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Effect of Iron Supplementation on Thyroid Hormone Levels and Resting Metabolic Rate in Two College Female Athletes: A Case Study

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Iron plays an important role in thyroid hormone metabolism; thus, iron deficiency anemia may lead to alterations in resting metabolic rate (RMR). Based on this premise, two iron-deficient-anemic female athletes, 18 (A1) and 21 (A2) years of age, were supplemented with 23 mg/day of elemental iron to assess its effects on iron and thyroid hormone status and RMR at 0, 8, and 16 weeks. Anemia was clinically corrected in both subjects (hemoglobin: A1 = 11.0 to 13.0 to 12.6 g/dL and A2 = 11.5 to 13.9 to 12.6 g/dL, 0 to 8 to 16 weeks, respectively). Serum ferritin (SF) concentration also improved in both subjects (A1: 5.0 to 11.0 to 15.0 ng/dL and A2: 5.0 to 16.0 to 20.0 ng/dL; 0 to 8 to 16 weeks, respectively); however, 16 weeks of iron supplementation did not fully replete iron stores. A2 increased dietary iron and ascorbic acid intakes from 8 to 16 weeks, possibly accounting for her higher SF concentrations. RMR and total thyroxine changed over time: A1 increased while A2 decreased in these variables. Although clinical correction of iron deficiency anemia occurred after 16 weeks of low-level iron supplementation, RMR and thyroid hormone metabolism were oppositely affected in the two subjects.

Key Words: anemia, exercise, mineral status, resting energy expenditure, women

Introduction

Iron deficiency may be the most common nutritional deficiency in the world and is a primary concern for about 15% of the world's population (12). Iron deficiency is related to alterations in a number of metabolic processes such as neurotransmitter synthesis, protein synthesis, and organogenesis resulting in impairments in immune function, cognitive performance and behavior, thermoregulatory performance, energy metabolism, and exercise or work performance (2). Some authors (8, 19) have found that a depletion of iron in the mitochondrial oxidative enzymes of rats decreases exercise endurance; this observation was also reported in humans (22).

There is evidence to suggest that iron depletion and iron deficiency anemia cause physiological changes in the body not only during exercise but also under resting conditions. Both rat studies (7, 13) and human studies (28) have revealed

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elevated concentrations of norepinephrine (NE) in the blood and urine of iron-deficient-anemic subjects (range: 44.4 to 125.3 μg NE/m^2/24 hours [28]). The studies with rats have also reported that the higher blood and urinary NE concentrations were associated with increased metabolic rates (7, 13). The study (28) in humans did not measure metabolic rate; thus, the hypothesis that iron deficiency anemia in humans is related to stimulation of metabolic rate has not been tested.

The association between iron status, thyroid hormone function, and metabolic rate has been studied in humans exposed to cold environmental conditions in order to assess the impact of enzymatic iron depletion on thermoregulation (3, 16). Martinez-Torres et al. (16) collected data on thyroid hormone concentrations and metabolic rate prior to cold exposure in iron-deficient-anemic, iron-depleted, and iron-sufficient subjects. Metabolic rate, but not thyroid hormone concentration, was higher in the iron-deficient-anemic group compared to the iron-depleted and iron-sufficient groups. Beard et al. (3) reported that 12 weeks of oral iron supplementation corrected anemia in iron-deficient-anemic subjects and improved thermoregulation, but did not normalize pre-cold exposure plasma thyroxine concentrations. Thus, there still exists a gap in the literature that connects iron status with thyroid hormone function and metabolic rate under steady state conditions.

Considering the potential implications of alterations in resting metabolic rate (RMR) on growth rate, body weight, and fatigue, research specifically in the area of iron deficiency anemia and its effect on thyroid hormone concentration and RMR in humans is needed. Such research would especially benefit those who are at particular risk for developing iron deficiency, such as pre-menopausal, physically active females (12).

The purpose of this case study was to determine the effect of long-term (16 weeks), low-level iron supplementation on thyroid hormone concentration and RMR in two iron-deficient-anemic college-age female athletes. Although a case study, these are the first data to examine the effect of long-term iron supplementation on thyroid hormone status and RMR in iron-deficient-anemic women under steady state conditions.

