

Assessment of subjective sleep quality in iron deficiency anaemia

Semiz Murat¹, Uslu Ali², Korkmaz Serdal³, Demir Süleyman⁴, Parlak İlknur⁵, Sencan Mehmet⁶, Aydın Bahattin⁵, Uncu Tunahan⁵

1. Gülhane Military Medical Faculty, Department of Psychiatry, Ankara, Turkey.
2. Eskişehir Military Hospital, Department of Internal Medicine, Eskişehir, Turkey.
3. Kayseri Education and Research Hospital, Division of Hematology, Kayseri, Turkey.
4. Department of Psychiatry, Dicle University, Diyarbakir, Turkey.
5. Cumhuriyet University Faculty of Medicine, Department of Internal Medicine, Sivas, Turkey.
6. Cumhuriyet University Faculty of Medicine, Department of Hematology, Sivas, Turkey.

Abstract

Objectives: We aimed to assess the effect of anemia on subjective sleep quality in patients with iron deficiency anemia (IDA).

Methods: One hundred and four patients diagnosed with IDA and 80 healthy individuals, who are gender and age matched, were included in the study. All participants were requested to fill 3 forms: a socio-demographic form (age, gender, marital status, income level and educational status), hospital anxiety and depression (HAD) scale and pittsburgh sleep quality index (PSQI).

Results: According to the HAD scale, the average anxiety score was found 9.24 ± 4.37 in patients and 7.58 ± 4.07 in controls. And, the average depression score was 7.53 ± 4.10 in patients and 6.41 ± 2.74 in controls. The total sleep quality score was 6.71 ± 3.02 in patients and 4.11 ± 1.64 in controls. There was a statistically significant difference in terms of anxiety, depression and sleep quality scores. Linear regression analysis showed no association between anxiety and depression with poor sleeping.

Conclusion: IDA affects sleep quality irrespective of psychological symptoms such as depression and anxiety.

Keywords: Iron deficiency anemia, sleep quality, anxiety

DOI: <http://dx.doi.org/10.4314/ahs.v15i2.40>

Introduction

After a negative iron balance in the body due to reasons such as chronic blood loss, increased iron demand, and absorption disorder, hemoglobin synthesis is compensated by mobilization of iron from stores and when the stores of iron fail to release adequate iron, iron deficiency anemia (IDA) develops¹. Just like in our country, iron deficiency is the most common cause of anemia in the world and is more prevalent in women than men^{2,3}. It has been known that more than 30% of those attending to hospitals in developed countries are anemic and the said ratio is much higher in developing countries.

In developed countries, 3% of adult males, 20% of adult females and 50% of pregnant women have iron deficiency anemia^{4,5}. Loss of appetite, tiredness, pale skin, lethargy, headache, tinnitus and impairments in cognitive and intellectual functions can be observed in IDA⁶. Iron plays a key role in the metabolism of monoamines in the brain thus iron deficiency leads to symptoms such as apathy, drowsiness, irritability and lack of attention occur due to impaired monoamine oxidase activity⁷. Patients affected from iron deficiency display many behavioral and emotional signs and have symptoms similar to the ones in depressive individuals⁸.

Sleep is the period of physiological, periodic and reversible changes in consciousness and behaviour⁹. It is defined as a reversible state where interaction of the organism with the environment is lost temporarily, partially and periodically¹⁰. Nearly 30-33% of the society has a significant sleep problem. The said ratio is higher in older adults, those having a psychiatric disorder and specific groups with learning difficulties¹¹⁻¹⁴. In various

Corresponding author:

Semiz Murat,
Gülhane Tıp Akademisi Psikiyatri AD,
TR-06020, Ankara, Turkey.
Email: drmuratsemiz@hotmail.com

studies, advanced age, female gender, stress, depression, anxiety, alcohol, substance abuse and physical diseases are the important factors causing sleep disorders^{15,16}.

