Study of Serum Hepcidin as a Potential Mediator of the Disrupted Iron Metabolism in Obese Adolescents

Submitted for Fulfillment of Ph.D in Childhood Studies
(Child Health and Nutrition)
Medical Studies Department

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2013

DEDICATION

To My Dear Father

Prof. Dr. Selim Ismail Moustafa

Who

Lives in my heart forever as a loving great father
and
Gracious adviser

He will be remembered for his kindness & warmth
radiated
not only to his family but also extended to his students
and friends all over the world

I owed him all the success and happiness in my entire life

And

To My Mother

Who

Was always there for me with her support & love

Abstract

Background: The prevalence of obesity continues to rise in both developed and developing nations. An association between iron status and obesity has been described in children and adults. Findings from recent reports suggest that body mass index and inflammation predict iron absorption and affect the response to iron fortification; a relationship that may be mediated by hepcidin. ***Aim of the work:*** The aim of this work was to determine iron status in obese adolescents. It aimed also to study the relation between serum hepcidin level and both iron as well as high sensitive CRP status in obese adolescents. ***Subjects and Methods****:* this work was conducted on 80 adolescents aging 12-14 years old, divided into two groups; obese and non obese. All children were subjected to full medical history taking, dietetic history, anthropometric measurements, determination of haemoglobin, serum iron, total iron binding capacity, transferrin saturation and serum ferritin, soluble serum transferrin receptor, hs- C-reactive protein and serum hepcidin. **Results:** Cases showed significantly lower levels of haemoglobin, serum iron, serum ferritin and transferrin saturation when compared to control group. Significant higher diastolic blood pressure, higher mean TIBC , sTfR, serum hepcidin and hs –CRP were also found. Serum hepcidin level correlated positively with BMI and hs- CRP, but negatively with iron level in obese group. **Conclusion:** Results of the present study appear to strengthen the hypothesis that obesity, as a low grade inflammation state, stimulates the production of many inflammatory markers such as CRP which can up-regulate hepcidin synthesis by adipocytes. As a result, increased hepcidin levels may lead to poor iron status in obesity.

Keywords: Obesity, Hepcidin, Iron deficiency, Children

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Acknowledgment

*First and above all, thanks to **GOD**, the most **Beneficial** and **Merciful** for helping me bring this work to light*

The sincere and honest help of many people, made it possible for this work to be accomplished. I wish to thank them all, even though I can list only a few names

*I am much obliged and deeply indebted to **Professor Dr.Hayam Kamal Nazif,** Professor of Pediatrics, Department of Medical Studies, Institute of Post graduate Childhood Studies, Ain Shams University, for her valuable help, competent guidance and fruitful criticism throughout the work*

*Production of this thesis wouldn't have been accomplished without the prodigious guidance, constant encouragement and experienced advice of **Prof. Dr. Azza Abd El Shaheed Abd Allah**,Professor of Child Health, Head of Medical Division, National Research Center , for whom I would like to express my deep gratitude and appreciation.*

*And I would like to express my deepest and sincere thanks to **Prof. Dr. Karima Abbass El Shamy**,Professor of Medical Physiology, National Research Center , for her faithful supervision and guidance and her overwhelming kindness that has been of great help throughout this work.*

*I wish to express my deep everlasting gratitude to **Prof. Dr .Manal Abd EL Moneam Mohsen,** Professor of Child Health, National research Center, for her kind supervision, valuable advice, comments and remarks.*

*I'm also so grateful to **Dr. Nevein Naim Fadl** Researcher of Medical Physiology, National Research Center, for her kind and generous cooperation in the practical part of this thesis.*

*This thesis is dedicated to all the children in the world, by whom and for whom this work existed, may **God** bless and cure them all.*

*Finally words are not enough to express my love and gratitude to my dear **Father**, **Prof. Dr. Selim Ismail Moustafa** , for his love and support throughout my life . I am greatly honoured and blessed to be his daughter; I owed him all the success and happiness in my previous and coming life, **THANKS DAD.***

