Evaluation of serum ferritin and hepcidin level and their association with obesity in Iraqi obese women

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Abstract. Obesity is a chronic disease renowned as a global epidemic. Prevalence of obesity proceeded as highly elevated to almost two-thirds of the world population, including Iraq. One of the major reasons of overweight and obesity is increasing food intake. Obese people are often suffering from chronic inflammatory state due to a variation in immune efficiency in the adipose tissue. Our research aims to assess the ferritin and hepcidin level in obese women with and without hypertensive. Eighty of obese women were participants as volunteers, as well as, 40 subjects as healthy control. Based on Body Mass Index (BMI), Waist Circumference (WC), Waist to Height Ratio (WHtR) and Waist to Hip Ratio (WHpR). Participants were divided into two categories, the: first with BMI ≥ 18.5 – 25 kg/m² as non-obese (control) and the, second with BMI ≥ 30 kg/m² as obese subjects. The studied parameters showed the following results: A significant elevation in TG, LDL, VLDL, glucose, AST, ALT, calcium, Creatinine, Uric acid, Urea, ferritin and hepcidin in obese (for both obese women and hypertensive obese women) compared with control group, while a significant decrease was noticed in HDL level in obese group as compared with control group. This study improved that ferritin and hepcidin can be considered as good markers to monitoring obesity, showing a high increase with increasing BMI.

Keywords: Obesity, obese hypertensive, Lipid profile, ferritin, hepcidin.

1. Introduction

Obesity is a complicated health issue that appears from multiple leading and contributing factors, including unhealthy lifestyles. Because of the complication of ideas, it is troublesome to decrease weight at the beginning and then to keep it[1]. The first stage in the assessment of obesity is the calculation of BMI. It is calculated by dividing weight (kg) by square height(m²). Where: BMI ≥ 18.5 – 25 kg/m² represents a non-obese (control), while BMI ≥ 30 kg/m² represents obese subjects. The obesity is a risk factor for atherogenic dyslipidemia, insulin resistance, hypertension, type 2 diabetes mellitus, coronary heart disease, sleep apnea, gall stones and osteoarthritis[2]. Obesity can be defined as: disturbance of body weight regulatory systems described by an accumulation of excess body lipid. Many metabolic pathways are included in the uptake, transport and storage of fats[3]. Hepcidin, a peptide with 25 amino acid found in serum and urine, act like a major regulator of iron metabolism by binding to the iron transporter ferroportin resulting in internalization and lysosomal degradation [4] and [5]. Ferritin, the major iron storage protein and disperse everywhere. Regulation of iron homeostasis is mostly through iron regulatory proteins (IRE)/iron-responsive elements (IRE) and hepcidin. Ferritin is used as a marker of iron deficiency in different healthcare facilities [6],[7]and[8]. Increase percentage of obesity come from environmental, habitual, and genetic circumstance. Despite genetic circumstance are necessary for evaluating person ability to becoming overweight, widely defined environmental circumstance such as changes in food cooking, agriculture, physical activity, and marketing, transportation. These lifestyle
steps affect obesity through their effects on diet and physical activity[9] and [10]. Hepcidin, a peptide with twenty-five amino acid found in serum and urine, work like a main regulator of iron metabolism by binding to the iron transporter ferroportin bring in internalization and lysosomal degeneration [4] and [5]. Ferritin, the major iron storage protein and disperse everywhere. Regulation of iron homeostasis is mostly through iron regulatory proteins (IRE)/iron-responsive elements (IRE) and hepcidin. Ferritin is applied as a sign of iron deficiency in several healthcare facilities [6] and [7] and [8]. Hepcidin is induced by an iron overload and by inflammation[11] and [12]. It inhibits iron entry into the circulation by blocking dietary intake in the duodenum, the freeing of recycled iron from macrophages and the way out of stored iron of hepatocytes. Varied signals responding to iron stores, erythropoietic activity and host defence collect to regulate hepcidin produced and thereby influence iron homeostasis. More hepcidin is produced by hepatocytes when iron is plentiful, limiting further iron absorption and release from stores. Ferritin is a sign of inflammation rather than iron case in overweight and obese people [8]. Consequently, hepcidin has emerged as a powerful biomarker for the diagnosis and supervision of a large spectrum of iron-regarding disorders. High hepcidin expression will reduction plasma iron levels, whereas weak hepcidin expression will growth iron concentration [13]. For decades it has been recognized that hypertension is very common in obese individuals. Several mechanisms by which obesity associated with hypertension including vascular injury, renal injury, sympathetic nervous system (SNS) overstimulation, renin-angiotensin-aldosterone system (RAAS) dysfunction and others [14]. Therefore, the present work will concentrate on correlating of serum ferritin and hepcidin with lipid profile, hypertension and body mass index to discover out whether it is right to consider ferritin and hepcidin as a true test of inflammatory in overweight and obese persons or not.