Due to the key role of iron in the metabolism of monoamines in the brain and the role of the same monoamines in sleep physiology, we stipulated that sleep quality might deteriorate in IDA. In this context, studies usually have been performed in pediatric populations. To the best of our knowledge, there exist no studies examining subjective sleep quality in adult patients with IDA. Therefore, we aimed evaluating sleep quality in adult patients diagnosed with IDA.

Materials and methods

Our study is a prospective and cross-sectional study which has been carried out at Cumhuriyet University, medical faculty, hematology clinic between January 2013 and June 2013. Ethical committee approval was obtained from the ethics committee of the medical faculty of Cumhuriyet University, and the study was in accordance with the declaration of Helsinki. One hundred and four patients diagnosed with IDA and gender and age matched 80 healthy individuals were included in the study. Loss of appetite and tiredness were the most common presentations. It was confirmed that there were no accompanying neurological or endocrinological diseases in patients with IDA.

The diagnosis of IDA was made by evaluating the levels of hemoglobin, transferrin saturation -calculated by the ratio of serum iron to serum iron binding capacity- and ferritin. Hemoglobin level below 13 mg/dL in men and 12 mg/dL in women, transferrin saturation ratio below 15%, and ferritin level below 15 ng/mL indicated IDA. The control group was composed of healthy volunteers who were regular blood donors in our hospital. Those having systemic diseases such as diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis and any medication use were excluded from the study. The participants were asked to complete a socio-demographic form (age, gender, marital status,

income level and educational status), hospital anxiety and depression scale and Pittsburgh sleep quality index.

Anxiety and depression parameters were tested by the hospital anxiety and depression scale (HAD). As the scores increase, depression and anxiety increase¹⁶⁻¹⁷. The Turkish version was developed by Aydemir¹⁸ et al. The Pittsburgh sleep quality index (PSQI) was used to measure sleep disturbance. It is consisted of 19 items and over 7 domains that include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction. Greater PSQI scores show worse sleep quality. A global sum of 6 or greater indicates a "poor" sleeper¹⁷⁻¹⁹. The Turkish version was developed by Agargun²⁰ et al.

Statistical analysis

SPSS 15.0 statistical program (SPSS, version 15.0 for Windows; SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables are presented as means \pm SDs, and categorical variables are presented as percentages. Independent-sample t- test were used to compare patients and healthy individuals with regard to the study variables. Chi-square tests were used to compare data presented as percentages. Correlation analysis was performed using Pearson's coefficient of correlation. Linear regression analysis was utilized to assess the contributions of age, anxiety, and depression to poor sleeping.

Results

The patient population (average age: 32.57 \pm 10.19 years) were composed of 104 patients [81 (77.9%) female and 23 (22.1%) male]. The control group (average age: 30.44 \pm 9.98 years) had similar socio-demographic characteristics and were composed of 80 healthy individuals [61 (76.2%) female and 19 (23.8%) male]. In terms of age and gender distribution, there was no statistically significant difference between the groups (t=1.42 p=0.16 ve $\chi^2=0.069$ p=0.793). The socio-demographic characteristics of the study groups are given in Table 1.

In terms of haemoglobin, hematocrit and MCV val-

Table 1. Socio-demographic characteristics of the study groups

	Patients n (%)	Controls n (%)	Statistics (χ^2)	p value
Gender				
Female	81 (77.9)	61 (76.2)	0.069	0.793
Male	23 (22.1)	19 (23.8)		
Educational status				
Primary school	33 (31.7)	27 (33.8)		
Secondary school	19 (18.3)	16 (20.0)	0.699	0.874
High school	36 (34.6)	28 (35.0)		
University	16 (15.4)	9 (11.2)		
Marital status				
Married	66 (63.5)	55 (68.8)	0.562	0.454
Single	38 (36.5)	25 (31.2)		
Income status				
Low-income	26 (25.0)	21 (26.2)	0.038	0.981
Middle-income	66 (63.5)	50 (62.5)		
High-income	12 (11.5)	9 (11.2)		

ues, there was a statistically significant difference between the groups (t=16.95, p=0.001; t=6.77, p=0.001; t=15.78, p=0.001, respectively). The other hemogram parameters did not show any differences between the

groups. The detailed hemogram values of the groups are shown in Table 2. In the patient group, the average serum ferritin level and total iron binding capacity were measured as 7.15 \pm 5.28 and 412.10 \pm 60.4, respectively. In HAD scale, the average anxiety score was found