Methods

Basic Design

This was a 16-week study, with all measurements taken at 0, 8, and 16 weeks. Twenty-three mg/day of elemental iron obtained from General Nutrition Center (Pittsburgh, PA), containing 72 mg/day as ferrous fumarate, was used for the iron supplementation.

Subjects

Prior to subject selection, permission was obtained from the University of Massachusetts Institutional Review Board for Research Involving Human Subjects. The two iron-deficient-anemic volunteers were competitive college female athletes (1 distance runner [A1], 1 swimmer [A2]) who were in training during the time of the study and reported being eumenorrheic. They were non-smokers, free of any chronic diseases, and free of iron supplementation (i.e., within the previous 6 months). Subjects were given an oral and written explanation of the study, including its risks,

benefits, and procedures. Prior to any testing, the two subjects were asked to read and sign an informed consent document that was witnessed by one of the investigators. Both subjects were iron-deficient-anemic based on the following criteria: a serum ferritin (SF) concentration < 12 ng/dL and a hemoglobin (Hb) concentration < 12 g/dL.

Experimental Protocol

All biochemical parameters were obtained from overnight (8 to 12 hour) fasting blood samples. Blood was drawn by venipuncture into three evacuated tubes (Vacutainer; Becton Dickinson, Rutherford, NJ). Two of the tubes were allowed to sit for 1 hour and then centrifuged (1500 rpm, 1000 X g) for 15 min at room temperature to recover serum. The serum fraction from one of these tubes was divided into aliquots and stored at –80 °C until assayed in one batch, at the end of the study, for thyroid hormone concentrations (plasma thyroid stimulating hormone (TSH), plasma total thyroxine (T_4), and free T_4 index). The serum from the other tube, along with a tube of whole blood, was immediately assayed for iron status parameters (Hb, hematocrit [Hct], SF). All blood analyses were performed at SmithKline-Beecham Corporation (Waltham, MA) via procedures cited in Henry (14). Hb concentration was determined colorimetrically by use of the cyanmethemoglobin method (percent coefficient of variation [%CV] = 0.6% to 1.4%) (14). Hct was determined via an electronic cell sizing and counting method (%CV = 1.1% to 1.8%) (14). SF and thyroid hormone concentrations were measured via radioimmunoassay techniques (%CV for SF = 6.7% to 7.0%; %CV for TSH = 5.0% to 7.6%; %CV for Total T_4 = 3.8% to 5.2%; there is no %CV for free T_4 index because it is a calculated value) (14).

RMR was measured for 30 min in the morning of each testing period following an 8- to 12-hour fast. Subjects were asked to perform no physical activity the morning of testing; however, the previous day's activities were not controlled. Subjects were required to rest comfortably in a reclining chair for about 15 min prior to RMR measurements. Subjects were placed under a canopy connected to a Medical Graphics Cardio$_2$Max System metabolic cart (Medical Graphics, St. Paul, MN) while awake and resting quietly in a reclining chair (%CV = 5%) (18, 30).

Sum of skinfolds was measured using Lange calipers (10 g mm, constant pressure; Cambridge Scientific Industries, Cambridge, MD). Three sites were measured on the right side of the body: triceps, suprailiac, and mid-thigh. Three measurements were performed at each site, and the average of the three trials was used as the representative score for each site (15). The same individual made all of the skinfold measurements to minimize error (%CV = 4.0% to 4.5%).

Aerobic capacity was measured in order to describe the level of fitness of the 2 subjects, who each participated in different sports. Maximal oxygen consumption ($\dot{V}O_2$max) was measured while subjects rode a bicycle ergometer connected to a Medical Graphics Cardio$_2$Max System metabolic cart (Medical Graphics, St. Paul, MN). The ergometer was set to a 40-W ramp protocol. Criteria used to ascertain if subjects reached their $\dot{V}O_2$max were as follows: oxygen consumption ($\dot{V}O_2$) decreased or remained the same despite an increase in exercise intensity; predicted maximal heart rate (Karvonen method; 20) was reached; and/or the Respiratory Exchange Ratio (RER) reached 1.0 or greater. Heart rate was monitored throughout the exercise test by a Polar Heart Rate Monitor (Polar Electro, Port Washington,

NY) and recorded each minute of exercise, along with a subjective rating of effort (Borg's Rating of Perceived Exertion [RPE] Scale; 6).

