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Research Article

Is there a Relationship between Poor Iron Status and The Severity of Depression? A Study carried out on Turkish Women Living in Germany

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Abstract

Background: It is widely accepted that many factors including medical comorbidity can influence the development of depression in women. There is no evidence, however, that specific medical diagnoses are independent markers for severity of depression.

Objective: This study aims to investigate the iron status of Turkish female patients with depression, to find out if the iron deficiency (ID) is a risk factor in depression. In addition, it also aims to investigate a possible relationship between reduced iron capacity and intensity of the disease.

Method: A retrospective chart review comparison study was carried out to investigate the iron status of Turkish women with a diagnosis of depression, aged between 18 to 43 years old, living in Germany. The iron parameters were measured in the blood of 180 Turkish women with depression, and of 102 Turkish women without depression. The depressed patients were further sub grouped as mild (n=28), moderate (n=74) and severe depression (n=78) by using Hamilton Depression Rating Scale D (HRS). The measurements for red blood cells (RBC), haemoglobin, free iron and ferritin of the participants in the Community Outpatient Clinic were recorded, and the data was statistically analysed.

Patients with a family history of a blood disorder except iron deficiency anaemia, patients with increased acute phase reactants, and those who were pregnant, or suffering from malignancies, diabetes mellitus, and/or mental disorders except depression were excluded from this study.

Results: We have found a significant negative correlation between ID and the severity of depression. Levels of reduce hemoglobin in peripheral blood, along with iron and ferritin and RBC were found in several of the patients suffering from severe depression.

Conclusion: These findings have been presented with consideration of their clinical implications of ID and depression with a view to conducting further research.

Keywords: Depression; Iron Deficiency; Turkish Women

Introduction

Iron is a major player in multiple processes in the body and is needed for the function of various enzymes and coenzymes including cytochrome C, catalase, and aromatic amino acid hydroxylases [1-3]. Iron provides the delivery of oxygen through hemoglobin to the body tissues. In addition, iron is also found in myoglobin and other iron enzymes that are required to use oxygen for the production of cellular energy. Iron balance is dependent on the body's iron stores, absorption and losses. Approximately, two-thirds of body iron is found mainly in the functional part of hemoglobin in the red blood cells. Most of the remaining is storage iron, mainly serum ferritin to be utilized when needed [4-7].

It is estimated that one-third of the world's population is anemic, the majority being due to iron deficiency (ID). Iron plays an important role in the oxygenation of brain tissue and the synthesis of many neurotransmitters and enzymes of the nervous system. The iron related enzymes are quite sensitive to depletion of iron throughout the body. In particular hydroxylases, which are needed for the synthesis of dopamine and serotonin, can malfunction with minor ID before any manifestation of anemia [8-10].

Iron deficiency anemia (IDA) is diagnosed when the hemoglobin concentration is lower than the level considered to be normal for the person's age, gender and physiological status, resulting in the reduced capacity of the red blood cells to deliver oxygen to body cells and tissues. Common clinical symptoms include, such as pale conjunctiva, shortness of breath, dizziness, and lethargy [11,12]. The main risk factors for iron deficiency anemia include a low intake of iron, poor absorption of iron from diets, chronic loss of iron (i.e. ulcer, metrorrhagia) and some specific periods of life when iron requirements are especially high, such as growth and pregnancy [13,14].

Free iron is toxic to cells as it acts as a catalyst in the formation of free radicals from reactive oxygen species in the process of oxidative stress and neuro-progression [15-18]. Ferritin serves to store iron in a non-toxic form, to deposit it in a safe form, and to transport it to areas where it is required. If the ferritin level is low, there is a risk for lack of iron, which could lead to anaemia. Low serum ferritin is the most specific lab test for iron deficiency anaemia [19-21]. However it is less sensitive, since its levels are increased in the blood by any type of acute or chronic inflammation [22-24], and these conditions may convert what would otherwise be a low level of ferritin from lack of iron, into a value in the normal range. For this reason, low ferritin levels carry more information than those in the normal range. A lower-than-normal level may be due to heavy menstrual bleeding, vegetarianism, intestinal conditions that cause poor absorption of iron, and long-term digestive tract bleeding [25,26].

Low ferritin may also indicate hypothyroidism, vitamin C deficiency or celiac disease [27,28]. Low serum ferritin levels are seen in some patients with restless legs syndrome, not necessarily related to anaemia, but perhaps due to low iron stores short of anaemia [29]. A falsely low blood ferritin is very uncommon, but can result from a hook effect of the measuring tools in extreme cases [30,31].

