" Study of Retinol ,the Retinol Binding protein 4 and Resistin in cases of overweight and obese Adolescents"

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Abstract

Introduction: Obesity is a leading cause of morbidity and mortality worldwide and is known to arise from an imbalance between energy intake and expenditure

Aim of this cross-sectional study: Study of Retinol ,the Retinol Binding protein 4 and Resistin ,To identify the relation between retinol, retinol binding protein 4, resistin hormones and BMI and to study the relationships between RBP4, insulin resistance and weight status in overweight and obese adolescents.

Methodology: This study is a case-control study included 88 children classified as forty five overweight and obese children and young adolescents attending nutrition Clinic, Children's Hospital, Ain shams University From january 2013 to November 2013. Forty three healthy children and young adolescents age and sex matched were included as control subjects..

Results Serum retinol and RBP4 levels of obese and overweight group were higher than those of control group, There was positive correlation between fasting serum retinol,RBP4 and anthropometric and clinical data (weight SDS, BMI SDS, waist/hip ratio, systolic, and diastolic blood pressure), laboratory data (Fasting serum insulin, HOMA-IR, total cholesterol, LDL-c), body composition data (body fat percent, fat mass and fat free mass), There were significant negative correlations between resistin and weight sds, BMI sds, cholesterol, triglycerides, LDL and TBF% , insulin& HOMA-IR,SBP,DBP,BMR in case group. There were significant positive correlations between resistin and HDL and TBW% in the case group.

Conclusion: RBP4 is positivity correlated to serum insulin level, HOMA/IR, and lipid profile, so RBP4 can be used as a marker for insulin resistance and obesity. Retinol (vitamin A) concentration was positively associated with measures of obesity and that vitamins A have a role on lipid metabolism, Studies with large sample size and high power are needed to explain the link between resistin and obesity associated insulin resistance especially in children.

Keywords: Childhood obesity, Insulin resistance, RBP4 ,Retinol and resistin.

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Alyaa Hossny Kamhawy

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List of abbreviations

AAP	American Academy of Pediatrics
Aldh1	aldehyde dehydrogenase 1
ANT	Anthropometry
BAT	brown adipose tissue
BC	body composition
BF	breastfed
BIA	bioelectrical impedance analysis
BIPAP	bilevel positive airway pressure
BMI	body mass index
BMR	basal metabolic rate
BP	blood pressure
BW	birth weight
CAD	coronary artery disease
CHD	coronary heart disease
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CT	Computed Tomography
CVD	cardiovascular disease
DEMPU	Diabetic, Endocrine and Metabolic Pediatric Unit
DEXA	Dual energy X-ray absorptiometry
DNA	deoxyribonucleic acid
ELISA	enzyme linked immunoassay

FDA	Food and Drug Administration
FF	Formula Fed
FFAs	free fatty acids
GLP-1	glucagon-link peptide-1
HDL	high-density lipoprotein
HDL-c	High density lipoprotein
HOMA	Homeostasis model assessment method
HSL	hormone sensitive lipase
IGF-1	insulin-like growth factor 1
IL-6	interleukin 6
IOTF	International Obesity Task Force
IR	insulin resistance
LDL-c	Low density lipoprotein
MCP	monocyte chemoattractant protein
MetS	metabolic syndrome
MRI	Magnetic Resonance Imaging
MTP	microsomal triglyceride transfer protein
N(%)	Number (Percentage)
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Study
OSA	obstructive sleep apnea
PAI-1	Plasminogen activator inhibitor 1

PBF	percentage body fat
PCOS	Polycystic ovary syndrome
RA	retinoic acid
Rald	retinaldehyde
RBP4	retinol binding protein 4
RELMs	resistin-like molecules
retn	resistin gene
RSG	rosiglitazone
SGA	small for gestational age
SNP	single nucleotide polymorphisms
T2D	type 2 diabetes
TNF-a	tumor necrosis factor a
TTR	transthyretin
TZDs	thiazolidinediones
UCP1	uncoupling protein 1
WAT	white adipose tissue
WC	Waist circumference
WHO	World Health Organization

Definitions:

