

The Association between Hematological and Inflammatory Factors and Stress Fractures among Female Military Recruits

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ABSTRACT

MERKEL, D., D. S. MORAN, R. YANOVICH, R. K. EVANS, A. S. FINESTONE, N. CONSTANTINI, and E. ISRAELI. The Association between Hematological and Inflammatory Factors and Stress Fractures among Female Military Recruits. *Med. Sci. Sports Exerc.*, Vol. 40, No. 11S, pp. S691–S697, 2008. **Background:** With the growing number of females accepted for combat-related military duties in the Israeli Defense Forces, their special needs should be addressed. Previous studies on females in combat training have found a high prevalence of iron deficiency at recruitment as well as an increased rate of stress fractures (SF) and overuse injuries during training when compared with males. The aim of this study was to assess the correlation between hematological and inflammatory variables and SF occurrence among military recruits during basic training. **Methods:** Three gender-integrated light infantry units were followed prospectively. Female recruits inducted for medic and dental assistants' courses were followed for comparison. Hemoglobin, iron, transferrin, ferritin, C-reactive protein, and interleukin-6 levels were measured for all participants at recruitment and at 2 and 4 months of training. SF were diagnosed radiographically or scintigraphically according to the Israeli Defense Forces protocol. **Results:** A total of 438 subjects were recruited (female combatants = 227, male combatants = 83, noncombatant females = 128). At induction, 18% of female combatants had anemia compared with 8% of males and 19% of noncombatants. Iron deficiency was noted in 40%, 6%, and 38%, respectively. There were no clinically significant changes during training. Twelve percent of female combatants developed SF, whereas none occurred among male combatants or noncombatants. Subjects sustaining an SF had significantly lower levels of serum iron and iron saturation. **Conclusions:** A high incidence of anemia as well as iron deficiency was found in this young asymptomatic cohort, with no significant change during training. The lower level of iron in female combatants sustaining SF warrants further investigation. **Key Words:** IRON DEFICIENCY, BASIC TRAINING, FEMALE SOLDIERS, ANEMIA

Military recruits entering combat units are similar to athletes in that their training may include several hours of physical activity daily. With the growing number of females engaging in combat-related military duties in the Israeli Defense Forces (IDF), the special needs of these women should be addressed. There are well known gender differences in aerobic fitness and strength performance. These are secondary to variables such as lower muscle mass, smaller body frames, higher body fat percentage, and lower cardiac output and oxygen carrying capacity in women. In many military settings, women are

required to train the same amount and alongside men and to use similar equipment to men. Because of this, women are at an increased risk for training-associated medical problems compared with men. Although some of these gender differences are inherent and cannot be changed significantly in a short period (e.g., cardiac output, bone density), other variables are modifiable (e.g., nutritional deficiencies), and their magnitude may be somewhat reduced. Furthermore, the control of these modifiable differences might be related to improved performance and prevention of overuse injuries such as stress fractures (SF).

Iron deficiency, with or without anemia, is known to reduce physical work capacity and mental performance (3,13,14). Therefore, iron deficiency should be avoided in situations that require maximal performance, such as field deployment. Nonanemic iron store deficiency is identified by low transferrin saturation and low ferritin levels without a decrease in hemoglobin (Hgb) levels. Iron deficiency can be classified into two stages according to its impact on red cell synthesis. Iron deficiency occurs as iron stores decline

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and a decrease in transport iron occurs. In this stage, there is an isolated decrease in serum ferritin levels or low transferrin saturation. Iron deficiency anemia occurs as the syntheses of iron-containing proteins, such as Hgb, become compromised to the point at which values fall below a specific cutoff (13).