Animal studies on post-weaning rats and mice have demonstrated that iron deficiency led to a deficits in intracellular dopamine concentrations and in the density of dopamine and dopamine transporter receptors, with variable amounts of loss by brain region [32-34]. In addition, ID effects the metabolism of 5-hydroxytryptamine in rat brain and this substance is the precursor in the synthesis serotonin, which is a major neurotransmitter regulating the mood and emotions in brain [35]. Its deficiency has been reported in relation to mental disorders including depression [36-45].

Significantly reduced extracellular concentrations of noradrenaline in rats were reported by researchers in the caudate putamen, due to reduced iron levels was reported as a result of changes in the expression of noradrenaline transport and noradrenaline receptor proteins in the locus ceruleus and basal ganglia [33,46]. A reduction in serotonin transporter binding was also shown in the nucleus accumbens in iron-deficient rats and the serotonin concentration in the brain was significantly correlated with serum iron level [47,48].

The iron related enzymes are quite sensitive to depletion of iron throughout the body. In particular hydroxylases, which are needed for the synthesis of dopamine and serotonin, can malfunction with minor iron deficiency before any manifestation of anaemia [49,50]. This is why there are so many symptoms associated with iron deficiency which may not necessarily be related to an anaemia. Well-documented mental consequences of ID include: diminished cognitive functions, affective disorders, a reduced ability for social adaptation, increased somatic morbidity such as fatigue and pain, and a decreased work capacity [51].

Depression is a mental disorder with a wide range of causes. It is influenced by diverse risk factors, including: age, gender, ethnicity, physical health, socioeconomic status, a history of sexual abuse and recent stressful life events. Epidemiological data from various cultures indicate that the prevalence of depression is twice as high in women as in men. In the aetiology, physical and psychosocial hypotheses have been proposed to explain the predominance of depression in women [52,53].

Reports suggest that women with physical comorbidity are more prone to developing depression. Women may experience different types of depression and menstrual disorders during their reproductive age, and symptoms may vary during preg-

nancy, postpartum and menopause [54,55]. A peak in first onsets of depression in women during their childbearing years needing particularly an increased iron requirements during menstruation and pregnancy has been reported [56]. There is no evidence, however, that specific medical laboratory diagnoses are independent markers for severity of depression in women.

Depressive disorders among the female Turkish immigrant population living in Germany, was reported to be relatively high, and often mischaracterized as somatic, rather than mental complaints [57,58]. Among others, cultural stigma can play an additional negative role in the appearance and diagnosis of depression, in uprooted Turkish women living in the West [59-61].

As far as we know, there has been no previous single report on a possible association between iron status and severity of depression. Hence, the present study is undertaken to investigate that ID may be involved in the development of depression of premenopausal Turkish women, living as immigrant in Germany.

Material and Methods

Study design: A retrospective chart review comparison study was conducted in a period of 12 months, from January to December 2013, to investigate an association between iron status and depression in Turkish women, aged between 18 to 43 years old. This was carried out at the community based internal medicine and psychiatric practices in Germany. Iron parameters in the blood of 180 Turkish women with depression and in 102 Turkish women of matching ages without depression were measured. The measurements for RBC, haemoglobin, serum iron and ferritin of the participants were recorded and results were later statistically analysed.

The examinations of the patients were carried out by a psychiatrist, and were diagnosed according to the International Classification of Diseases-10 (ICD-10, Kapital -V (F) [62]. The severity of the disease was further established by using the Hamilton Depression Rating Scale D (HRS) by means of structured interview [63]. The HRS's point system ranges from 0 to 63. Points <18 represent minor depression, 19-24 points correspond to moderate depression, and points > 25 fulfill the criteria for severe depression. Out of 180 patients 28 patients met the criteria of minor/mild depression, 74 moderate depression and 78 severe depression.

Exclusion criteria: Patients with a family history of blood disorder except IDA, the patients with increased C- reactive protein (CRP) and increased alanin-transaminase, those who were pregnant, and those suffering from malignancies, diabetes mellitus or mental disorders except depression were excluded from this study. Two control persons with psychosis and three with OCD were also excluded from the study.

Laboratory assessment: Biochemical measurements of hemoglobin and RBC were made in freshly taken peripheral blood with EDTA, ferritin and free iron in sera without EDTA. Hemoglobin levels and RBC were calculated by HemoCounter (BT-Pro-2401). Serum iron levels were determined by spectrophotometric method (Beckman Coulter AU 2700). Ferritin levels were measured by using immunoassay (Chemiluminometric technology on Advia Centaur xp).

