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Iron metabolism and hepcidin concentration in teenagers before and after exercise in relation to the HFE gene status

Barbara Kaczorowska-Hac
Department of Occupational Therapy, Gdansk University of Physical Education and Sport, Gdansk, Poland,
barbara.kaczorowska@awf.gda.pl

Marcin Luszczyk
Department of Physiology, Gdansk University of Physical Education and Sport, Gdansk, Poland

Jedrzej Antosiewicz
Department of Bioenergetics and Physiology of Exercise, Medical University of Gdansk, Gdansk, Poland

Jan Jacek Kaczor
Department of Muscle Neurobiology, Gdansk University of Physical Education and Sport, Gdansk, Poland

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Abstract

Background: The aim of the study was to compare the influence of exercise on iron metabolism and hepcidin concentration between carriers of His63Asp mutation (H63D polymorphism) and wild type HFE gene males. Iron is an essential micronutrient required for various biological processes. Systemic iron homeostasis is maintained in a hormone-like negative feedback mechanism by the 25-amino acid peptide hepcidin. Hepcidin controls duodenal iron absorption and iron recycling from senescent erythrocytes using tissue macrophages through the down-regulation of the sole known iron cell exporter, ferroportin-1. Exercise may induce an inflammatory response that leads to changes in iron metabolism. Material and methods: Iron, ferritin, hepcidin concentration and transferrin saturation were measured in carriers of His63Asp mutation of HFE and wild type teenagers before and after cycle ergometer exercise. Results: His63Asp carriers had higher basal hepcidin concentration than wild type probands ($p < 0.05$). Interestingly, the analysis of the correlation between iron and hepcidin concentration showed a positive tendency in H63D carriers, while the wild type group showed a negative tendency at the basal and post-exercise point. Conclusions: This study demonstrates that exercise has a distinct impact on iron metabolism through the hepcidin pathway with regard to the HFE gene status.

Keywords

HFE gene, hepcidin, iron, H63D polymorphism, exercise

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Barbara Kaczorowska-Hać[1 ABE], Marcin Łuszczyk[2 BC], Jędrzej Antosiewicz[3 D], Jan Jacek Kaczor[4 D]

[1] Department of Occupational Therapy, Gdansk University of Physical Education and Sport, Gdansk, Poland

[2] Department of Physiology, Gdansk University of Physical Education and Sport, Gdansk, Poland

[3] Department of Bioenergetics and Physiology of Exercise, Medical University of Gdansk, Gdansk, Poland

[4] Department of Muscle Neurobiology, Gdansk University of Physical Education and Sport, Gdansk, Poland

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Corresponding author: Corresponding author: Dr. Barbara Kaczorowska-Hac, Gdansk University of Physical Education and Sport - Department of Occupational Therapy; Gorskiego 1, Gdansk 80-336, Poland; phone no.: +48 58 5547334; e-mail: barbara.kaczorowska@awf.gda.pl.