The prevalence of anemia and iron deficiency among adolescents and young adults in Israel has not been fully assessed. A study of female military recruits found iron deficiency in 15% of participants and iron deficiency anemia in an additional 10% of subjects (8). In a report on combatant male recruits in an elite IDF unit, the prevalence of iron deficiency anemia at recruitment was 20%. After 6 months of training, anemia was found in 50%, with only 25% attributed to iron deficiency (20,21). In the US Army, iron deficiency prevalence among female military personnel was greater immediately after basic combat training (32.8%) compared with initial army entry and after permanent assignment (13.4% and 9.6%, respectively). The prevalence of iron deficiency anemia was also greatest immediately after basic combat training (20.9%) in comparison to initial entry to the army and permanent assignment groups (5.8% and 4.8%, respectively). Furthermore, the prevalence of iron deficiency anemia was greater in Hispanic (21.9%) and African American military personnel (22.9%) than in Caucasian military personnel (10.5%) (19).

Periods of training can stimulate an inflammatory reaction with elevation in interleukin-6 (IL-6). The concentration of IL-6 in plasma increases gradually during exercise and peaks at the end of the stress. It also induces the secretion of C-reactive protein (CRP) and hepcidin. Hepcidin synthesis is greatly increased during this inflammatory reaction with trapping of iron in macrophages, decreased plasma iron concentrations, and iron-restricted erythropoiesis characteristic of anemia of inflammation (10,12,15). Substantial evidence also indicates that IL-6-type cytokines have profound effects on bone metabolism by regulating osteoclast and osteoblast development and function (11,18).

It is estimated that stress fractures (SF) during basic training occur in as many as 14% of US female military recruits (16). Injuries of this type lead to morbidity ranging from minor pain to serious lifetime disability. Factors associated with SF include among others age, race, alcohol and tobacco use, and weight-bearing exercise (16). A history of regular exercise was protective against SF. In another report, females with SF had thinner cortices and lower area bone mineral density (2). Female combatants have a higher incidence of iron deficiency anemia and a higher occurrence of SF (2,8). No relationship has been reported between anemia and SF in any population. The aim of this prospective study was to assess the correlation between hematological and inflammatory parameters and to examine whether these parameters have an impact on the development of SF during basic training.

METHODS

Study participants. This study was part of a larger study assessing the health status of female IDF combatants during basic training. The study was approved by the IRB of the IDF and the US Army Research Institute of Environmental Medicine. The subjects participated after giving their free and informed voluntary consent.

The study sample consisted of three companies of female and male combatants, aged 18 to 20 yr, assigned to a combat unit (the Karakal unit) in the IDF. The unit was gender integrated with both genders taking equal part in training and combat duties. For comparison, we followed groups of noncombat female recruits in courses of dental assistant and of medics. Before recruitment, all subjects underwent a medical examination that found them to be healthy and eligible for service in the unit. Dropouts were soldiers that were transferred to other units in the army for various reasons. Blood samples were collected at induction and at 2 and 4 months. At 2 and 4 months, 195 and 173 of the female combatants were available for the study, respectively. The noncombatant group included 111 and 102, respectively, and the male combatant group included 58 and 54, respectively.

Data collection. Venous blood samples of approximately 30 mL were collected by antecubital venipuncture into tubes (BD Vacutainer, [®]2002 BD; Becton, Dickinson and Company, Franklin Lakes, NJ) containing the appropriate anticoagulant. All blood samples were taken during the morning hours (between 0700 and 0800 h), in a sitting position, after an overnight fast and no exercise. Samples were put in ice and sent within 6 h to be processed and analyzed in the Tel Hashomer Hospital Central Laboratories (Hematology and Biochemistry). Blood for IL-6 was collected in 5-mL silicone-coated tubes (BD Vacutainer SST II Advance; Becton, Dickinson and Company), allowed to sit for 30 min at room temperature, and immediately centrifuged at 4°C at 2000g for 15 min. Serum samples were then separated and stored at -70°C immediately after collection and remained frozen until analysis.

