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Serum Iron Metabolism Variables in Clinically Healthy Persons

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Abstract

BACKGROUND: In healthy persons, iron acquisition, trafficking and storage are strictly regulated processes due to the lack of a physiological pathway for the excretion of excess iron from the body. The liver, the duodenum and the bone marrow are involved in the regulation of iron metabolism.

MATERIAL: Subject to the testing were 60 healthy volunteers who took part in clinical trials.

METHODS: Case histories, physical check-up and demographic data including people's heights and weights, laboratory studies and tests using medical equipment.

RESULTS: None of the healthy persons were reported to have shown any deviation from the reference values for the serum markers of iron metabolism tested with the exception of hepcidin.

CONCLUSION: In healthy persons, there was only a positive correlation between iron level and IBC, and feedback between hepcidin serum levels and transferrin saturation.

Introduction

Iron homeostasis depends on a complex mechanism on the principle of feedback between the needs of the human body for iron and intestinal absorption. There is no physiological mechanism for the excretion of excess iron. The hepcidin hormone, discovered in 2001, is now considered to be the key regulator of iron homeostasis. The impaired regulation of hepcidin is the reason for many of the iron homeostasis disorders [1], [2].

In healthy persons, iron absorption, transport and storage are strictly controlled processes due to the lack of a physiological pathway for the excretion of excess iron from the body. The liver, the duodenum and the bone marrow are involved in the control of iron metabolism. Healthy elderly people have approx. 4 grams of iron in their bodies, about 3 grams of which are used to synthesize hemoglobin in the erythrocytes. When the erythrocytes get mature and die, their hemoglobin breaks down into its constituent parts-heme and globin. The heme-free iron is transferred from the transferrin to return to the heme synthesis cycle for erythropoiesis. These facts show that in a completely healthy adult, the body re-uses most of the available iron. Just 1 mg of iron is discharged from the body on a daily basis, mainly through the urine, faeces, enterocyte and epidermal desquamation in men, and through menstruation in women. Discharged iron is replaced by iron absorbed by the gastrointestinal tract through the food.

Material and Methods

Material

Subject to the testing were 60 healthy volunteers involved in clinical trials None of them had

any medical history, physical, laboratory, serological (HIV, HBV, HCV and acute HAV infection) testing as well as ECG and ultrasound data for current or past liver and gallbladder diseases, anemia, diabetes mellitus, cardiovascular, renal and other significant diseases, pregnancy, medication and toxic substance intake, including absolute alcohol over 20g daily, and any other conditions that could affect the results.

Methods

1. Case histories, physical check-up and demographic data.

2. Standard and specific disease-excluding laboratory blood and urine tests, immunological and virological studies.

3. Laboratory test for evaluation of iron exchange: - Serum iron (men: 12.5 – 26 mmol/L; women: 10.5 - 23 mmol/L); - TIBS (44 - 66 mmol/L); - transferrin saturation (Fe ÷ TIBC × 100% –20-40%); - serum ferritin (men: 20 – 280 mg/L women: 10 – 140 mg/L).

Case histories, physical check-up and demographic data including: height, weight, BMI [(kg/m^2 = body weight (kg)**/**Height (m^2)], waist circumference. The changes in body mass were calculated using the WHO-based BMI classification (Table 1) [2], [4].

Table 1: Assessment criteria for the changes in body mass according to the deviations from the WHO-based BMI [3], [4]

Group*	BMI (kg)/m2
Underweight by BMI	< 18.5
Normal weight by BMI	18.5 – 24.9
Overweight by BMI	25.0 – 29.9
Obesity by BMI	≥ 30.0
- Class 1	30.0 – 34.9
- Class 2	35.0 – 39.9
- Class 3	≥ 40

*****Other classes **–** morbid obesity (BMI - 40-50) and super obesity (BMI > 50).

Results

In none of the healthy persons we observed any deviation in the serum markers of iron metabolism tested from the reference values with the exception of hepcidin. Twelve of the investigated persons (20%) showed hepcidin below the lower reference value.

The mean values for the iron metabolism variables are given in Table 2.

The serum iron levels in healthy persons showed a positive correlation with IBC (Pearson correlation, r = 0.303, p = 0.019). There was also a reciprocal correlation between the serum hepcidin levels and transferrin saturation (Pearson correlation r = - 0.675, p = 0.0001).