INTRODUCTION

Iron is a trace mineral required for various biological processes, which include erythropoiesis, oxidative metabolism, DNA replication, and cellular immune response [1]. Systemic iron homeostasis is maintained in a hormone-like negative feedback mechanism by the liver-produced 25-amino acid peptide, hepcidin [2]. Hepcidin production is up-regulated by inflammation and iron loading and is suppressed in the setting of anemia and in response to hypoxia [3]. Hepcidin controls duodenal iron absorption and iron recycling from senescent erythrocytes using tissue macrophages through the down-regulation of the sole known iron transmembrane exporter, ferroportin-1. It operates by binding to the iron exporter ferroportin in iron-releasing target cells, mainly tissue macrophages and duodenal enterocytes, but also other cell types. The binding of hepcidin occludes iron efflux and triggers ubiquitination, internalization and lysosomal degradation of ferroportin [3]. Hepcidin expression restricts intestinal iron absorption, macrophage iron release and reduces body iron stores, thus limiting iron for erythropoiesis [4]. A variety of pathologic conditions are associated with inadequate hepcidin production. Deregulation of hepcidin expression is a common feature of hereditary hemochromatosis due to *HFE* gene mutation; therefore, low hepcidin causes iron overload. Hepcidin expression in the liver is mainly controlled by the BMP-SMAD pathway, and the BMP type I receptors ALK2 and ALK3 are responsible for iron-dependent hepcidin upregulation and basal hepcidin expression [5]. Regular exercise decreases body iron stores [6], and recently it has been suggested that hepcidin may be an important mediator in this process. Therefore, the purpose of the study was to compare the influence of exercise on iron metabolism and hepcidin concentration between carriers of His63Asp mutation (H63D polymorphism) and wild type *HFE* gene males. Taking into consideration exercise induced inflammatory response and its impact on hepcidin secretion, we evaluated hematologic parameters, iron metabolism and hepcidin concentration in six healthy male teenagers and six carriers of H63D *HFE* gene mutation before and after cycle ergometer exercise.

MATERIAL AND METHODS

Subjects

We analysed twelve male teenagers aged from 15 to 18 years (mean age 17.0 ±1.00 years): carriers of His63Asp mutation (H63D polymorphism) of *HFE* gene (n = 6) and wild type (n = 6).

All the probands were in good condition, and concomitant infections were excluded. The subjects' physical activity included informal exercise (running, swimming, team games or cycling) 2 hours per week in addition to their normal school physical education lessons (4 hours per week). Patients were requested to refrain from intense physical activity for the 2 days prior to testing. Before enrolment into the study, the patients underwent a complete physical check-up, carried out by a physician, aimed at detecting possible contraindications to the exercise test. The patients were measured and weighed using standard techniques. Z-score values were determined for body height, body mass and the body mass index (BMI) [7]. The body surface area (BSA) was calculated using the equation previously described [8]. To reduce a measurement error, the patients were familiarized with the experimental procedure. The patients then performed a cardiopulmonary exercise test (CPET). The exercise test was preceded and followed by a cardiopulmonary function test and blood assays.

All patients performed a CPET on an electrically braked cycle ergometer (ViaSprint 150P, Ergoline, Bitz, Germany). Before the five-minute warm-up at 1.5 $W \cdot kg^{-1}$, the patients had a three-minute resting period to allow for the recording of baseline cardiopulmonary values. The exercise intensity was then increased by steps of 25 $W \cdot min^{-1}$ until exhaustion. During the CPET, patients had to maintain a pedalling frequency between 50 and 60 $revolution \cdot min^{-1}$, at the investigators' strong verbal encouragement. It was judged that an exercise was at or near the maximal level when patients showed clinical signs of intense effort, were unable to maintain the required pedalling frequency and when at least one of the following criteria was met: the heart rate at peak exercise (HR_{peak}) of >180 $beats \cdot min^{-1}$ or a respiratory exchange ratio at peak exercise (RER_{peak}) of > 1.0.

During CPET, patients breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) connected to a calibrated respiratory gas analysis system (Jaeger Oxycon Pro, Viasis Healthcare GmbH, Höchberg, Germany). Oxygen uptake was determined on-line from breath-breath ventilation and metabolic gas exchange measurements averaged at ten-second intervals. The heart rate was monitored continuously by telemetry (Polar Monitors, Electro, Kempele, Finland). All equipment was calibrated according to the instructions of the manufacturer before every test. Peak oxygen uptake (VO_{2peak}) and other absolute values at peak exercise were calculated as the average value over the last thirty seconds prior to termination of the CPET as previously described [9].

There were no chronic disorders, i.e. hemochromatosis or hemoglobinopathies in parental families. Parents denied following a vegetarian diet, iron pills administration, and meat consumption was adequate for the patient's age. In order to exclude acute and chronic illnesses, all patients underwent physical examination and laboratory assays. Abdominal ultrasonography was also performed and no abnormalities were revealed.