Laboratory methods. Blood counts were performed on fresh blood using an automated analyzer (Cell-Dyn[®] 3000; Abbott Diagnostics, Abbott Park, IL) including Hgb, hematocrit, erythrocyte count, mean corpuscular volume, and mean corpuscular Hgb. Serum ferritin was measured with an electrochemiluminescence immunoassay (Roche Elecsys[®] 2010; Roche Diagnostics GmbH, Mannheim, Germany) with a reference range between 16 and 293 ng·mL⁻¹. Serum iron was measured with a commercial kit by Olympus (AU2700; reference range = 60–170 micg·dL⁻¹). Serum transferrin was measured with an immunoturbidimetric assay (Tina-quant[®] with Roche Diagnostics GmbH; reference range = 193–378 mg·dL⁻¹). The transferrin saturation was calculated according to the following formula: transferrin saturation (%) = serum iron / serum transferrin. IL-6 was

measured by enzyme-linked immunosorbent assay from Linco (Linco Research Inc., St. Charles, MO) on the Luminex Labmap 100 (Luminex Corp., Austin, TX). Interassay coefficient of variation was 12.7%. The sensitivity of this assay was 3.2 pg·mL⁻¹, and the reference range for IL-6 was <3.2–263 pg·mL⁻¹. Highly sensitive C-reactive protein (CRP) was performed by commercially available enzyme-linked immunosorbent assay test kits by Olympus (AU2700) with reference values 0–5 ng·mL⁻¹. Anemia was defined as hemoglobin (Hgb) <12 g·dL⁻¹ for females and Hgb <14 g·dL⁻¹ for males. Iron deficiency was defined when one of the following were present: a serum ferritin <12 ng·mL⁻¹ for females and <20 ng·mL⁻¹ for males or a transferrin saturation <16% (both gender).

All recruits were examined in the field by a team of orthopedists every 2–3 wk and screened for overuse injuries. Suspect SF were diagnosed and treated according to IDF protocol. In the IDF protocol, the diagnosis is supported by either radiography or scintigraphy. After diagnosis, soldiers are ordered to reduce physical activity and avoid any intense training. These limitations are kept for 2–8 wk depending on the severity of the SF. No changes in diet are implemented. The data were supplemented by data from the battalion physician's records and were verified clinically.

Statistical analysis. Data analysis was performed using SAS. Comparisons between three groups of recruits (female combatants, male combatants, and noncombatant females) over the three periods were performed using repeated-measures ANOVA, with adjustment for multiple comparisons by Tukey–Kramer (SAS, GLM, and LSMEANS). Comparing data for combatant females with and without SF was performed using Student's *t*-test.

RESULTS

At induction, the mean Hgb level for the female combatants (*n* = 227) was 12.7 ± 1.0 g·dL⁻¹, with 18% having iron deficiency anemia. The noncombatant group (*n* = 128) had a mean Hgb of 12.8 ± 1.1 g·dL⁻¹, with iron deficiency anemia appearing in 19%. The mean Hgb level for the male combatants (*n* = 83) was 15.2 ± 0.93 g·dL⁻¹, with iron deficiency anemia in 7.6%. Low transferrin saturation (<16%) was identified in 41% of female combatants, 28% of noncombatant females, and 6% of male combatants. Ferritin levels were less than 12 ng·mL⁻¹ in 88 (40%) female combatants, 45 (37%) noncombatant females, and less than 20 ng·mL⁻¹ in 5 male combatants (6%). The means of the hematological and inflammatory parameters measured at induction (time 0) are presented

in Table 1. Male combatants had higher iron, transferrin, transferrin saturation, and ferritin levels than both female groups in all three phases of testing (*P* < 0.05). Ferritin levels were also significantly lower among the female combatants compared with the noncombatant group at all three phases of testing. There were no differences in transferrin saturation or any of the other iron indices. No significant difference was found in IL-6 levels in these groups. CRP levels were higher in both female groups when compared with the male group. During the training, only changes in hematological variables iron and transferrin in the female combatants between 0 and 4 months were clinically significant. Variation of variables over time is presented in Figure 1.

