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Correlation between serum levels of hepcidin and ferritin in patients with metabolic syndrome in R. Macedonia

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ABSTRACT

The metabolic syndrome (MS) is a complex of interrelated risk factors for cardiovascular disease and diabetes. These factors include hyperglycemia, hypertension, high triacylglycerol levels, low HDL-cholesterol (HDL-c) levels, and abdominal obesity. Evidence suggests that iron influences glucose metabolism, even in the absence of significant iron overload. Iron stores, expressed as serum ferritin concentration, have been proposed to be a component of the insulin-resistance syndrome. In 1997, Moirand et al. first reported the presence of histologically proven liver iron overload in overweight subjects with abnormal glucose metabolism and dyslipidemia. The aim of this study was to evaluate the correlation between serum levels of hepcidin and ferritin in patients with metabolic syndrome in R.Macedonia. The study included 240 subjects - 60 males are with MS and 60 males as control group. 60 females are with MS and 60 females as control group. Individuals aged 18 years or older were eligible to participate in the study. In this analysis we included subjects with available complete data allowing their classification according to established criteria for MetS. In detail, the following features were considered: 1) abdominal obesity, defined as the presence of waist circumference ≥102 cm in men or ≥88 cm in women; 2) fasting plasma glucose ≥ 6.1

mmol/l or drug treatment for elevated blood glucose; 3) serum triglycerides ≥ 1.69 mmol/l or drug treatment for elevated triglycerides; 4) serum HDL cholesterol in men< 1.03 mmol/l and <1.29 mmol/l in women or drug treatment for low HDL-C; 5) blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure. Statistical analysis showed that males and females with MS had statistically higher ferritin levels than control group. Statistical analysis showed that males and females with MS had statistically higher hepcidin levels than control group. Serum ferritin levels significantly correlate with hepcidine in all participants with MS excluded females control group.Body mass, BMI, waist circumference, hip circumference, and WHR are statistically significant higher in subjects with MS compared to control groups. Concentrations of lipid parameters for all examinated groups. The concentrations of HDL-cholesterol, triglycerides and apo A are significantly increased in subjects with MS compared to control groups. It has been demonstrated that the prevalence of MS is increasing worldwide, largely the result of greater obesity and sedentary lifestyles. The concentration of serum hepcidin is associated with gender. Males hepcidine levels are higher than females levels. We found a statistically higher hepcidin levels in both groups with MS, compared to control groups, and males hepcidine levels are almost twice higher then females hepcidine levels in bout groups (control group and group with MS). The authors found a strong positive relationship between increased iron stores measured by the concentration of plasma ferritin and risk of type 2 diabetes, impaired glucose tolerance and metabolic syndrome in middle age and older people. The average concentration of ferritin in men is almost twice higher than in postmenopausal women, and three times higher than in premenopausal women with metabolic syndrome.

1. Introduction

The metabolic syndrome (MS) is a complex of interrelated risk factors for cardiovascular disease and diabetes. These factors include hyperglycemia, hypertension, high triacylglycerol levels, low HDL-cholesterol (HDL-c) levels, and abdominal obesity (de Carvalho et al., 2013, Alberti et al., 2009) . Separately the MS components increase the risk of diabetes, cardiovascular disease and all-cause mortality, but the full syndrome is associated with risk increases that are greater than the sum of the risk of each feature (Gami et al., 2007). It has been reported that the association of MS with cardiovascular disease increases total mortality 1.5 times and cardiovascular death 2.5 times (Sociedade Brasileira., 2005). People with MS also have a 5-fold higher risk of developing type 2 diabetes (de Carvalho et al., 2013). It has been demonstrated that the prevalence of MS is increasing worldwide, and for the adult population is estimated to be about 20 to 25%, largely the result of greater obesity and sedentary lifestyles (de Carvalho et al., 2013, Alberti et al., 2009).

Evidence suggests that iron influences glucose metabolism, even in the absence of significant iron overload (Fernandez-Real et al., 2002,Sam et al., 2013). Mildly elevated body iron stores are associated with increased fasting serum insulin and blood glucose (Sam et al., 2013, Tuomainen et al., 1997). The

underlying mechanism for the increased body iron stores in conditions of insulin resistance is unclear. Iron stores, expressed as serum ferritin concentration, have been proposed to be a component of the insulin-resistance syndrome. Indeed, the concentration of circulating ferritin was significantly associated with centrally distributed body fatness as well as with several other measurements of obesity (Fernandez-Real et al., 2002, Gillum, 2001). In the apparently healthy general population, serum levels of ferritin were also positively correlated with baseline serum glucose and with the area under the curve for glucose during the glucose oral tolerance test (Fernandez-Real et al., 2002, Tuomainen et al., 1997, Fernandez-Real et al., 2002). Ferritin levels also correlated with diastolic arterial blood pressure, even after adjustment for BMI (Fernandez-Real et al., 2002).