The study was officially approved by the Bioethical Committee of the Regional Medical Society in Gdansk NKBBN/523/2013 according to the Helsinki Declaration. Prior to the study, ethical approval of procedures and an informed consent of both the children and their parents were obtained.

Study organisation and methodology

Before exercise and five minutes after exercise blood samples were taken from an antecubital vein into single-use containers with an anticoagulant (EDTAK2). After collection, all of the samples were immediately placed at 4 C and, within 10 min of collection were centrifuged at 3000g at 4 C for 10 min.

Hepcidin serum levels were measured using a commercial ELISA kit (DRG Hepcidin ELISA kit; DRG Instruments GmbH, Germany) that included a 5-point reference curve from 0 to 140 ng/mL and two level internal quality controls automated on a DSX ELISA processing system (Dynex technologies, Technogenetics, Milan, Italy) according to the manufacturer's instructions.

The laboratory assays included a full blood count with reticulocytosis and microscopic evaluation, protein C concentration, aspartate and alanine transaminases activity, bilirubin, creatinine levels, HBsAg and anti-HCV antibodies. Blood count with reticulocytosis was performed using SYSMEX XE 2100, whereas, AST (aspartate aminotransferase), ALT (alanine aminotransferase), bilirubin, creatinine levels, HBsAg, a-HCV antibodies, ferritin, transferrin, and protein C concentration were performed using ARCHITECT CI 8200 (ABBOTT). All reagents

used were supplied by the manufacturer. Iron metabolism was also assessed by measuring iron concentration, ferritin, and transferrin saturation (SYSMEX XE 2100, Architect ci 8200, and Test 1 SDL).

To obtain the *HFE* gene status, patients underwent genetic testing for HFE mutations using Real-Time PCR and melting curve analysis methods with the *HFE* H63D S65C C282Y (TibMolbiol) LightMix in-vitro diagnostics kit and LightCycler 2.0 Instrument (ROCHE). Two fragments of the *HFE* gene were amplified simultaneously: 163 bp fragment containing two polymorphisms: c.187C>G (63 H/D), c.193A>T (65 S/C) and 284 bp fragment containing the c.845G>A (282 C/Y) polymorphism. The genotype results were detected in two different optical canals based on melting temperatures. The mutant type 63D allele displayed higher melting temperature (650C) than wild type H63, S65 allele (570C) and the mutant 65C allele (520C). The mutant 282Y allele displayed a higher melting temperature (620C) than the wild type C282 allele (560C). The patients' genotype profiles were compared to the standards supplied by the manufacturer.

All experimental and calculated values are presented as means ±SEM. Statistica 13.1 (Dell Inc. 2016) [10] was used for statistical analysis. Group differences in physical and fitness characteristics were analyzed by an unpaired Student's t test. Means of circulating components were compared using the repeated measures analyses of variance with Scheffe correction for multiple comparisons. When normality of data could not be established a nonparametric Wilcoxon or Mann–Whitney tests was used for paired and unpaired series, respectively. In all statistical analyses, the threshold for significance was set at $p < 0.05$.

The entire experiment was performed in the laboratory of Molecular Biology at the Medical University of Gdansk and in the laboratory of Physiology of Exercise at the Gdansk University of Physical Education and Sport.

RESULTS

There were no statistical differences in age, height, weight, BMI, BSA and absolute VO_{2peak} (L/min) between compared groups, whereas relative VO_{2peak} (mL/kg/min) and a centile of this parameter were statistically higher in the wild type *HFE* gene group; data are presented in Table 1.