Diagnosis of SF occurred throughout the training period, beginning at induction (Fig. 1). Of the 227 female combatants, 27 had SF (12%). None of the noncombatant females or the male combatants sustained an SF (Fig. 2).

Iron levels were significantly lower at 4 months among female combatants with the SF versus the nonstress fracture (NSF) group (Table 2). Transferrin levels were higher among the SF group only during training (months 2 and 4). There was a tendency toward elevated transferrin levels along with a reduction in ferritin during training, but this was not statistically significant. No significant differences were found in CRP and IL-6 levels in all three groups, but a significant positive correlation (*R* = 0.2, *P* < 0.003) was found between ferritin and CRP. Table 2 summarizes the differences between female combatants sustaining an SF and those that do not.

DISCUSSION

The present study analyzed hematological parameters in a population of new military recruits who engaged in prolonged physical training. The main findings of this cross-sectional study indicate that there might be a link between SF and iron deficiency anemia. The overall prevalence of iron deficiency among female and male recruits in the IDF is high: 18% in female combatants, 19% in noncombatant females, and 8% in male combatants. In contrast to previous reports in the IDF and other armies, there were no significant changes in Hgb levels and iron stores during the training period (19–21).

Ferritin levels were significantly lower among the female combatants compared with the noncombatant group at all three phases of the study. Iron and transferrin were significantly lower at induction, whereas the difference in transferrin saturation did not reach statistical significance. This could be explained by the simultaneous effect of

TABLE 1. Blood test results of study groups at induction.

	<i>n</i>	Hgb, g·dL ⁻¹	Iron, μg·dL ⁻¹	Transferrin, mg·dL ⁻¹	Transferrin Saturation, %	Ferritin, ng·mL ⁻¹	CRP, ng·mL ⁻¹	IL-6, pg·mL ⁻¹
Female combatants	227	12.7 ± 1.0	67.3 ± 44*	307 ± 61*	23.8 ± 19.0	17.4 ± 12.7*	2.49 ± 3	43.4 ± 87
Noncombatant females	128	12.8 ± 1.1	79.1 ± 45	331 ± 53	24.7 ± 14.7	21.6 ± 19.5	2.53 ± 4	34.2 ± 101
Male combatant	83	15.2 ± 0.9†	104.2 ± 4†	269 ± 48†	40.0 ± 18.5†	52.8 ± 36.2†	1.40 ± 1†	48.6 ± 81

* Significant differences (*P* < 0.05) between female combatants and noncombatant females.

† Significant differences (*P* < 0.05) between genders—male and female combatants and noncombatant females.

