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Department of Medical Studies for Children

Assessment of Chemerin and Apelin levels as potential predictors for Vascular Endothelial Function in Obese Children

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسببناك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدقة الله العظيم

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List of Abbreviations

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ACTH	Adrenocorticotrophic hormone
AgRP	Agouti-Related Peptide
Ang II	Angiotensin II
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
CART	Cocaine and Amphetamine-Regulated Transcript
CCRL2	Chemokine (C-C motif) Receptor-Like 2
CMKLR1	Chemokine Like Receptor-1
CRP	C-Reactive Protein
CT	Computerized Tomography
CSF	CerebroSpinal Fluid
CVD	Cardiovascular disease
CVS	CardioVascular System
DEMPU	Diabetes Endocrine and Metabolism Pediatric Unit
DM	Diabetes Mellitus
DEXA	Dual Energy X-ray Absorptiometry
FDA	Food and Drug Administration
FMD	Flow Mediated Dilation
GERD	GastroEsophageal Reflux Disease
Gi	G inhibitory
GPR1	G-Protein Receptor 1
GPCR	G Protein–Coupled Receptor
HDL	High-Density Lipoprotein
hs-CRP	High sensitive C-Reactive Protein
IBD	Inflammatory Bowel Disease
ICAM-1	Intercellular Adhesion Molecule 1
IDF	International Diabetes Federation
IL	Interleukin
LDL	Low-Density Lipoprotein
LH	Lateral Hypothalamus
LPS	Lipopolysaccharide
MAPK	Mitogen-Activated Protein Kinases
MRI	Magnetic Resonance imaging
Mc3r	Melanocortin-3 receptors
Mc4r	Melanocortin-4 receptors

List of Abbreviations

MCH	Melanin Concentrating Hormone
MSH	Melanocyte Stimulating Hormone
NAFLD	Non-Alcoholic Fatty Liver Disease
NO	Nitric Oxide
NPY	Neuropeptide Y
OSAS	Obstructive Sleep Apnea Syndrome
PC1	Prohormone Convertase 1
PCOS	Polycystic Ovary Syndrome
POMC	Pro-opiomelanocortin
PPAR	Peroxisome proliferator activated receptor
PTH	Parathyroid Hormone
PWV	Pulse Wave Velocity
PVN	ParaVentricular Nucleus
RAR- RES2	Retinoic Acid Receptor Responder 2
RH- PAT	Reactive Hyperemia Peripheral Arterial Tonometry
ROS	Reactive Oxygen Species
RAAS	Renin-Angiotensin-Aldosterone System
RT-PCR	Reverse Transcription PCR
SSC	Squamous Cell Carcinoma
SCFE	Slipped Capital Femoral Epiphysis
TIG2	Tazarotene-Induced Gene 2
TG	Triglyceride
TNF	Tumor Necrosis Factor
US	Ultrasound
VCAM-1	Vascular Cell Adhesion Molecule 1
VSMCs	Vascular Smooth Muscle Cells
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist/ Hip ratio

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Abstract

Abstract

Background: childhood obesity is now forming a global threat with subsequent health problems among which and most important is cardiovascular problems. It is now claimed that adipokines secreted by adipose tissue are responsible for such consequences. Newly discovered adipokines Chemerin and Apelin are under investigation for their link with obesity related co-morbidities. **Aim:** assessment of serum Chemerin and Apelin levels in a sample of Egyptian obese children and to determine the relationship between them with markers of inflammation and vascular endothelial cell activation in attempt to predict the risk for cardiovascular diseases in these children. **Method:** This comparative cross-sectional study was conducted on 45 obese subjects (BMI \geq 95th percentile) aged from 6 to 11 years recruited from Diabetes Endocrine and Metabolic Pediatric Unit at Cairo University Pediatric Hospital and Medical and Scientific Centre of Excellence, National Research Center compared to 45 healthy children age and sex matched . General examination, anthropometric assessment (weight, height, waist circumference, and hip circumference), and laboratory tests (Endothelial activation molecules (E-Selectin and ICAM-1), Chemerin, Apelin, lipid profile and hs-CRP) were done. **Results:** Serum Chemerin and Apelin levels were significantly higher in obese compared to non obese children. On correlating Chemerin and Apelin with anthropometric parameters among obese subjects it showed no significant correlation. Interestingly there was a significant correlation in the whole group when correlating Chemerin and Apelin with anthropometric parameters . On correlating Chemerin and Apelin with Lipid profile and measures of inflammation (hs-CRP) only Chemerin showed significant correlation in both obese and whole group while Apelin only showed a significant correlation in the whole group. No correlation was found between Chemerin and Apelin with Systolic BP zscore and

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Diastolic BPz score neither in the obese nor in the whole group. Moreover, we identified significant association between Chemerin and Apelin with the markers of endothelial activation (ICAM-1 and E-selectin) in the whole group but not in the obese. Multiple regression analyses confirmed that both Chemerin and Apelin are predictors for hs -CRP, ICAM-1 and E-selectin independent of BMI z score, age and sex. **Conclusion:** Our results showed an elevated serum level of both Chemerin and Apelin in obese children and suggest a possible correlation of Chemerin and Apelin with inflammatory (hs-CRP) and endothelial activation markers (ICAM-1 and E-selectin).