In 1997, Moirand et al. first reported the presence of histologically proven liver iron overload in overweight subjects with abnormal glucose metabolism and dyslipidemia (Nicola et al., 2012, Moirand et al., 1997). Nevertheless, the complex pathophysiological links between iron and metabolic derangements remain poorly understood (Dongiovanni et al., 2011). In the last ten years, hepcidin has emerged as the key iron-regulatory hormone (Ganz, 2011). It is a 25-amino-acid peptide predominantly synthesized in the liver (Park et al., 2001, Pigeon et al., 2001). Hepatic secretion of hepcidin in response to iron overload negatively regulates iron homeostasis. Hepcidin prevents iron efflux from enterocytes, macrophages and hepatocytes into the plasma by inducing internalization and degradation of the iron exporter ferroportin in these cells (Nemeth et al., 2004).

The aim of this study was to evaluate the correlation between serum levels of hepcidin and ferritin in patients with metabolic syndrome in R.Macedonia.

2. Materials and methods

The study included 240 subjects - 60 males are with MS and 60 males as control group. 60 females are with MS and 60 females as control group. Individuals aged 18 years or older were eligible to participate in the study. In this analysis we included subjects with available complete data allowing their classification according to established criteria for MetS. In detail, the following features were considered: 1) abdominal obesity, defined as the presence of waist circumference ≥102 cm in men or ≥88 cm in women; 2) fasting plasma glucose ≥ 6.1 mmol/l or drug treatment for elevated blood glucose; 3) serum triglycerides ≥ 1.69 mmol/l or drug treatment for elevated triglycerides; 4) serum HDL cholesterol in men< 1.03 mmol/l and <1.29 mmol/l in women or drug treatment for low HDL-C; 5) blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure. Subjects were considered to have MetS when they had at least three of the above-mentioned five traits.

Exclusion criteria were history of: cirrhosis or chronic hepatitis B and C, clinical evidence of bleeding in the previous 6 months, anemia (hemoglobin <120 g / L), treatment with iron in the previous year, alcohol consumption - women with daily consumption of alcohol > 40 g / day and men with daily alcohol consumption > 60 g / day, donation of blood in the previous 6 months, haemochromatosis, concomitant infections, malignant disease, chronic diseases other than diabetes mellitus type 2, immunosuppressive therapy, acute infections or invasive procedures (operations, catheterization) in the previous 6 months, neurological, endocrine or other systemic diseases, cardiovascular incident in the previous 6 months and pregnancies.

A written informed consent was obtained for all the subjects included in the study. All subjects filled out a questionnaire about the family history, physical activity and alcohol consumption. Subjects had light indoor clothes and were barefooted during the measurement of their height and weight. Their standing height was measured with stadiometer to the nearest 0.1 sm. Weight was measured using a digital weight scale eith a precision of 0.1 kg. Waist and hip were measured with the tape measure. Waist-to-hip ratio (WHR) was calculated by dividing the circumference of the waist by dividing of the hip. The blood samples were taken after overnight fast (12 hours). Blood pressure was measured using a mercury manometer. Lipid parameters, glucose, ferritin and transferine were measured in fresh sera by enzymatic methods, using biochemical analyzer Biosystems A25. Hepcidin was determined by ELISA kit (DRG Hepcidin-25 bioactive ELISA, Marburg).

The data are presented as mean± standard deviation (SD) and $p \leq 0.05$ is considered statistically significant. The results were done with the SPSS version 16, statistical significance was test with paired

Student's t – test, and Pearson correlation coefficient was used for correlatin of hepcidin and ferritin levels.

3. Results

All 240 participants were divided in 4 groups: males control group, females control group, males with MS, females with MS.

Table 1
Concentrations of transferine, ferritine and hepcidine in 4 groups : males control group, females control group, males with MS, females with MS.

