Research Article

Interplay of Serum Hepcidin Level with Female Sex Hormones, Obesity and Insulin Resistance Between Fertile and Postmenopausal Women.

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Abstract
Introduction: Hepcidin has emerged as the central regulatory molecule of systemic iron homeostasis . **Aim of the work:** First this study aimed to explore the possible influence of female sex hormones, obesity IR & fat distribution on hepcidin 25 level during menstrual cycle phases of fertile women and during postmenopausal state. Second to study the correlation of hepcidin to cardio metabolic risk variable: Anthropometric& laboratory investigations. **Subjects and Methods:** The present observational hospital-based study was conducted in Internal Medicine Department, Minia University Hospital from June 2016 to June 2017. This study included 160 women (96 fertile & 64 postmenopausal women) who were selected from attendant to outpatient clinic for checkup examination. both fertile & postmenopausal women classified according to BMI into obese & non-obese groups. **Results:** The present study was conducted in Minia University Hospital at Internal Medicine Department; outpatient-clinic. It included 160 women who were classified into fertile and postmenopausal groups. Both groups were sub-classified according to BMI into obese & non-obese subgroups .

Key words:
ALT: Alanine transaminase apo : Apoprotein ASOs: Antisense oligonucleotides

Introduction
Hepcidin has emerged as the central regulatory molecule of systemic iron homeostasis. It is a 25-amino acid peptide hormone that is produced and secreted predominantly by hepatocytes, and to lesser extent by adipose tissue circulates in the bloodstream, and is excreted by the kidneys[(1)]

By binding to the cellular iron exporter ferroportin (FPN) and inducing its internalization and degradation, hepcidin regulates cellular iron efflux. Elevated hepcidin levels cause decreased iron absorption from the gastrointestinal tract and prevent the release of iron from hepatocytes and macrophages, resulting in hypoferremia[(2)].

Conversely, low hepcidin levels cause an increase in iron absorption from the gastrointestinal tract and promote iron release from iron stores, resulting in hyperferremia, the synthesis of hepcidin is regulated by certain physiologic and pathologic processes. Hepcidin concentrations are decreased in situations that require increased concentrations of circulating iron. In case of increased erythropoiesis, for example in response to hypoxia, anemia, iron deficiency, or conditions characterized by ineffective erythropoiesis e.g. Thalassemia major and intermedia, a decreased hepcidin concentration will result in the release of stored iron and in an increase in the dietary iron absorption. on the other hand, infection and inflammation cause an increase in hepcidin synthesis[(3).]

Premenopausal non-pregnant women with regular menstrual cycle have higher estradiol 2 and low ferritin. Meanwhile, postmenopausal women have low estradiol and high ferritin. In addition, premenopausal women have significant lower hepcidin than postmenopausal women[(4)]

During menses serum iron and hepcidin decrease then rebound increase, then stabilize during second half of menstrual cycle[(5)].

Estrogen increases hepcidin gene expression in some studies but decrease in others. Recent in vitro fertilization study showed that circulating hepcidin 25 is reduced by endogenous estrogen production by marked gonadotropin stimulation, On the other hand, progesterone enhances hepcidin in experimental animals and cell culture. Hepcidin also increased after administration of progesterone among non-pregnant women undergo in- vitro fertilization [6]

These data encouraged us to investigate effect of female sex hormones on hepcidin level during fertile and postmenopausal state & thus may alter body iron homeostasis an aspect not studied before[7]. The relation between iron homeostasis & IR is bidirectional however the relation of insulin resistance (IR) & hepcidin is still unclear .In one study, insulin resistance purse as in type2 diabetes (T2DM) & polycystic ovary syndrome (PCOS) women is associated with inadequate hepcidin produced with reduced hepcidin concentration [8]

Metabolic syndrome is associated with higher hepcidin level which positively correlates to IR assessed by homeostasis model for the assessment of IR (HOMA-IR). Overweight and obese individuals have higher hepcidin compared to matched individuals & hepcidin was negatively correlated to HOMA-IR [9]

Aim of the work

First this study aimed to explore the possible influence of female sex hormones, obesity IR & fat distribution on hepcidin 25 levels during menstrual cycle phases of fertile women and during postmenopausal state.

Second to study the correlation of hepcidin to cardio metabolic risk variable: Anthropometric & laboratory investigations.

Subjects and methods

The present observational hospital-based study was conducted in Internal Medicine Department, Minia University Hospital from June 2016 to June 2017. This study included 160 women (96 fertile & 64 postmenopausal women) who were selected from attendant to outpatient clinic for checkup examination. both fertile & postmenopausal women classified according to BMI into obese & non-obese groups. The study protocol was approved by the Institutional Ethics Committee and carried out according to the ethical guidelines of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. Prior to inclusion, all participates gave written informed consent before enrolling in this study.

Exclusion criteria:

Women with one of the following criteria were excluded from the study: Age less than 20 years, pregnancy, lactation or irregular menses. Anemia which was defined as Hb <12gm/d1. Recent infection or inflammation.

Chronic inflammatory disease, autoimmune diseases or any systemic diseases as DM, CVD, liver & renal diseases.

Malignancy.

Any Medical or hormonal treatment affecting level of studied parameters within three months of the study, including hormonal contraception, insulin sensitizers, insulin and others.