Table 2. Hemogram values

	Patients mean \pm SD	Controls mean \pm SD	T	p
Haemoglobin	10.05 \pm 1.47	13.12 \pm 0.76	16.96	0.001*
Hematocrit	32.62 \pm 3.64	36.11 \pm 3.21	6.77	0.001*
MCV	70.28 \pm 7.84	85.24 \pm 3.67	15.78	0.001*
White Blood Cell	6.31 \pm 1.37	6.16 \pm 1.48	0.67	0.504
MCH	21.93 \pm 3.43	21.81 \pm 3.31	0.04	0.958
MCHC	30.90 \pm 3.28	31.07 \pm 3.60	0.33	0.741

*p<0.05, significant

MCV: mean corpuscular volume

MCH: mean corpuscular hemoglobin

MCHC: mean corpuscular hemoglobin concentration

9.24±4.37 in patients and 7.58±4.07 in controls (t=2.64, p=0.009). The average depression score was 7.53±4.10 in patients and 6.41±2.74 in controls (t=2.10, p=0.037). There was a statistically significant difference in terms of anxiety and depression scores. The number of patients who had an anxiety level above the cut-off score was 45 (43.3%) and it was 22 (27.5%) in the control group (x²= 4.856 p=0.028). The number of patients who had a depression score above the cut-off score was 49 (47.1%) and it was 26 (32.5%) in the control group (x²=4.00, p=0.045).

In PSQI, 70 (67.3%) patients and 32 (40.5%) controls reported a bad sleep quality. The number of patients who reported a bad sleep quality were statistically significantly higher than the controls (x²=13.072; p<0.001). The total sleep quality score was 6.71±3.02 in patients

and 4.11±1.64 in controls. In terms of total PSQI score, there was a statistically significant difference between the groups (t= 6.94, p<0.001).

With respect to the subscales of PSQI, subjective sleep score was found 1.33±0.81 in patients and 0.85±0.58 in controls, so, we have found a statistically significant difference between groups (t= 4.48, p<0.001). Sleep disorder score was 1.63±0.75 in patients and 0.93±0.57 in controls, so, we have found a statistically significant difference between groups (t=7.04, p<0.001). PSQI subscale scores of the groups are given in Table 3. In the regression analysis, we evaluated whether the presence of “sleep disorder” is associated with depression and anxiety. Linear regression analysis showed no association of anxiety (partial correlation coefficient: -0.176; p = 0.101) and depression (partial correlation coefficient: -0.086; p = 0.430) with poor sleeping.

Table 3. PSQI subscales

	Patients	Controls	Statistics	
	(mean ± SD)	(mean ± SD)	(t)	(p)
Subjective sleep quality	1.33 ± 0.81	0.85 ± 0.58	4.48	0.001*
Sleep latency	1.33 ± 0.81	0.73 ± 0.64	5.49	0.001*
Sleep duration	0.62 ± 0.84	0.56 ± 0.59	0.48	0.632
Habitual sleep efficiency	0.60 ± 0.77	0.38 ± 0.51	2.22	0.028*
Sleep disturbances	1.63 ± 0.75	0.93 ± 0.57	7.04	0.001*
Use of sleep medication	0.02 ± 0.20	0.00 ± 0.00	0.88	0.382
General dysfunction	1.19 ± 0.89	0.68 ± 0.63	4.40	0.001*
Total sleep disorder	6.71 ± 3.02	4.11 ± 1.64	6.94	0.001*