Variables	Males control group	Males with MS	p	Females control group	Females with MS	p
Transferin	279.97±56.28	264.4±61.47	0.151	232.86±35.43	246.62±40.95	0.053
Ferritin	120.17±70.66	197.95±142.57	0.000	69.02±49.36	118.98±70.31	0.000
Hepcidin	12.33±7.37	25.54±1.33	0.000	6.16±3.20	11.22±5.30	0.000

The concentration of ferritin in males control group was ranged from 9 to 309 (mean 120, 17 ± 70,669) and in females control group was ranged from 10 to 257 (mean 69,02 ± 49,36). The concentration of ferritin in males with MS was ranged from 34 to 668 (mean 197,95 ±142,57) and in females with MS was ranged from 11 to 456 (mean 118,98± 70,311). Statistical analysis showed that males and females with MS had statistically higher ferritin levels than control group.

The concentration of hepcidin in males control group was ranged from 3 to 36 (mean 12,337 ± 7,37) and in females control group was ranged from 1,235 to 14,748 (mean 6,163± 3,202). The concentration of hepcidin in males with MS was ranged from 2,474 to 85,98 (mean 25,54 ± 18,33) and in females with MS was ranged from 2,933 to 24,055 (mean 11,228± 5,302). Statistical analysis showed that males and females with MS had statistically higher hepcidin levels than control group.

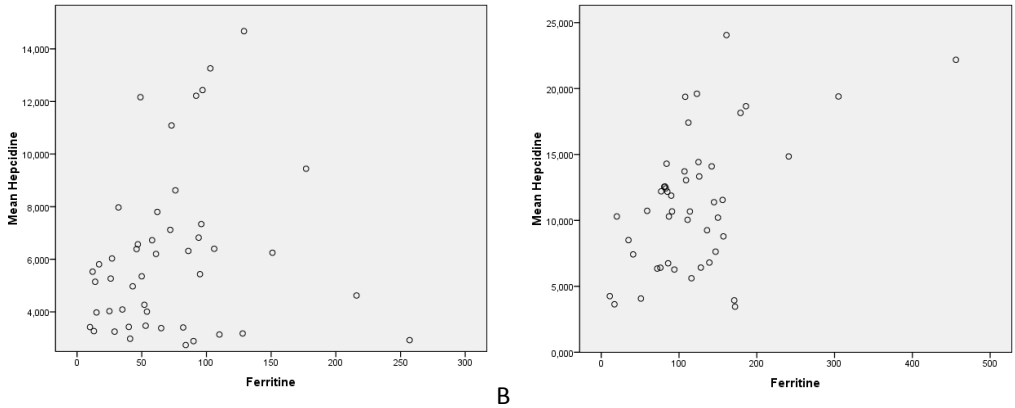
The anthropometric characteristics of each group are shown in Table 2.

Table 2
Anthropometric characteristic of participants.

Variables	males control group	males with MS	p	females control group	females with MS	p
Age (years)	39.73±12.256	51.03±7.94	0.000	43.57±12.183	54.70±6.426	0.000
Body mass (kg)	81.6±10.65	96.35±16.57	0.000	74.47±17.766	84.90±14.451	0.001
Hight (m)	174.83±7.547	174.18±9.19	0.67	164.18±6.299	160.85±7.424	0.009
BMI (kg/m2)	26.75±3.543	31.67±4.298	0.000	27.577±6.329	32.796±5.030	0.000
Waist circumference (cm)	91.33±11.419	109.68±13.25	0.000	92.002±14.702	107.45±12.222	0.000
Hip circumference (cm)	99.52±10.186	110±9.789	0.000	107.52±14.571	116.43±12.636	0.000
WHR	0.919±0.067	1.002±0.0683	0.000	0.855±0.072	0.932±0.067	0.000

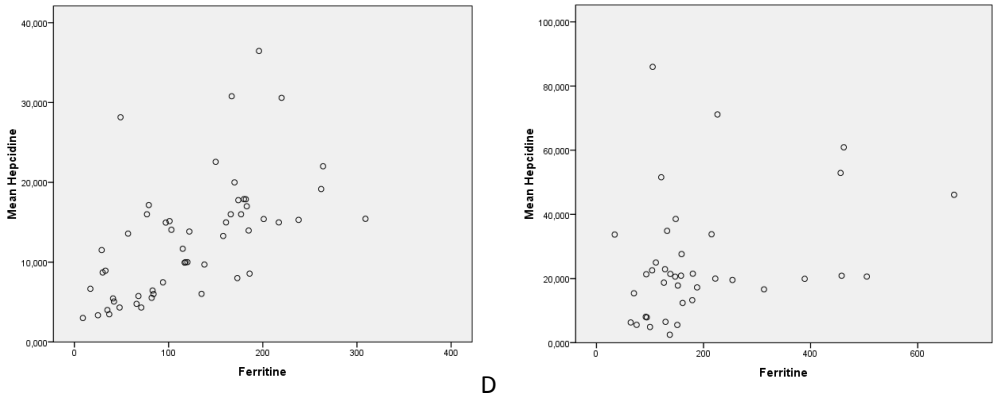
Table show that body mass, BMI, waist circumference, hip circumference, and WHR are statistically significant higher in subjects with MS compared to control groups.