Table 2: Serum iron metabolism variables in healthy people

	Iron metabolism variable	Healthy persons
Serum iron (mmol/L	Minimum	23.70
	Maximum	812,00
	Mean	18.30
	Median	16.80
	Standard deviation	4.66
IBC (mmol/L)	Minimum	10.80
	Maximum	30.2
	Mean	56.80
	Median	58.00
	Standard deviation	6.14
Ferritin (mg/l)	Minimum	45.00
	Maximum	73.5
	Mean	147.32
	Median	115.50
	Standard deviation	91.59
Transferrin saturation (%)	Minimum	68.00
	Maximum	397.00
	Mean	31.15
	Median	29.50
	Standard deviation	5.31
Hepcidin (ng/ml)	Minimum	21.00
	Maximum	40.01
	Mean	99.14
	Median	113.35
	Standard deviation	32.94

Relation of serum iron metabolism variables to sex, age and BMI

In the group of healthy persons, we identified that the serum iron, IBC and ferritin values were considerably higher with men than those with women (Table 3) and also that there was no significant differences in transferrin saturation (p = 0.143) and hepidine (p = 0.228) between both sexes.

Table 3: Serum iron metabolism variables (x± SD) relating to the sex of clinically healthy persons (Mann-Whitney)

	Variable	Healthy persons		
		Men	Women	P=
Serum iron (mmol/L	Mean	18.84	17.77	0.008
	Standard deviation	3.09	5.83	
IBC (mmol/L)	Mean	58.76	54.84	0.034
	Standard deviation	6.44	5.21	
Ferritin (mg/l)	Mean	152.83	141.80	0.002
	Standard deviation	72.14	108.62	
Transferrin saturation (%)	Mean	32.27	30.03	0.143
	Standard deviation	5.38	5.08	
Hepcidin (ng/ml)	Mean	94.80	103.47	0.228
	Standard deviation	34.26	31.54	

We identified no difference in the serum markers of iron metabolism of people under 45 years of age and those over 45 years old (Table 4). Furthermore, we could not prove any relation based on age.

Table 4: Serum iron metabolism variables (x± SD) for clinically healthy persons aged under 45 and those aged over 45 (Mann-Whitney)

	Variable	Healthy persons		
		< 45 r	> 45 r	P
Serum iron (mmol/L)	Mean	18.86	18.03	0.678
	Standard deviation	5.18	4.42	
IBC (mmol/L)	Mean	56.82	56.80	0.771
	Standard deviation	6.13	6.22	
Ferritin (mg/l)	Mean	127.10	157.43	0.327
	Standard deviation	66.05	101.25	
Transferrin saturation (%)	Mean	29.95	31.75	0.194
	Standard deviation	5.64	5.10	
Hepcidin (ng/ml)	Mean	108.72	94.35	0.111
	Standard deviation	26.24	35.15	

The average BMI value for the group of healthy persons was 23.01 ± 2.54 (ranging between 19.5 and 29.70), 50 (83%) of whom had normal body weight (BMI < 25) and the remaining 10 were overweight (BMI > 25 and < 30). No significant relation was identified between BMI and the serum iron metabolism variables (Table 5).

Table 5: Serum iron metabolism variables (x± SD) for clinically healthy persons, obese and not obese (BMI > 30 and < 30) (Mann-Whitney)

Variable	BMI group	Mean value	Standard Deviation	P =
Serum iron (mmol/L)	< 30	20.98	7.67	0.0001
	> 30	27.62	7.25	
IBC (mmol/L)	< 30	64.50	11.45	0.0001
	> 30	74.92	11.92	
Ferritin (mg/l)	< 30	194.68	192.83	0.0001
	> 30	355.93	231.10	
Transferrin saturation (%)	< 30	31.30	7.44	0.003
	> 30	35.38	7.24	
Hepcidin (ng/ml)	< 30	87.59	39.94	0.002
	> 30	64.65	39.15	

Discussion

In recent years, there has been an increased interest in the conditions and diseases accompanied by higher iron status and their evolution. Currently there are no sufficient comparative data available on the incidence and the characteristics of such disorders in people with chronic liver diseases compared to healthy people. For this purpose, we studied the serum iron metabolism in 60 healthy persons.

Iron is essential for a number of key biological processes including erythrocyte production, DNA synthesis and cellular respiration [3], [5], [6]. The normal iron content in the body of an adult man is 35-45 mg. iron per kilogram of body weight [3]. Most of the iron is combined with hemoglobin in the erythrocytes. The rest is distributed in the myoglobin in the muscles, in the tissue enzymes and the plasma transferin [3]. The liver parenchymal cells and the reticuloendothelial macrophages serve as a depot for storage of excess iron [3], [7]. In connection with its potential to take part in reactions as a transition metal, iron can be toxic in the cell [7], [1]. Iron-mediated generation of highly toxic Reactive Oxygen Species (ROS) plays a major role in the process leading to iron overload-related diseases [8].