Statistical assessment of the data was made using the 'Statistical package' for Social Sciences, on Windows version 15.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined.

Median and minimum-maximum values were used for variables by using normal distribution. Data with normal distribution was compared Student t-Test (for 2 variables) and ANOVA test (for more than two variables). Comparisons of continuous variables with asymmetric distribution were made by using the Mann-Whitney- U test (for two variables) and Kruskall-Wallis test (for more than two variables). Pearson's correlation-coefficient was used to investigate the relationship between iron variables and HRS. A 'p' value less than 0.05 was considered to be significant.

Results

The differences of iron parameters between patient's group and control's group were presented in Table 1. The mean age for patients was 28.67±6.55 and for the control group was 29.73±7.12. The mean numbers of the RBC was 4.39 (3.65-5.23) in the patients' group and 4.49 (2.96-6.15) in the control group.

Table 1. Statistical analysis of variables of patients against controls.

	Patients (n:180)	Controls (n:102)	p - values
Age	28.67±6.55	29.73±7.12	> .05*
RBC	4.39 (3.65-5.23)	4.49 (2.96-6.15)	< .001**
Hemoglobin	11.10 (8.60-13.70)	12.86 (10.20-14.60)	< .001**
Serum iron	50.92 (11.6-110)	69.2 1 (11.59-146)	< .001**
Ferritin	39.03 (2.60-99)	62.61 (9-114)	< .001**

* **Student t-test** (mean±SD)

** **Mann-Whitney-U** (median; min-max, significance < .05).

Hemoglobin concentration was 11.10 (8.60-13.70) for the patients and 12.86 (10.20-14.60) for the control group. Serum iron values were 50.92 (11.6-110) for the patients and 69.21 (11.59-146) were for the control group. Ferritin was found to be 39.03 (2.60-99) in patients and 62.61 (9-114) in controls. The differences were found to be significant in all parameters except age.

The Pearson's test was used to calculate the relationship between variables of iron parameters and depression. No relationship was shown between age and depression (r= 0.016, p>0.05). A significant negative relationship was found between reduced iron parameters and depression (r = - 0.369 p< .001 for the RBC, r = -0.760 p< .001 for the Hb, r =-0.660 p< .001 for the serum iron, r = 0.602 p< .001 for the ferritin respectively).

Table 2. Correlation between HRS and the variables.

	r - values *	p - values
Age	0.016	> .05
RBC	- 0.369	< .001
Hemoglobin	- 0.760	< .001
Serum iron	- 0.660	< .001
Ferritin	- 0.602	< .001

* Pearson's correlations coefficient

The findings were further evaluated to compare the variables within the subgroups of patients (i.e. mild, moderate, severe) by using HRS. Age difference within the subgroups of mild, moderate and severe depression is not significant (p> 0.05). Iron parameters: RBC (10^6/mm^3); 4.82 (2.96-6.15) for mild, 4.29 (3.14-5.70) for moderate, 4.04 (3.20-5.65) for severe depression, (p< 0.001), Hb (g/dl); 12.90 (11.00-13.60) for mild,

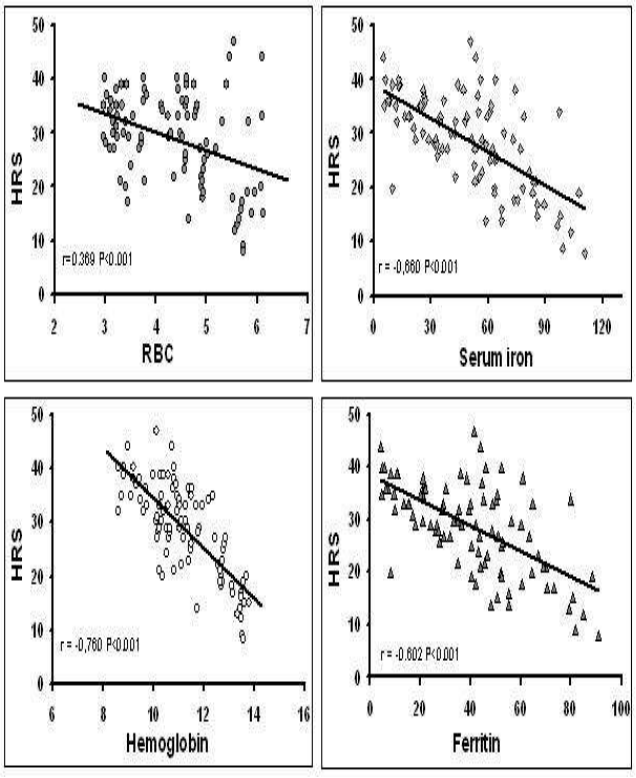

Figure 1. The linear regression analysis of RBC, haemoglobin, serum iron and ferritin versus depression score (HRS).