Serum ferritin levels significantly correlate with hepcidine in all participants with MS excluded females control group.



A B

Fig. 1. Correlation between hepcidin level and ferritin in females control group (r =0,205 p>0,01) (A) and females with MS (B) (r =0,439 ; p <0,01).



C D

Fig. 2. Correlation between hepcidin level and ferritin in males control group (r =0,591; p <0,01) (C) and males with MS (D) (r = 0,416 ; p < 0,01).

Table 3
Concentrations of lipid parameters in 4 groups: males control group, females control group, males with MS, females with MS.

Variables	Males control group	Males with MS	p	Females control group	Females with MS	p
Total cholesterol (mmol/l)	5.17±0.6	5.57±1.26	0.028	4.93±0.9	5.2±1.15	0.145
HDL-cholesterol(mmol/l)	1.41±0.33	1.19±0.29	0.000	1.57±0.42	1.32±0.27	0.000
LDL-cholesterol(mmol/l)	3.02±0.55	2.94±1.49	0.711	2.83±0.82	2.86±1.09	0.852
Triglycerides (mmol/l)	1.49±0.53	2.59±1.26	0.000	1.18±0.47	1.97±0.83	0.000
Apo A	112.62±57.61	89.42±30.78	0.007	136.47±48.4	99.93±28.66	0.000
Apo B	150.6± 33.29	179.22±30.78	0.000	148.04±39.41	161.22±31.13	0.044

Table 3 displays the concentrations of lipid parameters for all examinated groups. The concentrations of HDL- cholesterol and triglycerides are significantly increased in subjects with MS compared to control groups.

4. Discussion

It has been demonstrated that the prevalence of MS is increasing worldwide, largely the result of greater obesity and sedentary lifestyles. This is a problem because MS increase the risk of diabetes, cardiovascular disease and mortality. The concentration of serum hepcidine is associated with gender. Males hepcidine levels are higher than females levels.

We found a statistically higher hepcidin levels in both groups with MS, compared to control groups, and males hepcidine levels are almost twice higher then females hepcidine levels in bout groups (control group and group with MS).

In the recent years, a bulk of evidence, particularly from epidemiological studies (Bozzini et al., 2005, Sheu et al., 2003, Jiang et al., 2004, Jehn et al., 2007) have established a link between iron metabolism and insulin resistant states, including type 2 diabetes mellitus and the MetS (Rajpathak et al., 2009). On the other hand, some prospective studies (Jiang et al., 2004), (Jehn et al., 2007) have shown a positive association between baseline levels of ferritin, i.e. the best available serum marker of body iron stores (Cook et al., 2003), and development of type 2 diabetes. The authors found a strong positive relationship between increased iron stores measured by the concentration of plasma ferritin and risk of type 2 diabetes, impaired glucose tolerance and metabolic syndrome in middle age and older people (Liang et al., 2008).

The authors found the average concentration of ferritin in men is almost twice higher than in postmenopausal women, and three times higher than in premenopausal women with metabolic syndrome (Istvan et al., 2007). The authors found ferritin concentration in serum is positively related to dyslipidemia (Halle et al., 1997, Williams et al., 2002). The authors found ferritin is positively associated with increased triglycerides in females and males with MS (Megan et al., 2004).The authors found ferritin is connected to one or more of the characteristics of MS (Festa et al., 2002, Toumainen et al., 1997, Jehn et al., 2004,Bozzini et al., 2005).

Of note, when women with or without MS were stratified by ferritin levels, MS women with ferritin in the lower range had hepcidin levels significantly higher than non-MS counterpart. Since this was particularly evident in women with ferritin levels indicating true iron deficiency where hepcidin is generally almost completely suppressed (Traglia et al., 2011), this suggests that some MS-related factors may affect hepcidin in this subgroup. On the other hand, the influence of MS per se on hepcidin levels appears limited when iron stores are abundant.

Our results may warrant further studies on adults in this direction, particularly focusing on differences by gender.

5. Conclusion

The concentration of serum hepcidine is associated with gender. Males hepcidine levels are higher than females levels. The concentration of hepcidin was higher in males and females with MS compared to the control groups. The ferritine showed a high correlation with hepcidine levels in all examinated groups excluded females control group.

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