To assess dietary intake during the study, participants were asked to complete a 3-day dietary record, including 1 weekend day, three separate times during the study. The dietary records were evaluated using the University of Massachusetts Nutrient Data Bank.

Statistical Analyses

All data analyses were descriptive in an effort to search for trends that might indicate the need for further research. The investigators performed a qualitative analysis of any changes.

Results

Descriptive information about the subjects is presented in Table 1. A2 was taller and had a greater body weight, sum of skinfolds, and $\dot{V}O_2$max than A1. Dietary data are presented in Table 2. Average energy intake was lower for A1 than A2, especially at 16 weeks. In addition, iron, zinc, and ascorbic acid intakes were lower for A1 than

Table 1 Age, Height, Body Weight, Sum of Skinfolds (SS), and Maximal Oxygen Consumption ($\dot{V}O_2$max) of the Iron-Deficient-Anemic Subjects

Variable	0 Weeks	8 Weeks	16 Weeks	Difference[a]
Age (years)				
A1[b]	18			
A2[b]	21			
Height (cm)				
A1[b]	165.1			
A2[b]	174			
Body Weight (kg)				
A1[b]	51.4	53.6	56.0	+4.6
A2[b]	61.8	64.5	64.5	+2.7
SS (mm)				
A1[b]	44.7	47.0	51.2	+6.5
A2[b]	67.7	67.7	67.7	0
$\dot{V}O_2$max (ml/kg/min)				
A1[b]	41.8	38.2	38.7	–3.1
A2[b]	43.0	45.9	43.8	+0.8

[a]Calculated by subtracting value for 0 weeks from value for 16 weeks.
[b]A1 and A2 = Iron-deficient-anemic subjects who received 23 mg/day elemental iron (72 mg/day ferrous fumarate)

Table 2 Daily Dietary Intakes of the Iron-Deficient-Anemic Subjects

Intake	0 Weeks	8 Weeks	16 Weeks
Total kilocalories (kcals)			
A1[a]	1,282	1,525	975
A2[a]	2,295	1,809	2,621
% kcals carbohydrate			
A1[a]	73.1	55.4	77.6
A2[a]	67.8	58.2	68.0
% kcals fat			
A1[a]	18.2	23.8	14.9
A2[a]	21.2	26.8	19.7
% kcals protein			
A1[a]	13.2	27.1	10.6
A2[a]	14.5	17.8	10.3
Total dietary fiber (g)			
A1[a]	24.7	17.9	13.3
A2[a]	14.1	10.5	19.2
Iron (mg)			
A1[a]	16.0	17.5	9.1
A2[a]	18.1	17.6	32.5
Zinc (mg)			
A1[a]	7.7	7.0	3.0
A2[a]	8.0	10.7	11.3
Ascorbic acid (mg)			
A1[a]	133.4	192.8	153.2
A2[a]	229.9	185.2	291.9

Note. Analyses performed using Massachusetts Nutrient Data Bank
[a]A1 and A2 = Iron-deficient-anemic subjects who received 23 mg/day elemental iron (72 mg/day ferrous fumarate).

A2. Changes in iron status (Hb, Hct, SF) from 0 to 16 weeks are presented in Table 3. Both subjects had an increase in Hb, Hct, and SF over time. Absolute (kcal/day) and relative (kcal/kg) RMR differences between 0 and 16 weeks are presented for each subject in Table 4. A1 demonstrated a 21.1 and 10.7% increase in absolute and relative RMR, respectively, whereas A2 showed a 12.2 and 15.8% decline in absolute and relative RMR, respectively. Finally, TSH levels, total T_4 concentrations, and free T_4 index values from 0 to 16 weeks, are presented in Table 5. Both anemic subjects showed an increase in TSH over the course of the study.