*Special thanks to my **Mother**, on whose constant encouragement and endless love I had relied on throughout my life.*

*To my **Fiancée**, thank you for your support during completion of this work.*

Finally, you are all mentioned in my prayer of thanks to God

ABBREVIATIONS

AA	:	Amino acid
AAP	:	American Academy of Pediatrics
AHA	:	The American Heart Association
Arg	:	Arginine
Asp	:	Aspartic acid
ATCUN	:	Amino terminal Cu2+- Ni2+
B-blockers	:	Beta Blockers
BF	:	Breast Fed
BIPAP	:	Bi level positive airway pressure
BMI	:	Body mass index
BMP	:	Bone morphogenic protein
BP	:	Blood Pressure
BWT	:	Birth weight
Cap	:	capsules
CAD	:	Coronary artery disease
CBC	:	Complete blood cell count
CDC	:	Centers for disease control and prevention
CHr	:	Reticulocyte hemoglobin content
CPAP	:	Continuous positive airway pressure
CRP	:	C-reactive protein
CT	:	Computed Tomography
CVD	:	Cardiovascular disease
DcytB	:	Duodenal cytochrome B
DMT	:	Divalent metal transporter
DEXA	:	Dual energy X-ray absorptiometry
DHEA-S	:	Dehydroepiandrosterone-sulfate
DNA	:	Deoxyribonucleic acid
DM	:	Diabetes Mellitus
EDTA	:	Ethylene-diamine-tetra-acetic acid
ELISA	:	Enzyme –Linked Immunosorbant assay
EPP	:	Erythrocyte protoporphyrin
ER	:	Endoplasmic reticulum
FDA	:	The Food and Drug Administration
Fe^{2+}	:	Ferrous iron
Fe^{3+}	:	Ferric iron
FEP	:	Free erythrocyte protoporphyrin
FF	:	Fast Food
GH	:	Growth hormone
GIT	:	Gastrointestinal tract
GLP-1	:	Glucagon-link peptide-1

HAMP	:	Hepcidin anti-microbial peptide gene
Hb	:	Haemoglobin
HC	:	Hip circumference
HCP1	:	Heme carrier protein 1
HCT	:	Haematocrite
HDL	:	High-density lipoprotein
HFE	:	Hemochromatosis iron protein
HJV	:	Hemojuvelin
HO	:	Heme oxygenase
hs-CRP	:	high sensitive C-reactive protein
Ht	:	Height
HTN	:	Hypertension
ICP-MS	:	Inductively coupled plasma-mass spectrometry
ID	:	Iron deficiency
IDA	:	Iron deficiency anemia
IGF-1	:	Insulin like growth factor-1
IL	:	Interleukin
IOTF	:	International Obesity Task Force
IDE	:	Iron deficient erythropoiesis
JAK	:	Janus kinase
LDL	:	Low density lipoprotein
LEAP-1	:	liver-expressed antimicrobial peptide
LFTs	:	Liver function tests
Lys	:	Lysine
MCH	:	Mean corpuscular haemoglobin
MCHC	:	Mean corpuscular haemoglobin concentration
MCV	:	Mean corpuscular volume
MRI	:	Magnetic Resonance Imaging
MS	:	Metabolic syndrome
NA	:	Not available
NCHS	:	National Centre for Health and Statistics
NHANES	:	National Health and Nutrition Examination Study
NMR	:	Nuclear magnetic resonance
NS	:	Not significant
NSAIDs	:	Non-steroidal anti-inflammatory drugs
OSA	:	Obstructive sleep apnea
PCOS	:	Polycystic ovary syndrome
PP BMI	:	Prepregnancy body mass index
PWS	:	Prader – Willi syndrome
RE	:	reticuloendothelial