Table 1. Subject characteristics

	Wild (n = 6)	H63D (n = 6)
Age (y)	17.2 ±0.38	16.7 ±1.09
Height (cm)	175.0 ±2.84	177.7 ±3.39
Height [z-score]	-0.43 ±0.46	0.07 ±0.57
Weight (kg)	62.3 ±3.68	68.9 ±5.36
Weight [z-score]	-0.60 ±0.34	0.07 ±0.53
BMI ($kg \cdot m^2$)	20.3 ±0.89	21.6 ±0.87
BSA [m^2]	1.73 ±0.06	1.84 ±0.09
VO_{2peak} [$L \cdot min^{-1}$]	3.09 ±0.15	2.82 ±0.14
VO_{2peak} [$L \cdot min^{-1}$] (centiles)	45.8 ±7.68	41.7 ±13.3
VO_{2peak} [$mL \cdot kg^{-1} \cdot min^{-1}$]	49.9 ±2.31	41.3 ±1.29 *
VO_{2peak} [$mL \cdot kg^{-1} \cdot min^{-1}$] (centiles)	51.7 ±11.7	13.83 ±3.70 ^

Results are shown as means ±SEM. BMI – body mass index; BSA – body surface area; VO_{2peak} – oxygen uptake at peak exercise. Between groups * p = 0.009, ^p = 0.037

All biochemical parameters after exercise were calculated regarding plasma volume according to Berthoin [11]. The wild *HFE* gene group showed statistical higher hemoglobin concentration, number of RBC, and reticulocytosis before exercise, while hematocrit, leucocytes, neutrophils, and platelets were higher after the exercise. Controversially, in the H63D *HFE* gene polymorphism group, biochemical and morphological parameters did not differ before and after the exercise, despite a statistically higher number of leucocytes and platelets after exercise. Comparison between wild and polymorphism groups revealed that hemoglobin concentration after exercise was statistically higher in the H63D polymorphism group compared to the wild group. There was no statistical difference in hepcidin concentration before and after exercise in the wild group. Basal hepcidin concentration was statistically higher in the H63D polymorphism group than in the wild type group; data are presented in Table 2.

Table 2. Summary of participants' biochemistry at rest and after exercise

Biochemical marker	Wild (n=6)		H63D (n=6)	
	rest	after exercise	rest	after exercise
Hb [g/dl]	15.2 ±0.26	14.6 ±0.26 *	16.1 ±0.32	16.0 ±0.44 **
Ht [%]	44.5 ±1.03	47.4 ±1.01 ^	46.7 ±0.76	47.3 ±0.58
RBC [ml/dl]	5.17 ±0.14	4.90 ±0.11 •	5.47 ±0.12	5.45 ±0.17
Retic [%]	0.90 ±0.12	0.74 ±0.07 ▫	0.65 ±0.10	0.69 ±0.10
WBC [G/l]	4.81 ±0.18	6.74 ±0.17 *	5.63 ±0.82	6.98 ±1.34 ▫
ANC [G/l]	2.22 ±0.15	2.85 ±0.30 ▫	2.52 ±0.47	3.07 ±0.60
PLT [G/l]	219.7 ±7.50	245.5 ±11.0 °	227.2 ±24.0	243.6 ±27.8 °
CRP [mg/dl]	0.66 ±0.50	0.64 ±0.48	0.73 ±0.30	0.74 ±0.30
Fe [ug/dl]	85.7 ±11.2	85.2 ±10.4	132.7 ±24.0	141.5 ±28.7
Ferritin [ng/ml]	45.1 ±8.21	45.5 ±8.91	39.1 ±7.73	40.3 ±7.73
TSA [%]	25.3 ±3.07	23.0 ±2.57	36.5 ±5.35	37.1 ±6.23
Hepcidin [ng/ml]	4.87 ±0.52	4.60 ±0.52	7.18 ±0.82 ••	8.01 ±1.57

Results are shown as means ±SEM. Hb – hemoglobin concentration; Ht – hematocrit; RBC – red blood cells; WBC – white blood cells; ANC – absolute neutrophil count; PLT – platelets; CRP – C-reactive protein; Fe – iron; TSA – transferrin saturation.