- **Overweight:** is a child whose BMI from 85th to less than the 95th percentile for age and sex according to the World Health Organization Child Growth Charts Standards **(WHO, 2007)**
- **Obesity:** is a child whose BMI exceeding 95th percentile for age and sex according to the World Health Organization Child Growth Charts Standards **(WHO, 2007)**
- **Retinol-binding protein (RBP)-4** :is a recently discovered adipokine and is a protein that is the specific carrier for retinol in the blood. that has caused a controversial scientific discussion on whether and how it links to adiposity, insulin resistance, and type 2 diabetes (T2D) Its physiological function appears to bind retinol and prevent its loss through the kidneys. **.(Primoz et al,2011)**
- **Resistin** : Resistin is an adipokine secreted from adipose tissue, which is likely involved in the development of obesity and insulin resistance via its interaction with other organs, as well as affecting adipose tissue function. The impact of resistin treatment on lipolysis and adiponectin secretion in human visceral adipose tissue is currently unknown**(Chen et al.,2014)**
- **Adipose tissue (AT):**Mammals have two types of fat, white and brown adipose tissue (WAT and BAT, respectively), that carry out essentially opposite functions in whole body energy metabolism**, (Nedergaard et al.,2007)**White adipocytes are specialized in energy storage and their content of triglyceride constitutes the largest energy reserve of the body. Contrary, brown adipocytes have a high capacity for energy dissipation through adaptive thermogenesis due to the presence of the brown adipocyte-specific uncoupling protein 1 (UCP1) in the inner membrane of the abundant mitochondria**(Cannon and Nedergaard,2004)**
- **Adipocyte hormones**: These are proteins known as adipocytokine secreted by white adipose tissue (WAT) which include: Retinol Binding Protein 4 tumor necrosis factor, leptin, adipoctin, plasminogen activator inhibitor type -1(paI-1) and resistin **(HuHuang et al., 2006)**.

Introduction

Obesity in children and adolescents is a multi-factorial disorder, developed as a result of genetic and environmental changes, along with lack of physical activity resulting in imbalance in energy homeostasis, and accumulation of excess energy as fat. It is increasing at an alarming rate even in developing countries**. (Huang and McCrory , 2005)**

Genetic predisposition, environment in utero, and birth weight all affect obesity rates long before any active parenting occurs. (**Zhao and Grant ,2011)** Race, ethnicity, poverty, infant feeding practices, and the well-recognized cost disparity between healthy and less healthy foods play a role **(Van Cleave et al.,2010)**Children do not expend energy as in the past, and school vending machines, poor-quality school lunches, and the regrettable removal of physical education, recess, and health education classes are also factors in this issue**.** (**Eisenmann et al., 2011) (Rahman et al.,2011)** .

In last years, white adipose tissue (WAT) has been considered as an endocrine organ because of its capacity to secrete hormones and cytokines. Thus, adipose tissue is not only known for its capacity to store the excess of dietary energy in the form of triglycerides, but also is now recognized as a fundamental participant in the control of energy metabolism by secreting many proteins called adipocytokines such as retinol binding protein 4 (RBP4), resistin, tumor necrosis factor a (TNF-a), interleukin 6 (IL-6), leptin, vaspin, visfatin, omentin, chemerin, apelin, etc. **(Rasouli and Kern 2008) (Va´zquez-Vela et al., 2008)**

White adipose tissue is known to be involved in numerous physiological processes such as insulin-mediated functions, lipid and glucose metabolism, vascular changes and coagulation. These processes

are mainly mediated by adipokines that are secreted either from adipocytes or cells of the stromal-vascular fraction of adipose tissue. **(Sasche et al., 2011)**

Retinol-binding protein (RBP)-4 is a recently discovered adipokine that, in mice, increases insulin resistance in muscle and hepatic gluconeogenesis **(Yang et al., 2005)**. In humans, serum RBP4 concentrations are correlated with obesity and insulin resistance in adults in some studies **(Cho et al., 2006) (Graham et al.,2006)** but not in others (**Janke et al.,2006)** where In these studies, the major biological determinant of serum RBP4, *i.e.* vitamin A status, was not measured.

RBP4 is the specific transport protein for retinol in the blood, and alterations of retinol intake and vitamin A status affect hepatic release of RBP4 and circulating RBP4 **(Yang et al.,2005)** . It is unclear whether the link between RBP4 and insulin sensitivity occurs through retinol-dependent or retinol-independent mechanisms (**Muoio and Newgard,2006)**

Its physiological function appears to bind retinol and prevent its loss through the kidneys. **(Felipe et al., 2004)**

RBP4, although largely produced in the liver, is also made by adiposities, with increased levels in obesity contributing to impaired insulin action **(Yang et al., 2005).**

In another study they found a relationship between RBP-4, insulin sensitivity and the percentage trunk fat in individuals without features of insulin resistance (IR)**(Gavi. et al.,2007).** Retinol-binding protein 4 (RBP4) has been shown to be associated with insulin resistance (IR), metabolic indices and metabolic syndrome (MetS) in various patient populations and in obesity (**Toktam et al.,2012)**