2. Materials and Methods
The study was conducted at Department of Obesity Research and Therapy Unit in Al Kindy College of Medicine, Baghdad, Iraq, between September 2019–January 2020. Eighty female’s subjects were enrolled obesity and hypertension patients, with age range between (18-65 years). The diagnosis of obesity and hypertension was made based on the recommended criteria by WHO. All of them did not have any other diseases. The study was including 40 subjects as healthy control, with same age range. The 80 participants were divided into two groups, group I consists of 40 females with obesity, while group II consists of 40 females with obesity and hypertension.

Laboratory parameters were assessed on blood samples. The analyzed biochemical indices involved evaluated of serum glucose, uric acid, urea, total cholesterol, High-density lipoprotein (HDL), low-density lipoprotein (LDL), Triglycerides (TG), Creatinine, Fasting blood sugar (FBS), Calcium, Very low-density lipoprotein (VLDL), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT). These indices were assayed using laboratory kits (Agappe, India), (Linear, Spain) and (Human, Germany). The ELISA kits that were used for ferritin and hepcidin determination were (Monobind Inc, USA) and (Human, Germany), respectively. Statistical analyses were finished depending on the Statistical Package for the Social Sciences (version 26). Parameters were presented and analyzed using descriptive statistic mean ±standard deviation (mean ±SD). The relation between all indices in obese subjects with each other's were assessed using Pearson correlation coefficient and the probability calculation were done using ANOVA test, Duncan test, and student’s t-test.

3. Results and Discussion
Eighty female voluntaries aged between 18-65 years participated in the present study. The general demographic characteristics of these subjects are shown in Table 1.

Table 1. Demographic characteristics of female participants.
Parameters | Control, N=40 (mean ± SD) | Obese, N=40 (mean ± SD) | Obese with Hypertension, N=40 (mean ± SD)
---|---|---|---
Age (years) | (31.37±15.51) A | (32.43±10.77) A | (33.10±9.89) A
BMI(Kg/m2) | (22.85±1.64) B | (41.30±10.85) A | (42.53±11.87) A
WHR | (0.48±0.04) B | (0.74±0.12) A | (0.79±0.20) A
WHpR | (0.77±0.04) B | (0.95 ± 0.12) A | (0.93 ± 0.08) A
W.C. (cm) | (79.0±6.25) B | (119.43±16.30) A | (120.13±18.31) A
AIP | (0.31±0.08) A | (0.58±0.12) B | (0.64±0.12) B

*The different letters referred to significant differences between the compared groups, while similar letters referred to non-significant differences between the compared groups.

The age category (mean ±SD) among controls (31.37 ± 15.51), obese (32.43 ± 10.77) and Obese with Hypertension female (33.10 ± 9.89), there are no significant differences in age, which remove the age factor that may influence on the clinical parameters of the study.

The results of the category account (mean ± SD) of the BMI indicate:
- Control female (22.85± 1.64) compared with that of obese female (41.30± 1.64), show a highly significant.
- Controls females (22.85± 1.64) compared with that of obese with hypertension female (42.53 ± 11.87) show a highly significant.
- Obese (41.30± 1.64) compared with that of obese with hypertension female (42.53 ± 11.87) show a non-significant.

The results of the category account (mean±SD) of WHtR, WHpR and WC indicate:
- Control female compared with that of obese female, show a highly significant.
- Control female compared with that of obese with hypertension female, show a highly significant.
- Obese compared with that of obese with hypertension female, show a non-significant.

The results of the category account (mean±SD) to estimate Atherogenic Index of Plasma (AIP) indicates:
- Control female compared with that of obese female, show a highly significant.
- Control female compared with that of obese with hypertension female, show a highly significant.
- Obese compared with that of obese with hypertension female, show a non-significant.

In addition, the levels of serum lipid profile and other parameters among groups according to gender are presented in Table 2. The mean levels of cholesterol, TG, HDL, LDL, VLDL, glucose, AST, ALT, Calcium, uric acid, urea, ferritin and hepcidin in obese females had significantly higher when compared with the control group. Dissimilarly, the mean concentration of HDL value of obese had significantly lower when compared with that of control subjects.