*p<0.05, significant

Discussion

Iron deficiency has been reported to cause behavioral and developmental symptoms by affecting transmitters such as serotonin, noradrenaline and dopamine, myelination, and the metabolic activity in the neurons^{21,22}. It has been also reported that brain functions such as cognition and learning are affected in patients with IDA²³. Peirano et al.²⁴ reported that relative to controls, children with IDA showed: a) longer duration of REM sleep episodes in the first third and shorter in the last third; b) more REM sleep episodes in the first third and fewer in the second third; and c) shorter latency to the first REM sleep episode and shorter NREM stage 2. So, their results show that IDA is associated with long-lasting alterations in the temporal organization of sleep patterns²⁴. Peirano et al.²⁴ suggested that the changes in the neurotransmitter metabolism due to iron deficiency, psychological status or a possible restless leg syndrome (RLS) affected sleep negatively. These results could be explained by some mechanisms. One possible explanation for the differences that long-lasting effects of iron deficiency on the developing dopamine (DA) system are a promising example^{25,26}.

Iron has a complex effect on dopaminergic function. It is a cofactor for tyrosine hydroxylase and is integral to D2 receptor function²⁷. Neuromodulation by the DA system plays an important role in sleep regulation, including the modulation of REM sleep quality, quantity, and timing^{28,29}. Holst et al.³⁰, studied sleep-wake regulation in humans and combined pharmacogenetic and neurophysiologic methods to analyze the effects of the 3'-UTR variable-number-tandem-repeat polymorphism of the gene (DAT1, SLC6A3) encoding dopamine transporter. Their findings suggested that the dopamine transporter contributes to homeostatic sleep-wake regulation in humans. Fifel et al.³¹, investigated alterations of circadian rhythms in non-human primate models following lesion of the dopaminergic nigro-striatal system.

Their results are of clinical importance and stress that sleep/wake disturbances associated with DA loss may be more severely affected than previously thought, in particular in sub-optimal lighting conditions. The dynamic balance between neurotransmitter systems is another important consideration. The ultradian alternation of NREM sleep/REM sleep appears to be controlled by a permanent interacting balance between brainstem aminergic and cholinergic neuronal discharges³². An additional explanation could be differing

amounts of sleep alterations. In particular, RLS and periodic limb movements during sleep have been associated with conditions characterized by compromised iron status³³. It has been known that iron deficiency plays an important role in the pathophysiology of the RLS characterized by an irresistible urge to move legs as well as motor restlessness.

Iron treatment has been thought to increase sleep quality of the patients by decreasing RLS complaints. In a study of Allen et al.³⁴, prevalence of clinically significant RLS (RLS sufferers) was 23.9% in 251 patients with IDA, nine times higher than the general population. In another study, the said ratio was reported as 40%³⁵. Patients with RLS were excluded from this study. In the present study, nearly 68% of the patients with IDA were shown to have an impaired sleep quality. Our findings support the idea that sleep quality is impaired in a significant portion of patients with IDA.

Depression and anxiety disorders are among the psychological disorders that affect sleep quality negatively. In a study conducted by Onder et al., depressive disorder was found to be a common disorder in patients with anemia³⁶. In our study, similar to the literature, a major portion (nearly 45%) of the patients had high anxiety and depression scores. Son et al. reported that cognitive functions were worse in anemia patients when compared to healthy controls, which was shown to be associated with depressive disorder³⁷. In the present study, logistic regression analysis showed that anemia affected sleep quality irrespective of the psychological symptoms.

To the best of our knowledge, there is no study in the literature that evaluated the association between laboratory values and sleep quality in adult population having IDA. Yehuda and collague³⁸, examined hemoglobin levels and showed that sleep-deprived attention deficit hyperactivity disorder (ADHD) patients also suffer also from iron deficiency. However, Yehuda et al.³⁸, were not clear if iron deficiency was one of the core symptoms of this pediatric group or it was a consequence of poor food intake habits. Another study of the Yehuda³⁹, showed that iron deficiency might be associated with sleep disturbances and lower intelligence quality at pediatric population.

