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

Thesis
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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
BMD	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 protein
CT	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 glucose
IFT	intraflagellar transport
IGF	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
Tyr	tyrosine
TZD	thiazolidinediones
UK	united kingdom
UPD	maternal uniparental disomy
US	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).***