

ORIGINAL ARTICLE

The relationship between depression and serum ferritin level

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Objective: This study looks at the association of depression and serum ferritin level.

Design: Case–control study.

Setting: University hospital.

Subjects: Two hundred and five female medical students of Free University of Medical Sciences in Tehran were selected for the study (mean age; 24.5 ± 1.6 years). Of these, 13 subjects were excluded and finally 192 subjects took part in the study.

Interventions: A questionnaire was filled in by each participant for the diagnosis of depression to be made. Based on the Beck score, the students were grouped as depressed and healthy (67 depressed students and 125 healthy controls). The participants were evaluated in terms of hemoglobin (Hgb) level, serum ferritin, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), folic acid, vitamin B12 and Hgb simultaneously.

Results: The prevalence of depression in the study population was 34.7%. The mean ferritin level in students with depression was significantly lower than the healthy ones ($P < 0.001$). By changing the status from normal ferritin level to low ferritin level, odds of depression was increased by 1.92 ($P < 0.05$).

Conclusion: The study implies a possible association between depression and decreased ferritin level before the occurrence of anemia.

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Introduction

Depression is among the commonest psychological disorders. The rate has been estimated between 8 and 20% in the US (Kaplan *et al.*, 2003). Some causes of depression (genetic) are not liable to change, whereas some others are modifiable (Benton and Donohoe, 1999). Nutrition can play an important role in preventing depression. In fact, nutrient deficiencies can affect mental and cerebral mechanisms resulting in mood disorders such as depression (Benton

and Donohoe, 1999). The association of depression with some vitamin deficiencies (folic acid, vitamin B12, niacin and vitamin C) has been established (Kaplan *et al.*, 2003). Data from the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994) indicated that iron deficiency without anemia occurred in up to 11% of women (most often premenopausal) and 4% of men (Looker *et al.*, 1997). The patients affected by iron deficiency anemia show many mood and behavioral signs and symptoms similar to the depressed individuals. Of note, many of these signs and symptoms occur in the initial stage of iron deficiency (dropped serum ferritin level) before the establishment of frank anemia (Beard *et al.*, 1993). Many of the symptoms of depression in patients with iron deficiency anemia can be treated with iron supplementation therapy even before any improvement in RBC counts or indices. It seems that this phenomenon is due to the recovery of neurotransmitters

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and enzyme levels dependent on iron, unrelated to hemoglobin (Hgb) concentration (Kathlen and Escott-Stump, 2004). Whereas these results concur with some previous series (Lozell *et al.*, 2000; Mansson *et al.*, 2002; Beard *et al.*, 2005), there are some studies that have shown different results (Mansson *et al.*, 2002).

As there was no precedent to this study in Iran, we looked at the association of ferritin with depression.

Patients and methods

The present study was a case-control study, which was carried out during 2004–2005 at Free University of Medical Science in Tehran. A hundred and ninety-two female medical students, who were on their clinical rotation in the psychiatry department of Shahid Doctor Lavasani Hospital, were recruited. The study protocol was endorsed by the responsible ethics committee and written informed consent was obtained from each participant.

The students completed preliminary questionnaires inquiring into demographic characteristics, medical history and history of receiving any medication including iron or multivitamin supplements.

Given the difficulty of measuring leukocyte levels of vitamin C and niacin metabolites in urine in our country, each participant received one vitamin C tablet (250 mg) and one vitamin B complex tablet (containing 20 mg niacin, without iron) daily for 1 month before study.

First, the Beck questionnaire was given to each student to assess the presence of depression (see Appendix). A score of 10 or higher was considered as depression (Beck *et al.*, 1988).

Based on the Beck score, they were divided into two groups (67 depressed students and 125 healthy controls). Controls were matched to cases. At the same time, fasting blood sample (0800 hours) in sitting position was taken from each participant. The samples were used to check for serum ferritin levels (ELISA; Boeti, Italy), erythrocyte sedimentation rate (ESR) (Westergreen, Parsazmoon), C-reactive protein (CRP) (quantitative agglutination), B12, folic acid of serum (Radioimmunoassay, Parsazmoon) and Hgb, and the analyses were performed immediately after drawing the blood. Normal range for serum ferritin level is 15–200 µg/l and levels below 15 indicated iron deficiency (Kasper *et al.*, 2005).

Students who had Hgb level lower than 12 g/dl or a history of physical disease that is accompanied with mood disorders such as multiple sclerosis, Parkinson's disease and hypothyroidism (Kasper *et al.*, 2005) were not eligible for this study.

Students who were consuming drugs that could affect mood such as β blockers, calcium channel blockers and anticonvulsants (Kasper *et al.*, 2005), were excluded from the study.

As ferritin is one of the acute phase reactants and as inflammatory processes are accompanied with raised levels of these reactants, people with inflammatory disorders were excluded from the study. Disqualified for study were also the subjects who had high ESR, positive CRP, serum folic acid level < 4 ng/ml or B12 < 300 pg/ml.

Several studies have proposed a linkage between depression and folic acid and vitamin B12 deficiencies (Kaplan *et al.*, 2003). Students with serum folic acid levels lower than 4 ng/ml and serum vitamin B12 levels lower than 300 pg/ml were excluded from the study. Finally, seven people who were consuming iron supplements, one receiving corticosteroid, one with minor thalassemia, one with positive CRP, two with folic acid deficiency and one with vitamin B12 deficiency, were excluded from the study.

Statistical methods

SPSS software version 12 was used to analyze data. Student's *t*-test was used to compare mean serum ferritin levels between the two groups. Spearman correlation analysis was employed to examine the relationship between depression and serum ferritin level. In order to determine the degree of relationship between the two variables of depression and serum ferritin level, logistic regression was used. *P*-values less than 0.05 were considered as significant.