Table 3 Hemoglobin (Hb) Concentration, Hematocrit (Hct), and Serum Ferritin (SF) Concentration of the Iron-Deficient-Anemic Subjects

Variable	0 Weeks	8 Weeks	16 Weeks	Difference[a]
Hb (g/dL)				
A1[b]	11.0	13.0	12.6	+1.6
A2[b]	11.5	13.9	12.6	+1.1
Hct (%)				
A1[b]	34.4	40.3	39.4	+5.0
A2[b]	36.2	43.4	36.4	+0.2
SF (ng/dL)				
A1[b]	5.0	11.0	15.0	+10.0
A2[b]	5.0	16.0	20.0	+15.0

[a]Calculated by subtracting value for 0 weeks from value for 16 weeks.
[b]A1 and A2 = Iron-deficient-anemic subjects who received 23 mg/day elemental iron (72 mg/day ferrous fumarate).

Table 4 Absolute and Relative Resting Metabolic Rate (RMR) of the Iron-Deficient-Anemic Subjects

Variable	0 Weeks	8 Weeks	16 Weeks	Difference[a]
Absolute RMR (kcal/day)				
A1[b]	1,149	1,389	1,391	+242
A2[b]	1,563	1,400	1,372	–191
Relative RMR (kcal/day)				
A1[b]	22.4	25.9	24.8	+2.4
A2[b]	25.3	21.7	21.3	–4.0

[a]Calculated by subtracting value for 0 weeks from value for 16 weeks.
[b]A1 and A2 = Iron-deficient-anemic subjects who received 23 mg/day elemental iron (72 mg/day ferrous fumarate).

Discussion

Our study was the first to research the effect of long-term, low-level iron supplementation on RMR and thyroid hormone status in women athletes and found that iron supplementation oppositely impacted RMR and total T_4 in the 2 iron-deficient-anemic female athletes in this case study. Furthermore, 16 weeks of low-level iron

Table 5 Thyroid Stimulating Hormone Concentration (TSH), Total Thyroxine Concentration (Total T_4), and Free Thyroxine Index (Free T_4 Index) of the Iron-Deficient-Anemic Subjects

Variable	0 Weeks	8 Weeks	16 Weeks	Difference[a]
TSH (mIu/mL)				
A1[b]	2.3	2.5	3.4	+1.1
A2[b]	1.6	1.9	2.1	+0.5
Total T_4 (μg/dL)				
A1[b]	6.0	5.5	9.6	+3.6
A2[b]	9.9	9.4	6.0	–3.9
Free T_4 index (ng/dL)				
A1[b]	1.8	2.5	2.1	+0.3
A2[b]	2.3	2.2	2.1	–0.2

[a]Calculated by subtracting value for 0 weeks from value for 16 weeks.
[b]A1 and A2 = Iron-deficient-anemic subjects who received 23 mg/day elemental iron (72 mg/day ferrous fumarate).

supplementation was effective in correcting iron deficiency anemia, and these changes were above that which would have been attributed to the %CV. However, iron depletion, which was markedly improved after 16 weeks of iron supplementation, was completely corrected in only one of the iron-deficient-anemic participants (A2).

Beard et al. (3) also found that 12 weeks of iron supplementation was ineffective in fully repleting iron stores to a SF level of ≥ 20 ng/dL in both their iron-deficient-anemic and iron-depleted subjects. In both Beard et al.'s (3) study and in our investigation, the insufficient duration of iron therapy and the low dose of iron, respectively, were likely responsible for the inability to completely replete iron stores. A dose equivalent to at least 60 mg/day of elemental iron for at least 16 weeks is recommended to completely correct iron deficiency anemia and replete SF stores in adults (26). Rowland et al. (22) successfully repleted their iron-depleted subjects with 195 mg/day of elemental iron supplementation (ferrous sulfate) in only 4 weeks. We supplemented with a smaller than recommended dose of elemental iron in order to prevent gastrointestinal upset and constipation. Indeed, subjects did not report any gastrointestinal upset or constipation throughout the 16-week study period.

In contrast to the findings of other studies (3, 4, 11, 16), alterations in thyroid hormone levels and/or RMR as a result of iron deficiency were not obviously evident in our investigation. However, the opposing changes observed in RMR were above that which would have been attributed to the %CV. In addition, it would be expected that the RMR of A2 would have been about 15% greater than A1 due to her higher body weight. Although A2 had a 36% greater absolute RMR and a 13% greater relative RMR at week 0, there were virtually no differences between absolute RMR at 8 and 16 weeks, with A1 having a greater absolute RMR at 16 weeks.