We have found no significant relation between the sleep quality and laboratory values of the patients. In our study, lack of significant correlation between lab-

oratory values and sleep quality scores was not an expected result. Shariatpanaahi et al.⁴⁰ reported that there was a weak correlation between serum ferritin level and depression. In another study, it was shown that serum ferritin and hemoglobin levels had no significant relation with depression level. Similar to the results of the previous studies, the results of our study showed that the sleep quality level could not be evaluated through hemogram, serum iron and ferritin levels in patients with IDA.

Limitations

Our study had some limitations. The first limitation was evaluating depression anxiety and sleep quality through self-report scales. The second limitation was not performing polysomnographic measurements. There is a possible discrepancy between objective sleep evaluation (by EEG or by Actigraph) and subjective evaluation (PSQI). Conducting a cross-sectional study could have affected the results, too.

Conclusion

Subjective sleep quality was evaluated in patients with IDA in the present study. The results showed that IDA affects sleep quality irrespective of psychological symptoms such as depression and anxiety. And also, it was shown that subjective sleep quality was worse in patients with IDA when compared to the healthy controls. The effects of anemia treatment on sleep quality were not assessed due to the cross-sectional nature of the study. Further studies, where anemia patients should be followed-up for an extended period of time and evaluated by polysomnography, are required.

Conflict of interest statement:

There is no conflict of interest.

References

1. Dündar S. Demir eksikliği anemisi. Yasavul Ü, Çelik İ, Arıcı M. In Hacettepe İç Hastalıkları kitabı . 2B. Ankara, Hacettepe Üniversitesi Yayınları, 2004; p.867-72.
2. De Falco L, Sanchez M, Silvestri L, Kannengiesser C, Muckenthaler MU, Iolascon A, et al. Iron refractory iron deficiency anemia. *Haematologica*. 2013;98:845-53.
3. Turgut B. How Important is Anemia for the Clinician? *Balkan Med J* 2010;27:31-4.
4. Beutler E, Lichman M A, Coller B S:Iron deficiency, ed. Williams E, Hematology fifth edition .Philadelphia 1995;4905-11.

5. Lee R G. Iron deficiency and iron deficiency anemia Eds: Lee R.G, Bithell C.T, Foerster J: wintrobe's clinical Hematology 10 th edition,1999. Lea-Febiger. Chapter 34:979-1010.
6. Gümrük F , Altay Ç: Demir metabolizması ve demir eksikliği anemisi. *Katkı Pediatri Dergisi*. 1995;3:265-85.
7. Shoham S, Youdim MBH. Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases. *Cell Mol Biol (Noisy-le-grand)*. 2000;46:743-60.
8. Beard JD, Connor JR, Jones BC. Iron in the brain. *Nutr Rev*. 1993;51:157-70.
9. Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. 4th ed. Philadelphia: W.B. Saunders Company; 2005.
10. Yıldırım O, Alçelik A, Canan F, Aktaş G, Sit M, İşçi A, et al. Impaired subjective sleep quality in irritable bowel syndrome patients with a Type D personality. *Sleep and Biological Rhythms*, 2013;11:135-8.
11. Stores G. Clinical diagnosis and misdiagnosis of sleep disorders. *J Neurol Neurosurg Psychiatry* 2007;78:1293-7.
12. Senthilvel E, Auckley D, Dasarathy J. Evaluation of sleep disorders in the primary care setting: history taking compared to questionnaires. *J Clin Sleep Med*. 2011;7:41-8.
13. Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R. Morbidity associated with sleep disorders in primary care: a longitudinal cohort study. *Prim Care Companion J Clin Psychiatry*. 2007;9:338-45.
14. Kahraman M. Clinical update on epidemiology, pathogenesis and nonpharmacological treatment of insomnia. *Türk Nöroloji Dergisi*. 2006;12:87-97.
15. Chokroverty S. Overview of sleep & sleep disorders. *Indian J Med Res*. 2010;131:126-40.
16. Gulec Cakın T, Yoruk O, Gulec M, Selvi Y, Boysan M, Oral E, Yucel A, Mazlumoglu MR. Benefits of submucous resection on sleep quality, daytime and dream anxiety in patients with nasal septal deviation. *Sleep and Biological Rhythms*. 2013;11:227-36.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr. Scand*. 1983;67:361-70.
18. Aydemir Ö, Güvenir T, Küey L. Validity and reliability of Turkish version of Hospital Anxiety and Depression Scale. *Turkish Journal of Psychiatry* 1997;8:280-7.
19. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193-213.

