor)
OGTT oral glucose tolerance tests

Oxm Oxyntomodulin

PAI-1 plasminogen activator inhibitor-1

PC1 Prohormone convertase-1
PCOS Polycystic ovary syndrome

PHD plant homeodomain

PHF6 plant homeodomain-like finger6

PKCs protein kinases C
POMC proopiomelanocortin
PP Pancreatic polypeptide

PPAR-gamma peroxisome proliferator-activated receptor gamma

PPARγ peroxisomal proliferator-activated receptor-γ

PVN paraventricular

PWS Prader-Willi syndrome

PYY Peptide YY

QUICKI Quantitative insulin sensitivity check index

REE Resting Energy Expenditure

RMR resting metabolic rate RYGB Roux-en-Y gastric bypass

Ser Serine

SES Socioeconomic status
SGA small for gestational age

SIM1 single-minded homolog 1 (Drosophila)
SNPs single nucleotide polymorphisms
SOCS-3 Supressor of Cytokine Signalling 3

T2DM type 2 diabetes mellitus

Thr thereonine

TNF tumour necrosis facor TNF- α tumour necrosis factor α TRH thyroid relasing hormone

TRKB/NTRK2 neurotrophic tyrosine kinase receptor

Tvr tyrosine

TZD thiazolidinediones UK united kingdom

UPD maternal uniparental disomyUS united states of America

VCAM-1 vascular cell adhesion molecule-1 VLDL very low density lipoprotein

WC Waist Circumference

WHO World Health Organization

WHR waist-to-hip ratio

α-MSH alpha melanocyte stimulating hormone

SNRPN small nuclear ribonucleoprotein polypeptide N

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Introduction

Obesity has become a pandemic, with more than a billion people affected worldwide (*Kimm and Obarzanek 2002*). Consensus committees have recommended that children and adolescents be considered overweight or obese if the Body Mass Index (BMI) exceeds the 85th or 95th percentiles respectively (*Freemark et al., 2006*). Over the past 30 yr, the frequency of overweight children (BMI greater than the 85th percentile for age and sex) has tripled (*Thibault and Rolland 2003*).

Obesity is a complex disease that involves interactions between environmental and genetic factors. Obesity results from an imbalance between food intake and energy expenditure over several years. The genetic approach both in animal models and in humans has allowed immense progress in the understanding of body weight regulation (Clement et al., 2006).

Genetic syndromes with obesity represent unique opportunities to gain insight into the control of energy balance. Prader Willi syndrome and Bardet Biedl syndrome are among the most common causes of genetic obesity (*Delrue et al.*,2004 and Mutch et al.,2006)

Insulin resistance is a state in which a given concentration of insulin produces a less-than-expected biological effect (*Olatunbosun et al.*, 2007). The clinical diagnosis of the metabolic syndrome defines a patient with abnormal glucose metabolism, hypertension, hyperlipidemia and obesity (*Keskin et al.*, 2004). The strong relationship between obesity and insulin resistance in most patients underpins the metabolic syndrome and the associated risk of type 2 diabetes and vascular disease (*Prins et al.*, 2005). Identifying individuals with insulin resistance is therefore important in primary care settings to select the best preventive and therapeutic interventions (*Ybarra et al.*, 2005).

In PWS subjects, insulin resistance is lower and insulin sensitivity is higher, and also there is a dissociation between beta-cell secretion and the degree of obesity compared with obese controls (*Talebizadeh et al.*,2005 and Krochik et al.,2006).

Although Bardet-Biedl syndrome (BBS) was described more than 80 years ago, there exist little data on the natural history and pathogenesis of the various manifestations of the disorder including obesity, diabetes and metabolic characteristics of glucose and fat metabolism (*U.S. National Institutes of Health Clinical Center (CC)*,2006).

Aim of Work

Assessment of anthropometric measurements including BMI, waist circumference, and waist/hip ratio in obese patients with Prader-Willi and Bardet-Biedl syndromes and comparing them with age and sex matched subjects with simple obesity.

Evaluation of insulin resistance in obese patients with Prader Willi and Bardet Biedl syndromes clinically by searching for acanthosis nigricans, and on the laboratory level by using Homeostatic Model Assessment (HOMA).

Compare the degree of insulin resistance in obese patients with Prader-Willi and Bardet-Biedl syndromes with age, sex and BMI matched subjects with simple obesity.

The patients and their parents will be counselled according to the results of the study.

Childhood Obesity

Introduction

Obesity has become a pandemic, with more than a billion people affected worldwide (*Kimm and Obarzanek 2002*). Over the past 30 yr, the frequency of overweight children, defined as a body mass index (BMI) greater than the 85th percentile for age and sex, has tripled (*Thibault and Rolland 2003*). More than 30% of children in the United States are overweight or obese (BMI > 95th percentile) (*Fox 2003*). Data from the International Obesity Task Force indicate that 22 million of the world's children under 5 yr of age are overweight or obese (*Deitel 2002*). Obesity has replaced malnutrition as the major nutritional problem in some parts of Africa, with overweight/obesity being as much as four times more common than malnutrition (*Du Toit and Van Der Merwe 2003*).

More than two thirds of children 10 yr and older who are obese will become obese adults (*Must*, 2003). Obesity in young adults decreases life expectancy by 5–20 yr (*St-Onge and Heymsfeild 2003*). Pediatric obesity-related hospital costs have increased 3-fold during the past 20 yr, and continue to rise (*Goran et al.*, 2003). The increased frequency and severity of childhood obesity is accompanied by the expected medical complications. One in four overweight children in the 6- to 12-yr age group has impaired glucose tolerance, and 60% of these children have at least one risk factor for heart disease (*Steinberger and Daniels 2003*). Childhood obesity threatens to thwart the reduction in cardiovascular mortality achieved over the past decade through control of hypertension, hyperlipidemia, and smoking (*Magarey et al.*, 2003).