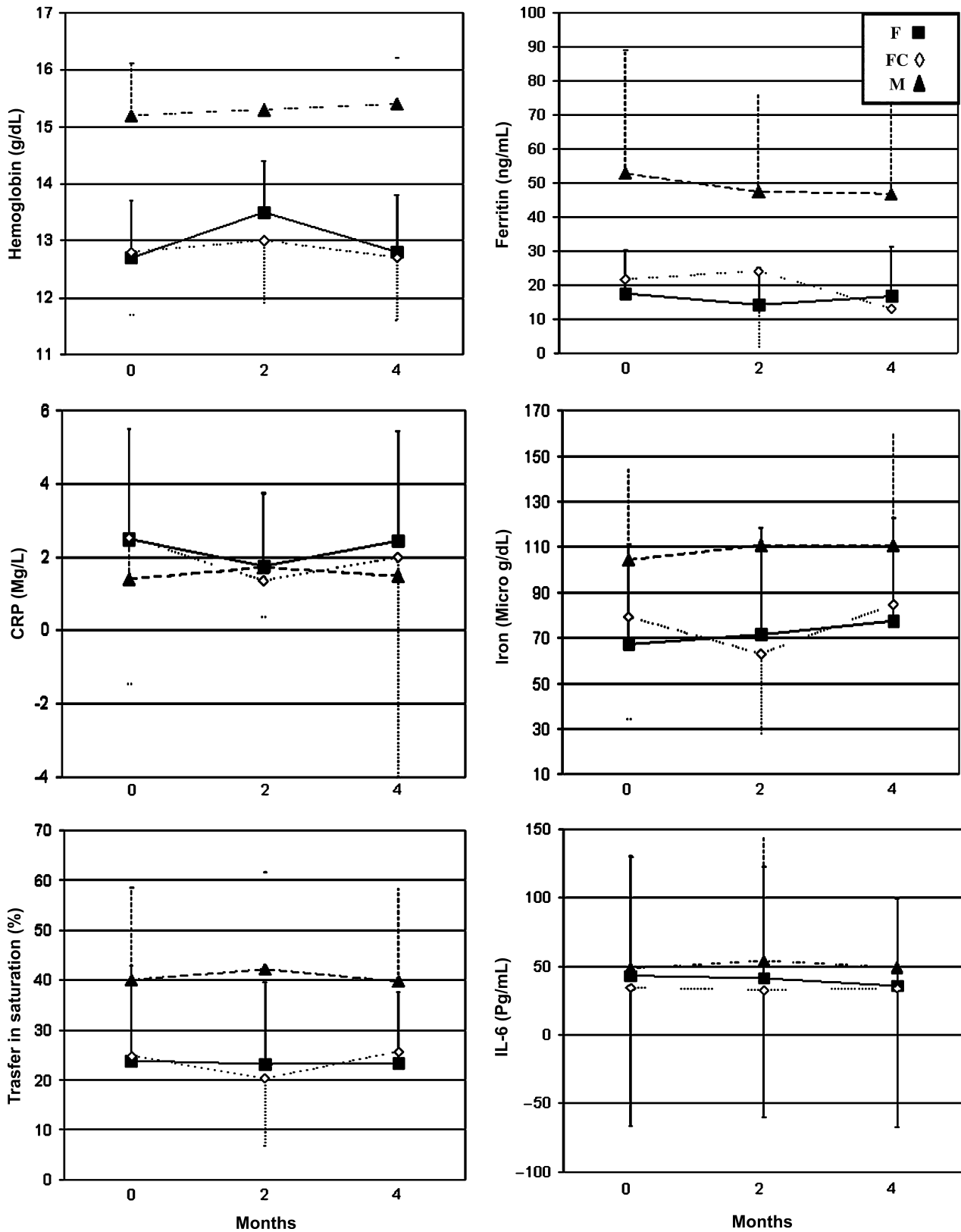


FIGURE 1—Hematological profile of the three groups participating in the 4-month basic training at the recruiting day (0) and 2 and 4 months later (F—female combatants, squares; M—male combatants, triangles; and NCF—noncombatant females, diamonds). Significant differences were found only in the noncombatant females in Hgb and transferrin levels between induction and 2 months ($P < 0.05$).