Within group change for exercise: * p = 0.028, ^ p = 0.003, • p = 0.018, ▫ p = 0.046, °° p = 0.022, ° p = 0.027
Between groups difference at rest: •• p = 0.045
Between groups change for exercise: ** p = 0.030

Correlation between iron and hepcidin concentration revealed a statistically insignificant positive tendency in the H63D *HFE* gene polymorphism group, a statistically insignificant negative tendency in the wild group, both at the basal and the post-exercise points; data are presented in Figures 1 and 2.

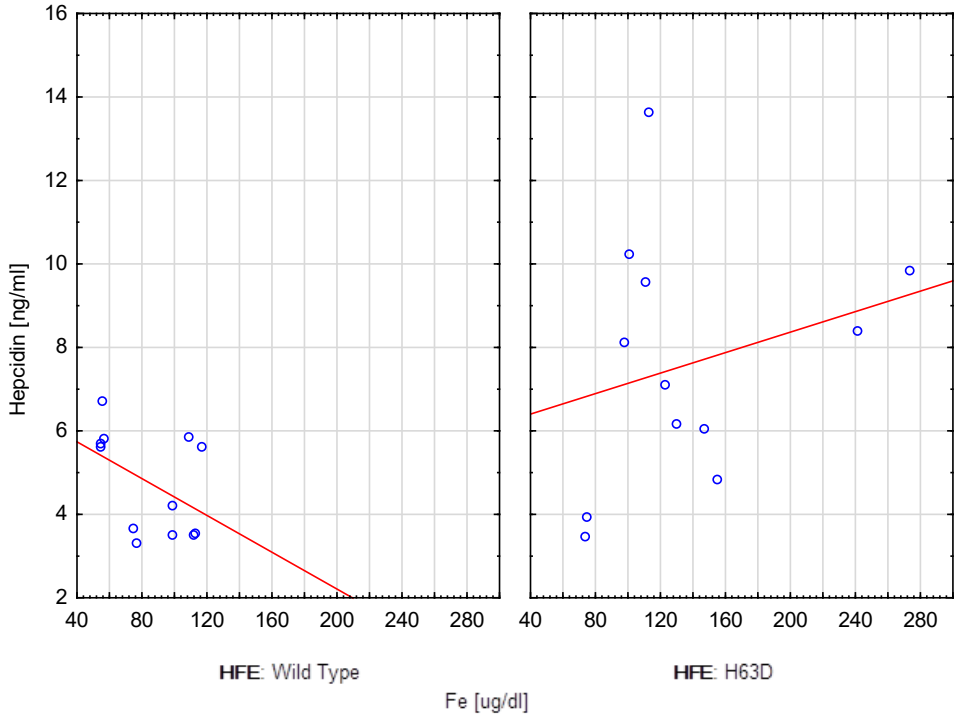

Fig. 1. Correlation between iron (Fe) and hepcidin concentration. There were no statistical differences

Wild Type: y = 6.6198 - 0.022*x; r = -0.4534; p = 0.1388; r2 = 0.2055
H63D: y = 5.9111 + 0.0123*x; r = 0.2573; p = 0.4194; r2 = 0.0662