R/F ratio	:	Ratio of serum transferrin receptor to serum ferritin
RBCs	:	Red blood cells
RNA	:	Ribonucleic acid
RDW	:	Red – cell distribution width
SDS	:	Standard deviation scores
SES	:	Socioeconomic status
SGA	:	Small for Gestational Age
SI	:	Serum iron
SMR	:	sexual maturity rating
SPSS	:	Statistical Package for the Social Sciences
sTfR	:	Serum transferrin receptor
TF	:	Serum transferrin
TfR	:	transferrin receptor
TGF	:	Transforming growth factor
TGF-β	:	Transforming growth factor-β
TIBC	:	Total iron binding capacity
TNF α	:	Tumour necrosis factor alpha
TR	:	Timed release
Trp	:	Tryponine
TS%	:	Transferrin saturation percentage
TV	:	Television
UCP-2	:	uncoupling-2
UK	:	United Kingdom
UIBC	:	Unsaturated or latent iron binding capacity
UNICEF	:	United Nations Children's Fund
US	:	United State
USA	:	United State of America
USF	:	Upstream stimulation factor
W/H ratio	:	Waist / Hip ratio
WBCs	:	White blood cells
WC	:	Waist circumference
Wt	:	Weight
WHR	:	Waist/Hip ratio
WHO	:	World Health Organization

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Introduction

Nutrition in childhood has a significant impact on lifelong health. Obesity and iron deficiency are two of the most common nutritional disorders worldwide ***(Harris, 2004)*** .

Obesity, a disease defined by an excess accumulation of body fat to the extent that health is adversely affected has become a global public health concern ***(WHO ,2000)*** .

Obesity is diagnosed by body mass index equal to or greater than 95th percentile for age and sex in a given population where BMI is calculated by dividing the weight in kilograms by the height in meters squared *BMI = Weight (kg) / Ht (m2)* ***(Washington ,2005)*** .

The prevalence of childhood overweight and obesity is increasing, with the worldwide prevalence having doubled or tripled in industrialized countries over the past few decades ***(Wang & lobstein, 2006)***.

The same trends have been observed in developing countries , for example in Egypt , studies have found that the prevalence of childhood obesity increased markedly as ***El Damatti et al (1996)*** reported a prevalence rate of over weight and obesity to be 13.4 % and 6.7 % respectively , ***Hafez et al (2000)*** reported prevalence rate to be 14 % and 7 % respectively while ***Mansour et al (2004)*** reported prevalence of overweight and obesity to be 14 % and 11 % respectively .

Iron deficiency continues to be the most prevalent single micronutrient deficiency disease in the world, affecting billions of people ***(Stoltzfus, 2001).***

The development of iron deficiency occurs in stages, beginning with the depletion of iron stores, followed by diminished iron transport, and finally the depletion of iron-containing proteins and enzymes,

including hemoglobin, which results in iron deficiency anemia ***(Celsing ,1986)*** .

Data from the third National Health and Nutrition Examination Survey (NHANES III) ,1988-1994 determined that overweight American children were twice as likely to be iron deficient than normal-weight children ***(Nead et al.,2004)*** .

The association between iron status and obesity is one that should be explored , as obesity and iron deficiency are diseases that continue to evolve worldwide, and both have significant public health implications ***(McClung and Karl, 2009)*** .

A number of different factors have been typically proposed to explain the association between iron deficiency and obesity. Eating unbalanced meals e.g. low cost fast food that are particularly rich in carbohydrates and fat but contain a low quantity of essential nutrients such as iron has been claimed as the most important cause for this association ***(Seltzer & Mayer, 1963)***.

Radically changing this sound point of view, a recent study investigating the intake of heme and non heme iron in a convenience sample of more than 200 obese subjects showed that differences in iron intake , or of dietary factors known to affect iron absorption , were not associated with the lower serum iron concentrations found in obese patients ***(Menzie et al.,2008)*** .

Adipose tissue is now recognized as an endocrine organ that can contribute to the inflammatory process by secreting pro-inflammatory cytokines, also named adipokines, and the resulted inflammatory state may have an important pathogenic role in some obesity-related co morbidities ***(Nathan, 2008)***.

Some studies have recently supported the idea that iron deficiency could represent one of the co morbidities associated with the typical