IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 5 Ser. 11 (May. 2019), PP 47-54
www.iosrjournals.org

Correlation of Iron Deficiency Anemia with Cognitive Function in Young Adults

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Abstract:
Introduction: *Iron deficiency anemia is the most common form of anemia. Iron is an essential component of brain growth, myelination, and is required for cell differentiation, protein synthesis, hormone production and fundamental aspects of cellular energy metabolism and functioning. It has also been found that higher hemoglobin levels results in better CNS functions.*
AIM*: To assess the relationship between iron deficiency anemia and cognitive function in young adults.*
MATERIAL*: 100 young adults, 67 female and 33 male in age group of 20 - 22 yrs.*
METHODS*: For all subjects cognitive assessment scoring was done using MMSE, MoCA cognitive scales and serum samples were sent for determining Hb%, MCH, MCHC, MCV AND S.FERRITIN.*
Subjects were grouped into anemic and non anemic groups and further anemic group is sub grouped into mild, moderate and severe as per who criteria.
RESULTS*: In our study prevalence of anemia is 46% .females are more anemic than males. Cognitive scores are lesser in females compared to males. There is significant positive correlation between all parameters of anemia and cognitive scores. MoCA scores are more sensitive than MMSE for cognitive assessment.*
CONCLUSION*: Iron deficiency anemia is significantly correlated with cognition.*
DISCUSSION*: Iron deficiency anemia affects cognition by causing a decrease in the iron concentration in the brain, which causes a reduction in the neurotransmitter levels. This, in turn, causes impaired transmitter functions, leading to hypomyelination and delayed neuromaturation. Anemia affects cognition by its direct neurochemical effect and by its indirect effect on behavior.*
Keywords*: iron deficiency anemia, MMSE, MoCA, serum ferritin*

Date of Submission: 07-05-2019 Date of acceptance: 23-05-2019

I. Introduction

Anemia is a global public health problem affecting both developing and developed countries. Anemia is an indicator of both poor nutrition and poor health. Pregnant women, infants, young children and adolescents are more vulnerable for this problem. Anemia is a debilitating condition that commonly causes tiredness, lethargy, and dyspnoea, and often signals more serious health problems. Iron deficiency (ID) is a major health problem worldwide affecting more than a quarter of the world's population [1].

Anemia is a late sign of nutritional deficiency.Iron Deficiency Anemia is the third leading cause of Disability Adjusted Life Years (DALYs) for females aged 15–44 years[2]. Iron deficiency anemia (IDA) is the most common form of anemia affecting 43% of the world's children [3], more than 50% of women of reproductive age [4] and 3% of men [5]. Though anemia is a major health problem for adults, it affects only 24 % of men[6].

Iron is an essential component of brain growth, myelination influencing nerve impulse conduction, and is required for cell differentiation, protein synthesis, hormone production and fundamental aspects of cellular energy metabolism and functioning [7,8]. Iron is also essential for a number of enzymes involved in neurotransmitter synthesis including tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (nor epinephrine and dopamine) [8]. Animal studies point to the high vulnerability of the developing hippocampus and frontal cortex to early iron deficiency (ID). Iron deficiency mediates metabolic and structural changes in the hippocampus and frontal cortex of developing rats during infancy. The period of infancy is characterized by peak hippocampal and cortical regional development, as well as myelinogenesis, dendritogenesis, and synaptogenesis in the brain and changes in these processes underlie deficits in spatial learning and memory processes [7,9]. Moreover, the neuronal metabolic marker cytochrome c oxidase (CytOx) loss has been found to be marked in the highly metabolic hippocampal areas CA1 and CA3 and in the frontal lobes of the cortex in the ID rat brain [10]. Furthermore, iron deficiency causes abnormal protein scaffolding for microtubule extension and retraction in brain regions involved in recognition memory processing [7]. Iron proteins have key roles in normal brain function and the processes of brain development, including neurogenesis, myelination, synaptic development, and neurotransmitter metabolism [11-13]. In adult life, iron uptake by the brain still occurs, though at levels significantly lower than those during development[14]. Iron levels in the brain can be altered by peripheral iron levels and iron nutrition. Effects of iron nutrition on the brain have been studied. Deficiency of iron, which plays an important role in oxygen transport and storage, may lead to cerebral hypoxia and cognitive decline [15]. In human life, adolescence and early adulthood together constitute a vulnerable and crucial period where major social, psychological, and biological changes occur resulting in the highest nutrient requirement[16]. The academic performance during higher education influences the career resulting in shaping an individual's socioeconomic status, health, and health-related behaviours[17]. Nutrition is one of the most important and modifiable environmental factor that may affect the neurocognitive development, which in turn has an impact on academic performance[18].

Many studies have demonstrated the correlation between iron deficiency anemia and cognitive dysfunction mainly in children. It has been proved that non anemic children performed significantly better in cognitive function tests than mildly and moderately anemic children [19]. It has also been found that higher haemoglobin levels results in better CNS functions [20]. The cognitive function in subjects can be assessed by the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) score.The MoCA is a novel international brief cognitive screening tool developed for the detection of cognitive dysfunction (21). Recent studies showed that the MoCA was more sensitive to mild cognitive impairment than the (MMSE) (22,23). The aim of the present study is to assess cognitive performance in Iron Deficiency Anemia patients with Montreal Cognitive Assessment (MoCA).