Results

All study participants were in their reproductive years with a mean age of 24.5 ± 1.6 years. Mean serum ferritin levels were 26.95 ± 11.3 and 38.36 ± 17.1 in depressed and healthy participants, respectively (Table 1).

In depressed individuals it ranged between 2 and 103, and in healthy ones between 2 and 197.9 µg/l. Student's *t*-test showed that serum ferritin levels of the two groups were significantly different (*P* < 0.001).

Spearman correlation coefficient for ferritin and depression was -0.167 and statistically significant (*P* = 0.01). It showed little and negative relation.

To measure odds ratio, serum ferritin level was transformed into a dummy variable (ferritin levels ≤ 15 or > 15)

Table 1 Comparison between mean and standard deviation of Hgb, Hct, folate, B12, ESR, ferritin and Beck score in depressed and control groups

Group	Number	Hgb(g/dl) M ± s.d.	Hct (%) M ± s.d.	Folate (ng/ml) M ± s.d.	B12 (pg/ml) M ± s.d.	Ferritin (µg/l) M ± s.d.	ESR M ± s.d.	Beck score
Depressed	67	12.6 ± 0.5	37.5 ± 1.5	9 ± 1.8	502 ± 62.44	26.95 ± 11.3	7.8 ± 2.3	6 ± 2.4
Control	125	13.7 ± 1.1	41 ± 3.1	8 ± 1.41	478 ± 42.16	38.36 ± 17.1	8.1 ± 2.4	16.1 ± 5.1

Abbreviations: ESR, estimated sedimentation rate; Hct, Hematocrit; Hgb, hemoglobin.

and its relation with depression was examined using logistic regression analysis. The equation (Logit (π) = $-0.827 + 0.625X$, Exp 0.625 = 1.92) showed that changing the status from normal ferritin level to low ferritin level increases the odds of depression by 1.92 ($P < 0.05$).

Total prevalence of iron deficiency (serum ferritin ≤ 15 ng/l) in the study population was 29.5%, higher than what was reported in NHANES III (11%) (Looker et al., 1997).

The frequency of iron deficiency was significantly higher in depressed participants compared to the healthy ones (40.3 vs 23.8%; $P < 0.05$).

The prevalence of depression in married students was 31.7%, which was not significantly different from the single students (35.5%; $P > 0.05$).

Discussion

The current study evaluated the relation between serum ferritin level and depression. It has been shown that mean ferritin levels were within normal range in both groups. However, it was 11 $\mu\text{g/l}$ lower in depressed students than in healthy students.

Iron deficiency was observed in 29.5% of the participants, which seems rather high. In addition, the frequency of iron deficiency was 15% higher in depressed participants than healthy ones. A clinical trial recently conducted in Sweden showed that iron supplementation could diminish depressive symptoms in students compared to the control group (Mansson et al., 2002). In another study in the US, prescription of iron led to decreased depression in mothers with iron deficiency anemia compared to the controls (Beard et al., 2005). In a study in the US, infants with severe iron deficiency anemia were followed up for a 10-year period. The study revealed that these infants later had lower psychomotor scores. Depressed mood, anxiety and difficulty in concentration were more common in these children (Lozell et al., 2000).

A study in the US, based on the MMPI questionnaire, reported that serum iron, ferritin and Hgb level were not associated with depression (Hunt and Peland, 1999). It is notable that the participants of that study were not evaluated with regards to inflammatory diseases, thalassemia, use of iron or multivitamin supplements and some other drugs that could affect serum ferritin level. Neither were the indicators of inflammatory process examined (ESR and CRP). Any of the mentioned disorders and/or positive ESR or CRP tests could increase or be accompanied with increased ferritin level (Kasper et al., 2005).

The fact that mean serum ferritin level was lower in depressed students than in healthy ones can indicate the possible role of iron in brain function and the establishment of depressive mood. Iron plays an important role in the oxygenation of brain parenchyma and the synthesis of many neurotransmitters and enzymes of the nervous system (Beard et al., 1993). Iron acts on the molecular level and its effect

on depression may be multifactorial with positive and negative effects. For example, as a negative effect on depression, a sufficient amount of iron is particularly needed for the synthesis of dopamine, a neurotransmitter that plays a significant role in mood disorders (Paul et al., 2002). In depression, we face depressed levels of blood dopamine (Kaplan et al., 2003).

In our study, the correlation coefficient was low; however, the amount or the direction is important. It showed an inverse correlation between serum ferritin level and depression that seems important. The figure is low because the role of iron on depression is due to the sum of its positive and negative effects with resultant to the negative effects.

It seems necessary that iron supplementation, in treating symptoms of depressive patients, should be evaluated in a clinical trial.

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Appendix

BECK questionnaire

- 1 0 I do not feel sad.
1 I feel sad.
2 I am sad all time and I cannot snap out of it .
3 I am sad or unhappy that I can't stand it.
- 2 0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.
- 3 0 I do not feel like a failure.
1 I feel I have more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.
- 4 0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.
- 5 0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.
- 6 0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.
- 7 0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.
- 8 0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.
- 9 0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.
- 10 0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.
- 11 0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.
- 12 0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.

Continued

- 2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.
- 13 0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I cannot make decisions at all anymore.
- 14 0 I don't feel I look any worse than I used to.
1 I am worried than I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.
- 15 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I cannot do anything at all.
- 16 0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.
- 17 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am tired to do anything.
- 18 0 My appetite is no worse than usual.
1 My appetite is no as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.
- 19 0 I haven't loss much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pound.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by
Eating less. Yes _____ No _____
- 20 0 I am no worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems than I cannot think about anything else.
- 21 0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.