| Parameters | Controls, N=40 (mean ± SD) | Healthy Obese, N=40 (mean ± SD) | Obese with Hypertension, N=40(mean ± SD) |
|---|---|---|---|
| FBS (mg/dL) | (94.86±9.21) B | (103.10±16.13) A | (107.38±20.47) A |
| Cholesterol(mg/dl) | (152.74±17.83) B | (261.07±61.93) A | (277.13±74.72) A |
| HDL(mg/dl) | (48.4±4.29) B | (38.02±5.3) A | (38.28±6.27) A |
| LDL(mg/dl) | (85.39±16.44) B | (209.06±64.67) A | (181.3±68.85) A |
| VLDL(mg/dl) | (19.72±2.96) C | (29.31±6.30) B | (33.36±6.62) A |
| TG(mg/dl) | (99.10±14.78) C | (146.33±32.38) B | (166.92±33.13) A |
| ALT(U/L) | (22.37±5.22) A | (34.40±21.12) B | (49.43±25.00) C |
| AST (U/L) | (28.53±6.0) A | (43.87±18.17) B | (64.73±32.89) C |
| Urea(mg/dL) | (26.30±6.49) B | (32.06±9.19) A | (35.52±6.98) A |
| Uric acid(mg/dL) | (4.73±0.79) B | (5.40±1.38) A | (5.78±1.29) A |
| Creatinine(mg/dL) | (0.63±0.07) C | (0.73±0.08) B | (0.78±0.08) A |
Calcium (mg/dl) (8.87±0.88) A (8.74±0.65) A, B (8.45±0.59) B
Hepcidin (Pg/ml) (1344.38±825.88) B (2536.75±444.91) A (2591.41±252.94) A
Ferritin (Pg/ml) (21.15±26.78) B (47.05±39.21) A (49.13±34.80) A

*The different letters referred to significant differences between the compared groups, while similar letters referred to non-significant differences between the compared groups.

4. Correlation Study

The correlation coefficient (r) test was used for describing the association between the ferritin and hepcidin with other parameters which appeared the following results in the obese: there is a significant correlation between serum ferritin levels and age, BMI, WHPR, AIP, urea. Also, the following results in the obese with hypertension: there is a significant correlation between serum ferritin levels and age, ferritin, BMI, WHPR, AIP, WHtP, cholesterol, HDL, LDL, TG and urea. The results of this study indicated that there is no such correlation between hepcidin and other parameters, as illustrated in Tables 3 and 4.

Table 3. Correlation between ferritin and hepcidin with different parameters in obese group.

| Parameters | Hepcidin R | Hepcidin S | Ferritin R | Ferritin S |
|------------|------------|------------|------------|------------|
| Age        | .118       | .541       | .632**     | .000       |
| BMI        | .093       | .632       | -.453*     | .014       |
| W.C        | -.127      | .511       | -.340      | .071       |
| WHPR       | .341       | .070       | .485**     | .008       |
| WHtR       | .155       | .421       | -.223      | .245       |
| AIP        | .358       | .057       | .455*      | .013       |
| FBS        | -.288      | .129       | -.051      | .793       |
| Urea       | .067       | .730       | -.542**    | .002       |
| Creatinin  | .078       | .681       | .010       | .957       |
| ALT        | .107       | .573       | .112       | .556       |
| AST        | .084       | .657       | .041       | .828       |
| Cholesterol| .247       | .188       | -.092      | .631       |
| HDL        | .238       | .206       | -.053      | .782       |
| LDL        | .162       | .391       | -.149      | .431       |
| Triglyceride| .153      | .419       | .335       | .070       |
| VLDL       | .157       | .407       | .333       | .072       |
| Calcium    | .264       | .159       | .069       | .719       |
| UA         | .237       | .206       | -.129      | .496       |
| Hepcidin   | 1          | -          | -.273      | .144       |
| Ferritin   | -.273      | .144       | 1          | -          |

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Table 4. Correlation between ferritin and hepcidin with different parameters in obese with hypertension group.

| Parameters | Hepcidin R | Hepcidin S | Ferritin R | Ferritin S |
|------------|------------|------------|------------|------------|
| Age        | .118       | .541       | .632**     | .000       |
| BMI        | .093       | .632       | -.453*     | .014       |
| W.C        | -.127      | .511       | -.340      | .071       |
| WHPR       | .341       | .070       | .485**     | .008       |
5. Discussion

Obesity has become globally a main health risk in the wide world, which lead to many medical and public health complications[15]. The WHO has defined obesity in terms of BMI and there is a strong curvilinear correlation with relative body fat mass[16]. The BMI cannot be considered as distribution of fat on one’s body; so, it cannot be utilized to monitoring central obesity. The WC estimates visceral fat and central obesity, but it does not account for height. Studies, found that, in contrast to BMI and WC, WHtR and WHpR might also be related with cardiovascular diseases[17]. Moreover, BMI used to represent the total body fat quantity, while WC, WHpR and WHtR used as surrogates for the centralization of body fat [18] and [19]. Upper results have been appeared clearly increased in BMI, WC, WHtR, WHpR, glucose, lipid profile, FBS, ALT, AST, Urea, Uracil acid, Creatinine, Calcium, ferritin and hepcidin in females obese. In other hand, there was a decrease in HDL in obese subjects compared with control one. In sera specimen, the results of lipid Profile agree with other studies, Abulnaja et.al. [20], Al-Saadi, N. H. [21], Elffers D.W.et. al. [22], Sari M.I. et.al. [23] and Agarwa P. et.al. [24].