II. Material and Methods

. Cross sectional study

Inclusion criteria:

100 medical students in age group of 18 – 22 yrs
same socioeconomic status

Exclusion criteria:

known case of anemia or on haematinic therapy, other types of anemia ex. Nutritional anemia having jaundice or any hematologic disorder those who suffered from acute and chronic diseases, those on long term medications ,hearing and visual defects, neurocognitive problems. Samples of students are sent for analysis of blood parameters like Hb%, MCV, MCH, MCHC ,S.ferritin to diagnose Anemia .Cognitive testing was done using MMSE and MoCA test Based on results the students are divided into iron Deficiency Anemic and Non Anemic groups. Anemic students are further divided into Mild ,Moderate and Severe Anemic based of WHO values . Correlation between Anemia and cognitive performance was done.

DATA COLLECTION

Data collection was done in medical college and comprised of administration of interviewer administered questionnaire, history taking, clinical examination and collection of venous blood for investigation. The cognitive tests were conducted using MMSE, MoCA questionnaires.Laboratory analysis Assessment of cognitive function Methods.

1. Laboratory analysis

Five millilitres of venous blood collected by veni puncture of the ante cubital vein of the arm of each participant under strict aseptic conditions into vacutainer tubes containing EDTA using sterile disposable syringes and needles. Complete Blood Count was done in a NABL accredited lab using the automated Cell Counter properly calibrated and standardized daily. The following results obtained.

2. Cognitive scales

MMSE - Mini - Mental State Scale
MoCA -Montreal Cognitive Assesment as mentioned in review of literature

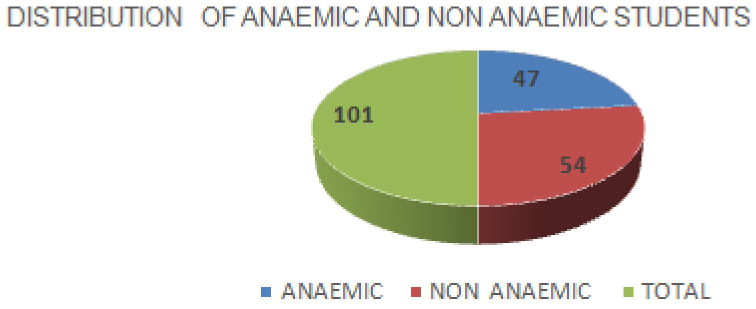
Data entry and Statistical Analysis

Data was entered into Microsoft Excel sheet and analyzed using IBM SPSS Statistics for Windows, Version 22.0.

Descriptive statistics were expressed as Means and percentages. Inferential statistical analysis was done using chi-square tests for nominal and ordinal variables, and ANOVA tests for interval variables.

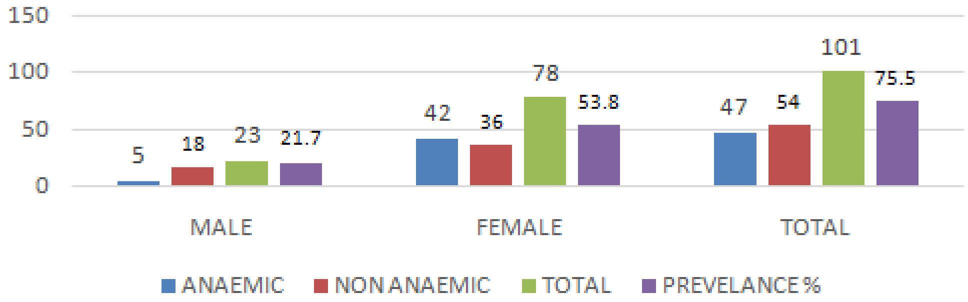
P-value of <0.05 will be considered statistically significant