Key words:

Obese children – Chemerin – Apelin- Inflammation-Endothelial activation
-hs-CRP

Introduction

Introduction

Obesity in children and adolescents has become an increasing clinical and public health concern (*Semiz et al., 2007*). The prevalence of childhood obesity in both the developing countries and the Middle East has shown a significant increase (*James, 2004*). In Egypt obesity has a high prevalence and became a problem in Egyptian youth (*Hadhood et al., 2017*).

The impact of childhood obesity on public health is profound, as it has been shown that it is a major risk factor for many health complications among which and most dangerous is cardiovascular diseases and with consequent decrease in life expectancy (*Lee , 2009*).Of the most serious cardiovascular complications of obesity is endothelial dysfunction and subsequent atherosclerosis. Atherosclerotic plaques formation is the most important part in atherosclerotic disease and it was found that lesions grow slowly during childhood forming raised lesions in adolescents and young adults (*Libby, 2000*).

One early phase of atherosclerosis involves endothelial dysfunction with recruitment of inflammatory cells from the circulation and their transendothelial migration. This process is predominantly mediated by cellular adhesion molecules, which are expressed on the vascular endothelium and on circulating leukocytes in response to several inflammatory stimuli. Cellular adhesion molecules are involved in the rolling and tethering of leukocytes on the vascular wall as well as inducing firm adhesion of inflammatory cells at the vascular surface. Several lines of evidence supported a crucial role of adhesion molecules in the development of endothelial dysfunction, atherosclerosis and atherosclerotic plaque instability (*Blankenberg et al., 2003*).

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One of the mechanisms that connect obesity with these comorbidities is the secretion of so-called adipokines by the adipose tissue itself. Adipokines are involved in the regulation of a variety of systemic processes such as food intake and nutrient metabolism, insulin sensitivity, and inflammation (*Katsareli and Dedoussis, 2014*).

Of the adipokines that may be responsible for such co- morbidities are the adipokines Chemerin and Apelin.

Chemerin is an adipokine that has been reported to act as a chemotactic factor for specific subsets of immune-regulatory antigen-presenting cells controlling the immune responses at the sites of inflammation or tissue injury (*Parolini et al., 2007, Hart and Greaves, 2010*). In clinical studies it was found that elevated Chemerin serum level was associated with increased body mass index (BMI) in both adult (*Bozaoglu et al., 2009, Fatima et al., 2013*) and children (*Landgraf et al., 2012*). Furthermore, adult obese patients with metabolic syndrome had elevated Chemerin levels associated with cardiovascular risk factors such as hyperglycemia, dyslipidemia, and hypertension (*Stejskal et al., 2008*). Increased serum Chemerin in patients with metabolic syndrome has been linked to the presence of coronary artery disease (*Dong et al., 2011*). This may be due to the fact that human vascular endothelial cells express the chemerin receptor CMKRL1, and binding of chemerin to its receptor reduces endothelium-derived nitric oxide (*Neves et al., 2014*) and enhances expression and secretion of cell adhesion molecules (*Dimitriadis et al., 2018*) and this may explain the link between Chemerin, inflammation ,endothelial dysfunction and atherosclerosis (*Rhee, 2011, Yoo et al., 2012*).

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The other adipokine under investigation is Apelin. Apelin is an adipokine, produced by white adipose tissue (*Kleinz and Davenport, 2005*) and its receptor is expressed in kidney, heart and endothelium (*Boucher et al., 2005*) and researches showed that it may contribute to the link between increased adipose tissue mass and obesity related metabolic diseases (*Castan-Laurell et al., 2011*). Apelin has been shown to be responsible for endothelial dysfunction through inducing expression of cell adhesion molecules and chemokines both in vivo (*Malyszko et al., 2008 a*) and in vitro (*Lu et al., 2012*) and thus may be involved in the initiation of endothelial inflammation related atherosclerosis.

Due to the fact that endothelial cell damage or injury is invariably associated with such clinical conditions as thrombosis, hypertension, renal failure and atherosclerosis, studies in children might allow better insight into the link between Chemerin and Apelin and the early stages of obesity-related disease particularly cardiovascular diseases as children present earlier stages in pathogenesis.