Table 3. Statistical analysis of variables within subgroups - patients

	Patients with mild depression (n:28)	Patients with moderate depression (n:74)	Patients with severe depression (n:78)	p-values
Age	29.50 (18-40)	28.00 (11-42)	30.00 (18-42)	> .05*
RBC	4.82 (2.96-6.15)	4.29 (3.14-5.70)	4.04 (3.20-5.65)	< .001*
Hemoglobin	12.90 (11.00-13.60)	11.25 (9.90-13.70)	10.15 (8.60-12.40)	< .001*
Serum iron	79.23±16.76	55.33±19.55	36.58±14.23	< .001**
Ferritin	65.86±18.98	42.84±20.09	25.78±16.65	< .001**

* **Kruskall Wallis** (median; min-max, significant level is 0.05).

** **One-Way ANOVA** (mean± SD)

11.25 (9.90-13.70) for moderate, 10.15 (8.60-12.40) for severe depression (p< 0.001), serum Iron (µg/dl); 79.23±16.76 for mild, 55.33±19.55 for moderate, 36.58±14.23 for severe depression (p< 0.001), ferritin (ng/ml) 65.86±18.98 for mild, 42.84±20.09 for moderate and 25.78±16.65 (p< 0.001), (Table 3, Figure 1).

Discussion

The current study evaluated the relation between serum iron parameters and depression of women in childbearing age. The results demonstrated a significant association between ID and depression. To examine further the issue of ID as a medical condition that might indicate co-morbid depression, we undertook this exploratory study to analyse the relationship between iron- related laboratory parameters and the severity of depression in Turkish female patients; who were diagnosed according to ICD-10.

In agreement with some of the previous studies, our results showed that women with depression tend to have lower iron in their blood than women without depression [64,65]. Reduced iron parameters (i.e. hemoglobin, free serum iron, RBC and ferritin) in sera of patients with depression were also found to associate significantly with severity of depression. The results demonstrated a negative correlation between reduced iron parameters and the intensity of depression in female patients. In practice, haemoglobin concentration is considered to be an indicator for iron deficiency anaemia. However, iron deficiency anaemia is usually assessed by measuring haemoglobin levels but alone this approach lacks both specificity and sensitivity [66].

These findings may remind us a possible causal relationship between iron deficiency and depression in women. We find it difficult, however, to sort out whether ID is a cause of depression itself, or a contributing risk factor in the increased severity of the disease. Nevertheless, this association has to be taken into consideration in the management of this condition. It is, therefore, indispensable to investigate cause of iron deficiency no matter if an anaemia exists. It is important to know that iron deficiency is treatable, and necessary advice over the causes of iron deficiency from relevant medical specialties has to be sought. Iron deficiency, therefore, has to be corrected before the treatment of depression begins [67].

Previous studies suggested that iron may be involved in the molecular level maintaining the cognitive functions [15,17,38]. Failure to identify and treat earlier stages of iron deficiency is concerning given the neurocognitive implications of iron deficiency without anaemia. A sufficient amount of iron is particularly needed for the synthesis of neurotransmitter that plays a significant role in mood disorders [65].

We did not attempt in this study, however, to investigate the entity of anaemia; which would have required further diagnostic laboratory investigation. We chose, therefore, to investigate the most relevant laboratory iron parameters in patients with or without visible iron deficiency anaemia.

Oxidative stress-mediated damage depends on the level of cellular and total body iron status because an excess iron pool produces the most harmful free radicals (hydroxyls) through the Fenton reaction. Ferritins have a central role in the protection against oxidative damage, in which oxidative stress is a major factor in inflammatory, malignant and metabolic diseases [21]. Intracellular ferritin is found in the cytosol of many cells in the body. Ferritin is also found in extracellular fluids such as serum, synovial fluids and milk.