In obesity, the adipocytes are full of TGs and the hypertrophied adipocytes have no space for extra room to store more TGs, hence the liver will receive a magnificent amounts of TGs, consequently liver increases the secretion of VLDLs[25]. Also, the expression of lipoprotein lipase in adipose tissue is reduced during obesity, which results in the defect of lipolysis [26]. Furthermore, the increasing of TG level increases the exchange of cholesterol esters and TG between VLDL and HDL by Cholesteryl Ester Transfer Protein (CETP), which causes to decrease the concentration of HDL cholesterol in the plasma, as well as a reduction of the TG content in LDL[25].In sera specimen, the results of ALT and AST agree with two studies, Yang Z. et.al. [27] and Kawamoto R. et.al. [28]. Increasing level of visceral fat and fat deposited in obese skeletal muscle and liver. The hepatocytes release elevated amounts of ALT and AST with increasing liver fat [29].In sera specimen, the results of urea in agreement with different studies, Scaglione R. et.al.[30], Ray A.S. et.al.[29].

Obesity imposes a hemodynamic burden to the kidneys, which is characterized by glomerular hyperfiltration and microalbuminuria with elevating kidney dysfunction, propose a fundamental variation in metabolism of nitrogen to obese, when compared with normal BMI individuals. So, the observation that obese individuals conserve nitrogen greater efficiently might be accounted for either by a decreasing rate of amino acid oxidation, or an increasing rate of rescue of urea nitrogen [30]. In
Hyperuricemia occurs as a result of the elevated production of uric acid, low uric acid excretion, or both [33]. In obese persons, other factors cause hyperuricemia, is an elevated exogenous proteins consumption and endogenous of uric acid production [34]. In sera specimen, the results of Creatinine in agreement with other studies, Okoro et.al. [35], Alaje A.K. et.al. [36]. Obesity and hypertension may elevate the hazard for chronic kidney disease [37], glomerular hyperfiltration [38] and end-stage renal disease [41]. This may explain the elevation of blood creatinine levels. In sera specimen, the results of Calcium agree with other studies by Dalfardi et.al. [40] and Hamoui et al [41].

Furthermore, results of hepcidin agree with different studies, Tussing-Humphreys L.M. et.al.[42], Sanad M. et.al.[43], sal E. et.al.[44] and Auguet T. et.al.[45]. Hepatocytes are the predominant producers of hepcidin. High levels of hepcidin are produced by hepatocytes when iron is abundant, limiting further absorption of iron and release from stores. IL-6 acts as a hepcidin stimulator. Obesity can be accompanied an elevated range of pro-inflammatory cytokines such as IL-6. It produced and increased by visceral adipose tissue. That hepcidin elevated when IL-6 rise [46]. In sera specimen, the results of Ferritin are in agreement with different researches, Shattanw K.K. et.al. [47], Ryan B.J. et.al.[48], Shim Y.S. et.al.[7], Khan A. et.al.[8] and hitha H. et.al.[49]. Hepcidin (a hormone) that regulates iron flow in plasma, it is induced by an iron overload and by inflammation [11] and [12], and it also, inhibits iron entry into the circulation by blocking the dietary absorption by the duodenum, the release of the recycled iron from the macrophages and exit the stored iron from the hepatocytes. Varied signals that respond to the iron stores, erythropoietic activity and host defence converge to regulate hepcidin secretion and therefore affect the iron homeostasis. Hepatocytes are the predominant producers of hepcidin. High level of hepcidin is produced by hepatocytes when iron is abundant, which limits the absorption of further iron and releases from stores [50]. Ferritin is a marker for inflammation instead of iron status in overweight and obese people. Being an acute phase reactant, a high level of ferritin secondary of subclinical overweight inflammation and Obese people can mask the underlying deficiency of iron [8].

6. Conclusions
In summary, the results of this study revealed a strong relationship between obesity, ferritin and hepcidin in the serum of obese females. Where, both obese females and obese with hypertension females showed even a greater level of ferritin and hepcidin which could refer to the importance of these parameters as a pathway between obesity and the induction of hypertension. Also, confirm the correlation of ferritin and hepcidin with lipid profile, hypertension and BMI.

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8. Conflicts of Interest
The authors declare no conflict of interest.

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