Previous ovarian surgery.

Results

The present study was conducted in Minia University Hospital at Internal Medicine Department; outpatient-clinic. It included 160 women who were classified into fertile and postmenopausal groups. Both groups were subclassified according to BMI into obese & non-obese subgroups.

Fertile women were 96 subjects aged from 22 to 43 years with mean ±SD 32.5 ±5.9. Obese fertile women: they included 60 subjects aged from 23-41 years with mean± SD of 32.7±5.4

Non-obese fertile women: they included 36 subjects aged from 22-43 years with mean±SD of 32.3±6.7

Postmenopausal women were 64 subjects aged from 47 to 70 years with mean±SD of 57.1±6.6.

Obese postmenopausal women: They included 40 women aged from (47-70) years with mean± SD of 58.1±6

Non-obese postmenopausal women: they included 24 women aged from (47-70) years with mean±SD of 56.6±6.9

Table (1) shows demographic characteristics of studied subjects.

Fertile women were comparable to postmenopausal women as regard: weight, height, BMI, obesity percentage, waist circumference, WHR & IR signs. However, post-menopausal had

statistically significant higher age, hip circumference, SBP & diastolic blood pressure (DBP) (p. values of <0.001, 0.007, 0.001 & 0.001 respectively).

Table (1): Demographic Characteristics of Studied Subjects.

Variables	Fertile (n=96)	Post menopause (n=64)	p-value
Age: (years)			
Range	(22-43)	(47-70)	<0.001*
Mean ± SD	32.5±5.9	57.1±6.6	
Weight: (kg)			
Range	(50-95)	(60-92)	0.797
Mean ± SD	76.2±11.6	76.6±9.6	
Height: (cm)			
Range	(151-174)	(156-172)	0.360
Mean ± SD	163.4±5.1	162.8±3	
BMI: (Kg/m2)			
Range	(20.3-35)	(22.3-35)	0.482
Mean ± SD	28.5±4.3	29±4.2	
Obesity(a)			
Non-obese: (%)	36(37.5%)	24(37.5%)	1
Obese: (%)	60(62.5%)	40(62.5%)	
Waist circumference: (cm)			
Range	(83-120)	(88-129)	0.108
Mean ± SD	102.7±11	105.5±10.5	
HIP circumference: (cm)			
Range	(96-115)	(98-121)	0.007*
Mean ± SD	104.8±4.8	107±5.2	
WIIR Range	(0.8-1.1)	(0.8-1.1)	0.879
Mean ± SD	1±0.1	1±0.1	
IR Signs(b),			0.232
No: (%)	63(65.6%)	36(56.3%)	
Yes: (%)	33(34.4%)	28(43.8%)	
SBP: (mmHg)			
Range	(110-140)	(105-145)	0.001*
Mean ± SD	123±9.6	128.4±11	
DBP: (mmHg)			
Range	(60-86)	(65-86)	0.001*
Mean ± SD	74.9±7.5	78.5±6.1	

BMI = body mass index, WHR= waist hip ratio, IR= insulin resistance, SBP= systolic blood pressure, DBP= diastolic blood pressure, a: obesity means BMI>30 kg/ m2, b: IR signs as skin tags, acanthosis nigricans, central obesity. Quantitative data are expressed as mean ± SD & compared by using Independent samples t test. Qualitative data are expressed as percentage & compared by using Chi square test. *: Significant level at p value < 0.05.

Discussion

Hepcidin has emerged as the central regulatory molecule of systemic iron homeostasis. It is produced and secreted predominantly by hepatocytes, but also subcutaneous and visceral adipose tissue, may contribute to systemic hepcidin levels. Heart, kidney, retina, monocytes, macrophages, alveolar cells, and pancreatic f3 cells has also been described.[9] These tissues have a considerable low level of hepcidin gene expression in comparison to the liver and its significance is still remaining uncertain. Hepcidin circulates in the bloodstream, then is excreted by the kidneys. It regulates cellular iron efflux by binding to the cellular iron exporter FNP and inducing its

internalization and degradation, .Hepcidin production increases in response to iron loading, and this prevents further absorption of dietary iron and the development of iron overload. Hemorrhage, hemolysis, decreased Hb, hypoxia or injections of Epo, all result in a rapid decrease in hepcidin. Hepcidin is rapidly increased by inflammatory and infectious stimuli & may contribute to the development of IRA[10].

The relation of IR & serum ferritin is bidirectional Postmenopausal women had higher IR & abdominal fat compared to fertile women who were BMI match In addition, the body undergo several physiological changes during menopause as decreased estrogen & progesterone levels and increased ferritin & hepcidin levels Increased ferritin was attributed to cessation of menses[11]

Recommendation:

Further population-based study with large number of subjects. Further studies to assess therapeutic use of insulin sensitizers to lower hepcidin level in hyper-hepcidemic conditions as dysmetabolic iron overload syndrome, malignancy, inflammatory conditions & IRA.

Further studies to assess therapeutic use of progesterone, estrogen or both in diseases associated with low hepcidin levels as ineffective erythropoiesis to avoid iron overload conditions.

Further studies to assess role of hepcidin lowering agents in dysmetabolic iron overload syndrome.

Further study to assess the effect of controlling cardiometabolic risk factors in lowering hepcidin level in a longitudinal studies.

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