Furthermore, A2 had a lower relative RMR than A1 at 8 and 16 weeks, which paralleled the decrease in A2's total T_4 concentration.

Nutritional iron deficiency anemia has been shown to significantly reduce circulating levels of T_4-5' deiodinase (T_4-5'D) in rats, the iron-dependent enzyme responsible for the conversion of T_4 to triiodothyronine (T_3), resulting in suppression of the conversion of T_4 to T_3 (4). T_3 is capable of increasing metabolic rate in rats (3) and humans (27), via stimulation of the oxidative production of adenosine triphosphate. In our investigation, there were no apparent differences in concentrations of free T_4 index from 0 to 16 weeks in either subject. However, there were alterations in TSH and total T_4 concentrations, which were above that which would have been attributed to the %CV for these variables. Beard et al. (3) demonstrated that low plasma T_4 levels in iron-deficient-anemic subjects resulted in an inability to properly thermoregulate following cold exposure. Twelve weeks of oral iron supplementation (78 mg/day iron as ferrous sulfate) both corrected the iron deficiency anemia and improved ability to thermoregulate in their iron-deficient-anemic women (3). Although Beard et al. (3) observed improvements in plasma T_4 concentration as a result of iron supplementation, the levels were not fully corrected.

Menstrual cycle phase was not controlled in our investigation, and the failure to do so may have confounded our results. The estimated average daily blood loss for pre-menopausal women is 1.5 mg (17), equivalent to a total monthly decline in SF concentration of about 4.5 ng/dL (assuming that 10 mg of iron is equivalent to 1 ng/dL SF) (7). Additionally, Webb (29) determined that there is an increase above normal in both body temperature and metabolic rate during the luteal phase (last 14 days) of the menstrual cycle. Beard et al. (3) controlled for this increase by testing their subjects during the follicular phase (first 14 days) of their menstrual cycles.

With regard to dietary intake, it is important to note that A1 consumed fewer kilocalories (kcals) than A2 over the course of the study. This was coupled with a much lower iron consumption from 8 to 16 weeks compared to A2. In addition, A2 consumed more vitamin C in her diet and a greater amount of zinc. It is well documented that vitamin C enhances iron absorption and that zinc and iron interact with one another. Nonetheless, zinc intake in both of the subjects was below the Recommended Dietary Allowance (RDA) of 12 mg/day (17). Although our subjects consumed below the RDA for zinc, they had similar intakes as many individuals; it has been reported that large segments of the U.S. population are consuming zinc levels one-half or less of the RDA (25). The trend toward lower intakes of red meat and higher intakes of dietary fiber in U.S. diets raises concern about the adequacy of zinc nutriture (17, 23). The combination of a lower energy intake and high levels of physical activity, coupled with decreased dietary iron and zinc intake, may be the reason that A1 did not completely replete her iron stores and why her RMR was not changed from 8 to 16 weeks.

The fact that A1 was a distance runner and A2 a swimmer may have also played a role in why A1 did not completely replete her iron stores. Iron depletion occurs with greater frequency among certain types of athletes. In general, endurance athletes of both sexes who participate in aerobic sports such as cross-country running and cross-country skiing have a higher incidence of iron depletion than those athletes who participate in anaerobic sports (21, 24). This phenomenon is thought to result from losses of iron-containing substances in the urine and feces of these athletes due to gastrointestinal bleeding, as well as from myoglobinuria due to myofibrillar stress and hemoglobinuria due to intravascular hemolysis (5, 21, 67).

In conclusion, iron deficiency anemia, but not iron depletion, was corrected after 16 weeks of low-level iron supplementation in two college-age female athletes. Our data suggest that the alterations in RMR and thyroid hormone levels could have been a result of iron deficiency anemia, although other factors such as low energy intake, higher iron and ascorbic acid intakes, and not controlling for menstrual cycle during data collection may have confounded our results. Nonetheless, such alterations could have negative ramifications on athletic performance and overall health by impairing the development of lean body mass and increasing fatigue in female athletes. Therefore, additional research in this area should be conducted involving larger sample sizes, a higher dosage of iron, and control for menstrual cycle phase.

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