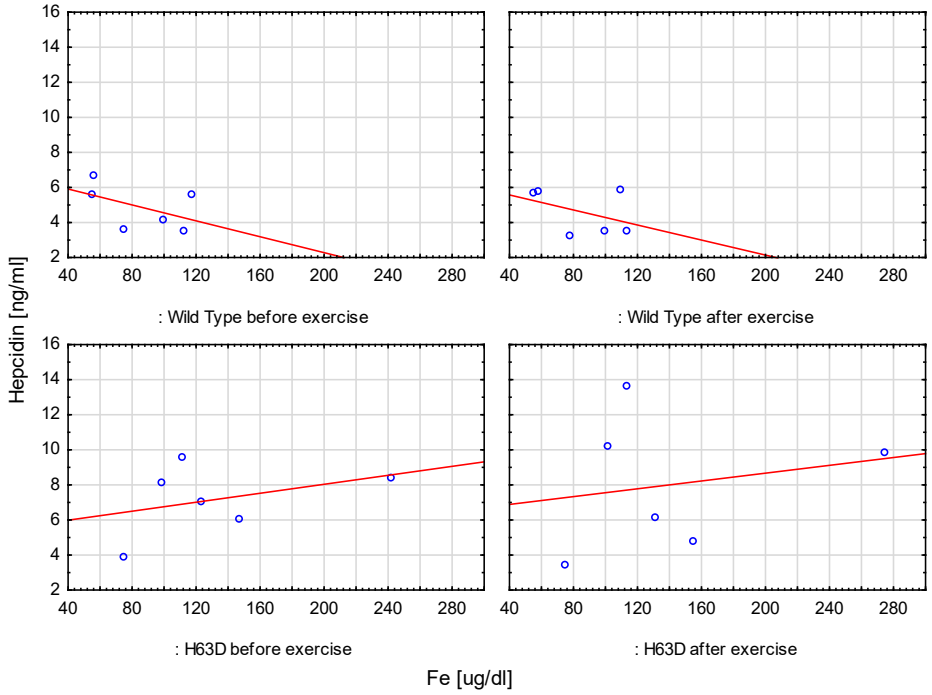

Fig. 2. Correlation between iron (Fe) and hepcidin concentration in *HFE* groups before and after exercise. There were no statistical differences

Wild Type group before exercise: y = 6.8145 - 0.0227*x; r = -0.4858; p = 0.3286; r2 = 0.2360
Wild Type group after exercise: y = 6.4279 - 0.0214*x; r = -0.4277; p = 0.3976; r2 = 0.1829
H63D group before exercise: y = 5.4773 + 0.0128*x; r = 0.3749; p = 0.4640; r2 = 0.1406
H63D group after exercise: y = 6.4384 + 0.0111*x; r = 0.2038; p = 0.6986; r2 = 0.0415

DISCUSSION

In this study we showed that H63D carriers of *HFE* gene showed higher basal hepcidin concentration than wild type probands. Interestingly, the analysis of correlation between iron and hepcidin concentration showed a positive tendency in H63D carriers, while presenting a negative tendency at the basal and the post-exercise point for the wild types. Moreover, male H63D carriers showed higher hemoglobin concentration than the unburdened children.

Exercise training influences the immune function, metabolism, and health. The changes observed in hematologic parameters and iron metabolism due to training are complex and still poorly understood. Physiological iron balance is tightly controlled at the cellular and systemic level by iron regulatory proteins and the iron regulatory hormone, hepcidin. This small liver-produced peptide hormone inhibits intestinal iron absorption, and macrophage iron recycling, thereby decreasing body iron availability [12]. Hepcidin expression is regulated by body iron status, interleukin-6 (IL-6), erythropoietic activity of the bone marrow, and hypoxia [13]. It was described that intense exercise induces a significant increase in plasma Il-6 [14] resulting in hepcidin gene expression [15]. Hepcidin is also expressed in response to elevated iron concentration and exercise, but depressed during hypoxia [3, 16]. Clinical research has demonstrated that peak hepcidin levels occur 3 hrs following the peak of IL-6 [17]. The relationship between hepcidin and IL-6 was confirmed while investigating the response to a single dose of exercise: endurance [18] and interval exercise [19]. In addition, Roecker and co-workers observed a considerable increase in the hepcidin level 24 h after a 42.2-km marathon run in female athletes [20]. Scientific studies which have been carried out concerning IL-6 production, iron metabolism, and hepcidin secretion have not considered the contribution of inherited traits which lead to increased intestinal absorption of iron and their possible influence on exercise. Hereditary hemochromatosis (HH) is a metabolic disorder caused by mutations of genes that control iron balance leading to tissue iron overload [21]. Classical HH is associated with mutations in *HFE* genes. Target organs and tissues affected by HH include the liver, heart, pancreas, joints, and skin, with cirrhosis and diabetes mellitus representing late signs of a disease in patients with markedly elevated liver iron concentration [22]. The high population of *HFE* gene polymorphism raises high interest in its role in the human system. Although, the potential impact of the His63Asp mutation (H63D polymorphism) of the *HFE* gene on increased hemoglobin concentration has already been described, its entire role still remains unknown.