Since there is no physiological pathway for the removal of excess iron from the body, iron acquisition, metabolism and storage must be strictly regulated [2], [6], [9]. A large number of new iron-regulating molecules, including iron transporters and soluble mediators, have been identified in recent years. Divalent Metal Transporter-1 (DMT1, also known as Nramp2) is a multifunctional transmembrane protein [4], [10], [11] responsible for the passage of non-food iron through the apical surface of the absorbing enterocytes in the duodenum. Ferroportin (also known as MTP1, Ireg1) transports iron into the blood. As a portable metal, iron undergoes reduction and oxidation reactions during this cell intake [7], [11]. Iron circulates in the plasma by binding to glyco protein, transferrin (Tf). The iron delivering Tf is absorbed by the cell to form compounds with transferrin receptor 1, TrfR [3], [7], [10].

Regulation of the iron metabolism involves many organs – the duodenum, the liver, the bone marrow. The identification of hepcidin-peptide emphasizes the importance of the liver in iron homeostasis. Hepcidin is an antimicrobial peptide that is isolated from human urine and blood [3], [6]. It is synthesized in the liver hepatocytes. Hepcidin synthesis in the liver is sensitive to iron levels-it increases in the presence of excessive iron and decreases in cases of iron deficiency [12], [13], [14].

Interestingly, the synthesis of hepcidin is also regulated by inflammatory signals and by the inflammatory cytokines IL-1 and IL-6 [1], [15]. The role of the Kupffer cells in the regulation of hepcidin levels in inflammation is disputable.

Hepcidin plays a major role in iron metabolism by inhibiting intestinal iron metabolism and iron release by the macrophages [7], by binding to ferroportin and inducing cellular penetration and degradation [15].

In conclusion, a better understanding of the molecular mechanisms that regulate the iron homeostasis can help develop therapeutic strategies and diagnostic methods for the detection of liver diseases in their early stages before they could turn into chronic diseases and cause irreversible liver damage.

In healthy persons there is only a positive correlation between iron level and IBC, and feedback between hepcidin serum levels and transferrin saturation.

References

1. Kaplan J, O'Halloran TV. Iron metabolism in eukaryotes: Mars and Venus at it again. Science. 1996; 271:1510-1512. https://doi.org/10.1126/science.271.5255.1510 PMid:8599104

2. Knutson M, Wessling-Resnick M. Iron metabolism in the reticuloendothelial system. Crit Rev Biochem Mol Biol. 2003; 38:61-88. https://doi.org/10.1080/713609210 PMid:12641343

3. Antonov K. Chronic viral hepatitis. Current state and prospects. Medinfo. 2007; 7(11): 30-32.

4. Gastroenterology and Hepatology, edited by Prof. Z. Krastev and Prof. K. Chernev (add year of publication).

5. Adzharov D, Petkova G, Koseva O. Iron as a pathogenetic factor in chronic HCV infection. Bulgarian Hepatogastroenterology. 2005; 2:33-37.

6. Grigorov N. Abdominal Echography in the Gastroenterology Manual. Diagnostics in a row. L Dinkov, S Stoynov. PIKS Ltd., Sofia, 1997:279-290.

7. Andrews NC. Disorders of iron metabolism. N Engl J Med. 1999; 341:1986-1995. https://doi.org/10.1056/NEJM199912233412607 PMid:10607817

8. Liu Z, Qiao J, Nagy T, Xiong MP. ROS-triggered degradable iron-chelating nanogels: Safely improving iron elimination in vivo. J Control Release. 2018; 283:84-93. https://doi.org/10.1016/j.jconrel.2018.05.025 PMid:29792889

9. Pietrangelo A. Pathogens, Metabolic Adaptation, and Human Diseases–An Iron-Thrifty Genetic Model. Gastroenterology. 2015; 149(4):834–838. https://doi.org/10.1053/j.gastro.2015.08.003 PMid:26291901

10. Nai A, Lidonnici MR, Rausa M, et al. The second transferrin receptor regulates red blood cell production in mice. Blood. 2015; 125(7):1170–1179. https://doi.org/10.1182/blood-2014-08-596254 PMid:25499454 PMCid:PMC4399753

11. Andrews NC, Iron metabolism: iron deficiency and iron overload, Annu Rev Genomics Hum Genet. 2000;1:75-98. https://doi.org/10.1146/annurev.genom.1.1.75 PMid:11701625

12. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 2004; 306(5704):2090–2093. https://doi.org/10.1126/science.1104742 PMid:15514116

13. Zumerle S, Mathieu JR, Delga S, et al. Targeted disruption of hepcidin in the liver recapitulates the hemochromatotic phenotype. Blood. 2014; 123(23):3646–3650. https://doi.org/10.1182/blood-2014-01-550467 PMid:24646470

14. Wang CY, Babitt JL. Hepcidin regulation in the anemia of inflammation. Curr Opin Hematol. 2016; 23(3):189–197. https://doi.org/10.1097/MOH.0000000000000236 PMid:26886082 PMCid:PMC4993159

15. McCord JM. Iron, free radicals, and oxidative injury. Semin Hematol. 1998; 35:5-12. PMid:9460805