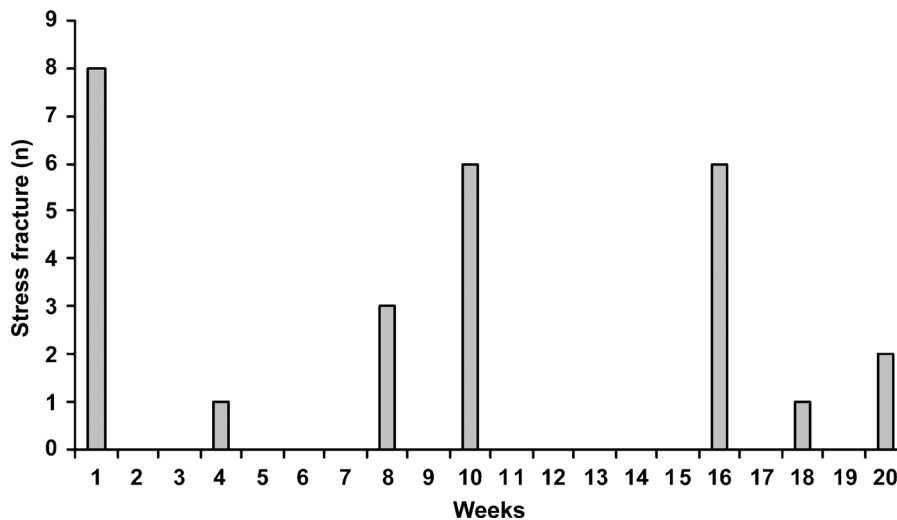


FIGURE 2—Occurrence of SF over time throughout the 20-wk training period. The timing of SF was recorded according to symptoms (local pain) and was validated by bone scan or radiography.

opposing factors on transferrin levels. On one hand, there is iron deficiency with secondary elevation of transferrin levels. On the other hand, there is the effect of an inflammatory state that can cause a decrease in transferrin levels.

Commonly, iron deficiency and anemia are a result of poor diet and growth spurt in adolescence, exacerbated in females by menstrual blood loss. The gastrointestinal and urinary tracts have also been implicated as sources of blood loss, especially after intense endurance events, most likely due to transient ischemia resulting from vasoconstriction of the splanchnic and renal vessels during exercise (1,5,24). In addition to the mechanisms listed above, engagement in strenuous exercise may also cause “sports anemia” that has been reported in up to 30% and 50% of males and females, respectively, varying with the type of physical activity, most notably being more pronounced in long distance runners (4,6,9,25). There are many contributing factors for “sports anemia”: delusional pseudoanemia, intravascular mechanical hemolysis, and iron loss (7,26). Another possible new explanation is the relation of inflammatory reactions to strenuous physical activity (12,23). The current study did not reveal a decrement in iron stores throughout the training period. Possible explanations for this are the relatively lower intensity of the training program in this unit, which is not gender-segregated, and the short follow-up. In previous IDF studies, decrements in iron stores were reported, but the study groups were comprised

of soldiers serving in elite units with an intense training program that were followed for a year (20,21).

Recent studies on iron metabolism have linked inflammation to the reduction in iron stores through the effect of hepcidin (see below) (12). In our study, the lower iron stores in female combatants at induction could be caused by some of the group training intensely at home before induction. Thus, the impact of intense training could have lowered the iron stores before induction. Another part of this group had volunteered for community work in a special program initiated by the IDF and had lived out of home for a year before recruitment. This could also have had a large impact on dietary intake, specifically iron and calcium intake.

It is estimated that SF during basic training occur in as many as 14% of US female military recruits (16). We have found a 12% prevalence of SF among female combatants whereas there were no occurrences among male combatants and noncombatant females. It should be emphasized that the training program of the Karakal unit was modified and adapted for women. This might explain the low incidence of SF in males who trained with the females. The noncombatant group did not engage in physical training.

We did not find any previous report exploring the possible correlation of hematologic indices and SF that we report here. More specifically, we found a correlation between low serum iron levels and transferrin saturation with the occurrence of SF, whereas no such relationship was found

TABLE 2. Levels of iron-related variables for female combatants with stress fractures (SF) and without stress fractures (NSF) with calculated *P* values according to *t*-test.