Low serum ferritin is the most sensitive test to detect and manage iron-related disorders, such as iron deficiency anaemia while high levels of ferritin have been associated with malignant disease and tissue damage. Many studies emphasize that iron deficiency may be under recognized by many communities and undertreated [24]. It was also suggested that the ID should be checked, when necessary, iron supplementation, in treating symptoms of depressive patients, should be evaluated further [42,44,45].

Women of reproductive age are at particularly high risk of iron deficiency and its consequences. Premenopausal women usually have low iron status because of iron loss in menstrual blood. Women appear to be particularly vulnerable to comorbid medical conditions, such as migraine, hypothyroidism, celiac disease, Restless-Leg-Syndrome or ID. This is why there are so many symptoms associated with ID which may not necessarily be related to anemia [35,36]; all of which can make depression more difficult to identify and treat successfully. There is a considerable overlap between the two subjects. The question arises as to whether there might be a set of symptoms and perceptions that are shared by ID which might be indicators of depression in addition to the symptoms traditionally attributed to it.

It is widely accepted that many factors including cultures and ethnicity can influence the development of depression in women [68-70]. Our findings may indicate that ID has a strong association in women with Turkish ethnicity. Further, we assume that inadequate treatment may lead to a prolonged duration of depression in patients, with a reduced quality of life as well as other possible side effects. Our results emphasize the need for physicians to be mindful of depressive cases requiring the intervention of iron supplementation, rather than purely anti-depressive treatment [67].

The ability to recognize the depressive symptoms as mentally significant is sometimes difficult, as the same symptoms can be characteristic of non-mental medical conditions. For example, increased fatigue and pain, poor memory, concentration

and disturbed cognitive functions can be present in ID [5,38]. For this reason, we would like to draw the attention of physicians on overlapping or similar symptoms in the assessment of intensity of depression by using HRS.

Our study has several limitations. Firstly, the findings may not be representative of all Turkish women with depression, as the study was conducted in one medical outpatient practice. A further comparative study should be carried out on more Turkish patients, as well as non-Turkish women with depression. It is also essential for a matching study to be carried out in patients living in mainland Turkey.

Secondly, this study is cross-sectional and lacks the capability of showing a firm causal relationship between the symptoms of depression and declined iron status we measured.

A link between mental illness and physical disease is complex. Causal criteria can be used to study this possible link. Strength-Causal inferences are more easily made about strong associations. Weak associations, on the other hand, are much more likely to be the result of unsuspected biases [71]. Further work is required to integrate standard clinical epidemiological concepts.

For certain diagnoses, depression predates the onset of the physical illness: for example, in the case of diabetes. On the other hand, other symptoms such as chronic insomnia, pain and fatigue can, for a while, predate depression. It has been suggested that depression worsens the course of certain pre-existing physical illnesses, such as osteoporosis or coronary artery disease [72,73].

Thirdly, while ferritin in peripheral blood is known to correspond to the total body iron reservoir, it may, however, be found as increased by liver damage or by an inflammatory process as an acute phase protein [74]. We have, therefore, excluded patients with high level ALT and CRP from this study.

The suitability of the age of controls was tested statistically by null hypothesis. The age difference between the control group and the patients has failed to reject null hypothesis. Thus it proves the suitability and reliability for this study.

Turkish community represent the biggest ethnic population living in Germany. Distress associated with immigration among the Turkish population was reported to be relatively high. The inability to articulate distress and tendency to somatic presentation is quite common [75]. It was suggested that comorbid physical illness such as ID could be an additional precipitating factor in the development of depression in Turkish women living in Germany [61].

The role of social stigma on reporting depression is often seen in Turkish culture as degrading, as a patient's resistance to report depression is usually associated with fear of embarrassment or shaming their family. It is important for a doctor to have some appreciation as to how ethnic features including lifestyle, eating habits and nutrition (i.e. ID) will affect the presentation of depression in association with physical health [76,77].

Conclusions

We examined if ID is a risk factor for depression among Turkish women living in Germany. Based on our findings, we hypothesized that ID in Turkish women at least is a risk factor for the severity of depression. Further work is required to establish a causal association.

Clinically these findings are potentially useful; as these factors can be measured with relative ease during routine visits, regardless of the chief complaint or illness. Substitution of iron can improve the treatment of depression, by reducing cost, suffering and the prolonging of depressive illness. Thus, we recommend that these factors should be taken into consideration in the diagnosis, treatment and follow-up of the patients with depression.

These findings have been presented with the consideration of their clinical implications and with a view to conducting further research.

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