In the presented paper, we compared hematological parameters, iron metabolism and hepcidin concentration in six healthy teenagers and six carriers of His63Asp mutation (H63D polymorphism) of *HFE* gene before and after incremental cycling exercise until exhaustion. It cannot be excluded that statistically significant changes in the number of white blood cells and platelets noted in both groups, regarding plasma volume calculation [11], reflect an exercise-induced inflammation response. The complex decline in hemoglobin concentration, hematocrit, number of red blood cells and reticulocytosis after the experiment on the wild type group can be attributed to adaptive processes that include hemodilution [23]. On the contrary, the parameters of red blood cells for the H63D polymorphism group remained unchanged. However, it has been proposed that greater quantities of iron entering maturing erythrocytes are incorporated into hemoglobin in persons with hemochromatosis, with concomitant hemodilution probably resulting in a stable concentration [24, 25].

Surprisingly, mean concentration of iron, ferritin, and transferrin saturation before the experiment were normal and did not significantly change after exercise. Reports considering adaptive iron balance due to exercise are controversial [6, 26, 27, 28]. Available studies reflect a combination of multifocal factors suggesting the predominant role of hepcidin as a main mediator of iron metabolism and its deficiency or resistance mediating the hyperabsorption of iron [23, 25, 26, 29]. The central pathogenic role of hepcidin in the regulation of iron absorption and release from macrophages has been undoubtedly confirmed, though its precise mechanism is still not well understood [29, 30]. Nevertheless, an inappropriately low hepcidin level has been demonstrated in the serum of hemochromatosis patients [31, 32]. Other authors observed that basal hepcidin levels of C282Y/C282Y homozygotes and C282Y/H63D compound heterozygotes at diagnosis were similar to and even higher than the levels in wild types, but they were relatively deficient when considering the patients' iron load [33–36]. By contrast, in our experiment the base hepcidin concentration was statistically higher in the H63D polymorphism group than in the wild type group. Moreover, the correlation between iron and hepcidin concentration revealed a non-statistically positive tendency in the H63D *HFE* gene polymorphism group and a non-statistically negative tendency in the wild group at both basal and after exercise points. Thus, iron metabolism seems to take a distinct hepcidin pathway depending on the modulating effect of the *HFE* genotype (wild type, H63D polymorphism), baseline iron load, or more likely on the iron pool or iron overload [37–39]. The analyzed H63D carriers did not present systemic iron overload; this might be the reason why the correlation between hepcidin and iron concentration was contrary to that in other reports considering HH models. Interestingly, in the conducted trial, it was noted, that the absolute values of VO_{2peak} normalized for the body mass and a centile of this parameter were statistically higher in the wild type *HFE* gene group. The provided findings suggest altered oxygen efficiency in the carrier group and the need for further research. Although, the number of tested teenagers was limited, which calls for cautious interpretation, we maintain that based on our findings and other reports, an accurate clinical knowledge of underlying *HFE* genotype would prompt the proper medical care of individuals with the hemochromatotic phenotype. We believe that further work considering more samples would provide intelligible conclusions.

CONCLUSIONS

This study demonstrates the impact of exercise on hepcidin concentration and iron metabolism regarding the *HFE* gene status. Iron is an essential trace element required to support physical functions in the human body. Our results suggest that hepcidin is the main regulator of iron homeostasis, and that coexisting H63D *HFE* gene polymorphism has a modulating impact on its secretion.

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