		<i>n</i>	Iron, μg·dL ⁻¹	<i>P</i>	Transferrin, mg·dL ⁻¹	<i>P</i>	Transferrin Saturation, %	<i>P</i>	Ferritin, ng·mL ⁻¹	<i>P</i>	CRP, ng·mL ⁻¹	<i>P</i>	IL-6, pg·mL ⁻¹	<i>P</i>
0 months	SF	27	54 ± 24	0.02	313 ± 58	0.6	21.8 ± 24	0.6	21 ± 12	0.17	4.12 ± 0.6	0.165	57 ± 62	0.3545
	NSF	198	70 ± 46		305 ± 76		25.7 ± 18		17 ± 16		1.88 ± 0.3		41 ± 88	
2 months	SF	22	55 ± 46	0.1	355 ± 80	0.04	17.4 ± 15	0.09	13 ± 10	0.16	2.46 ± 0.6	0.501	50 ± 62	0.492
	NSF	164	73 ± 47		316 ± 57		24.9 ± 16		17 ± 11		2.20 ± 0.2		39 ± 85	
4 months	SF	23	56 ± 35	0.004	370 ± 52	0.01	16.2 ± 11	0.004	15 ± 12	0.62	3.98 ± 0.6	0.297	50 ± 65	0.223
	NSF	126	81 ± 46		336 ± 56		24.7 ± 14		17 ± 15		2.07 ± 0.3		33 ± 63	

for ferritin levels. The dissimilar response could be a result of ferritin increment as an acute phase reactant, thus making it a less reliable marker for iron deficiency as training progressed. This conclusion is supported by the significant positive correlation found between ferritin and CRP.

Strenuous physical activity results in an acute-phase response, increasing the levels of various immunologically active agents. Several studies demonstrated changes in the status of inflammatory and anti-inflammatory parameters after exercise, for example, cytokine plasma concentrations such as IL-6, IL-1 receptor antagonist, and IL-10 (15,22). Transferrin and ferritin are also known to be reactive as acute phase reactants (17,22).

The cytokine IL-6 is an important inducer of hepcidin synthesis during acute inflammation both in mouse models and in humans. It appears that the IL-6-hepcidin axis is critically important for the iron deficiency response, and that hepcidin is the main mediator of iron deficiency of inflammation. In anemia of inflammation, iron retention by duodenal enterocytes and reticuloendothelial macrophages leads to markedly low transferrin saturation, iron-restricted erythropoiesis, and mild-to-moderate anemia (10,12,15). Substantial evidence indicates that the IL-6 types of cytokines potently induces osteoclastogenesis, promotes differentiation, and prevents apoptosis of committed osteoblastic cells toward a more mature phenotype, thus influencing bone resorption and formation by regulating the production of osteoclasts and osteoblasts (11,18).

The possible correlation between iron deficiency and SF can be explained by two mechanisms: dietary and cytokine effects on iron metabolism. The dietary effects could be through a common link of poor dietary habits with a low intake of iron leading to anemia and a low calcium intake alongside other critical elements, which exposes the female combatant to a higher risk of SF. An additional explanation

of the impact of cytokines is that overuse injuries, occurring during intense physical activity, can lead to SF. It can also lead to an elevation of acute phase reactants, such as IL-6 and CRP. The inflammatory state may cause iron deficiency through the effect of hepcidin. Further studies are warranted looking for the effect of the newly discovered proteins that participate in iron metabolism in relation to SF (11,12,18).

Our study has a few limitations. We succeeded in gathering a large cohort, but the number of combatants diagnosed with SF was comparatively low (none of the male combatants developed SF during basic training). Another problem was the timing of the diagnosis of SF and the blood tests. The serum half life of IL-6 and CRP is short, so we may have missed the peak levels of these factors in the serum. An additional problem with IL-6 is the wide range of normal values, possibly masking pathologic results.

In summary, we report a high prevalence of iron deficiency in female recruits (eight times that of males) at induction, with no significant change during the basic training period. We found a correlation between the low iron and the appearance of SF. As this correlation may not be causal, more studies should focus on the relationship between iron stores and SF with larger groups, frequent blood tests, and examining the role of novel proteins participating in iron metabolism. To prove a cause and effect correlation between iron deficiency and SF, it would be important to study prospectively whether correcting iron deficiency in female recruits before training would indeed lead to a decreased risk for the development of SF.

The opinions and assertions in this article are those of the authors and do not necessarily represent official interpretation, policy, or views of the US Department of Defense or the Israeli Defense Forces.

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