20. Ağargün MY, Kara H, Anlar Ö. Pittsburgh uyku kalitesi indeksi'nin geçerliliği ve güvenilirliği. *Türk Psikiyatri Dergisi*.1996;7(2):107-15.
21. Beard J. Iron deficiency alters brain development and functioning. *J Nutr*. 2003;133:468-72.
22. Cook J, Skikne B. Iron deficiency: definition and diagnosis. *J Intern Med*. 1989;226:349-55.
23. Beard JL. Iron deficiency and neural development: an update. *Arch Latinoam Nutr*. 1999;493:34-9.
24. Peirano PD, Algarín CR, Garrido MI, Lozoff B. Iron deficiency anemia in infancy is associated with altered temporal organization of sleep states in childhood. *Pediatr Res*. 2007;62:715-9.
25. Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR, et al. Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. *Behav Brain Res*. 2006;171:261-70.
26. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutr Rev*. 2006;64:34-43.
27. Kim J, Wessling-Resnick M. Iron and mechanisms of emotional behavior. *J Nutr Biochem*. 2014;25:1101-7.
28. Dziras K, Ribeiro S, Costa S, Santos LM, Lin S-C, Grosmark A, et al. Dopaminergic control of sleep-wake status. *J Neurosci*. 2006;26:10577-89.
29. Keating GL, Rye DB. Where you least expect it: dopamine in the pons and modulation of sleep and REM-sleep. *Sleep*. 2003;26:788-89.
30. Holst SC, Bersagliere A, Bachmann V, Berger W, Achermann P, Landolt HP. Dopaminergic role in regulating neurophysiological markers of sleep homeostasis in humans. *J Neurosci*. 2014;34:566-73.
31. Fifel K, Vezoli J, Dzahini K, Claustrat B, Leviel V, Kennedy H et al. Alteration of daily and circadian

- rhythms following dopamine depletion in MPTP treated non-human primates. *PLoS One*. 2014;23:9(1):e86240.
32. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci*. 2002;3:591-605.
33. Sadrzadeh SM, Saffari Y. Iron and brain disorders. *Am J Clin Pathol*. 2004;121:64-70.
34. Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *Am J Hematol*. 2013;88:261-4.
35. Akyol A, Kiylioglu N, Kadikoylu G, Bolaman AZ, Ozgel N. Iron deficiency anemia and restless legs syndrome: is there an electrophysiological abnormality? *Clin Neurol Neurosurg*. 2003;106:23-7.
36. Onder G, Penninx BW, Cesari M, Bandinelli S, Lauretani F, Bartali B, Gori AM, Pahor M, Ferrucci L. Anemia is associated with depression in older adults: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2005;60:1168-72.
37. Son SJ, Lee KS, Na DL, Seo SW, Kim CH, Kim JH et al. Anemia associated with depressive symptoms in mild cognitive impairment with severe white matter hyperintensities. *J Geriatr Psychiatry Neurol*. 2011;24:161-7.
38. Yehuda S, Rabinovitz-Shenkar S, Carasso RL. Effects of essential fatty acids in iron deficient and sleep-disturbed attention deficit hyperactivity disorder (ADHD) children. *Eur J Clin Nutr*. 2011;65:1167-9.
39. Yehuda S, Yehuda M. Long lasting effects of infancy iron deficiency--preliminary results. *J Neural Transm Suppl*. 2006;71:197-200.
40. Vahdat Shariatpanaahi M, Vahdat Shariatpanaahi Z, Moshtaaghi M, Shahbaazi SH, Abadi A. The relationship between depression and serum ferritin level. *Eur J Clin Nutr*. 2007;61:532-5.