III. Results

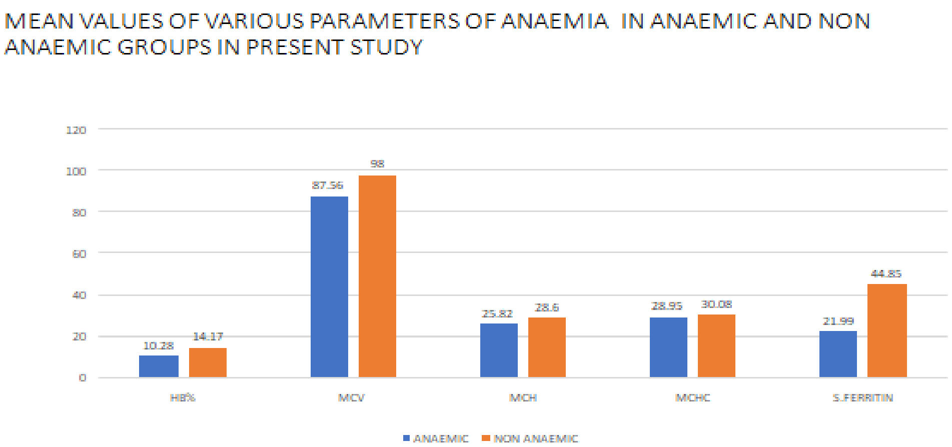


SEX DISTRIBUTION AMONG ANAEMIC AND NON ANAEMIC GROUPS AND PREVALENCE %

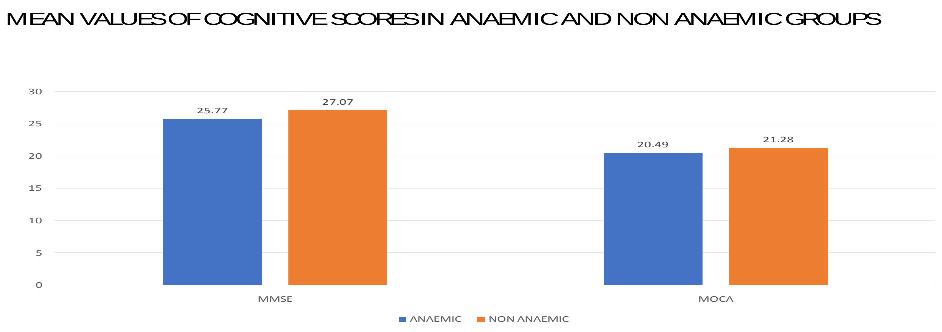
SEX	ANAEMIC	NON ANAEMIC	TOTAL	% PREVALENCE OF ANAEMIA
MALE	5	18	23	21.7
FEMALE	42	36	78	53.8
TOTAL	47	54	101	75.5



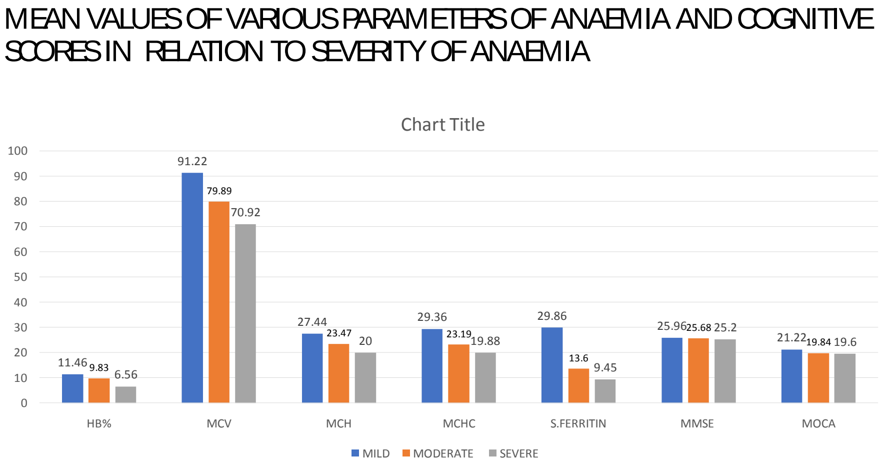
In the present study ,out of 23 males ,5 were anemic and 18 are Non anemic having a prevalence of 21.7% and out of 78 females ,36 are non anemic ,78 are anemic having a prevalence of 53.8% .The total prevalence of Anemia is 75.5%



In the present study the mean values of Hb%,MCV,MCH,MCHC,S.Ferritin in anemic and Non anemic groups are 10.28% gm% ,87.56 fl,25.82 pgm,28.95gm/dl,21.99 ng/ml and 14.17% gm% ,98 fl,28.6 pgm,30.08 gm/dl,44.85 ng/ml



The present study the mean values of cognitive scores tested by MMSE and MoCA in Anemic and Non Anemic group are 25.77 ,27.77 and 20.49,21.28 respectively.



In the present study, the mean values of various parameters of Anemia and cognitive scores in Mild ,moderate and Severe groups are Hb% is 11.46 gm% ,9.83 gm %,6.56 gm % ,MCV is 91.22 fl,79.89 fl,70.92 fl,MCH 27.44 pgm,23.47 pgm,20 pgm,MCHC 29.36gm/dl,23.19gm/dl,19.88gm/dl,Sferritin29.86 ng/ml,13.6 ng/ml,9.45 ng/ml,MMSE 25.96,25.68,25.2and MoCA 21.22,19.84,19.6 respectively.

IV. Discussion

Prevalence of Anemia in various studies		
Studies	Characteristics	Prevalence
India (WHO)	Non-pregnant women	74%
NFHS-3 [8]	Women	55%
Kapoor & Aneja	Adolescent girls.	50.8%
Vitull K. Gupta,	5-30 years females	89.5%
	5-20 years males	89.9%
Present study	20-25 yrs Male and female	75.5%

In the present study prevalence of Anemia is 75.5 % in 20-25 yrs Male and female as against 74% in india (WHO) study of Non Pregnant women , 55% in NFHS-3 [8] study of women ,50.8% in Kapoor & Aneja etal study of Adolescent girls.,89.5% and 89.9% in Vitull K. Gupta, study of 5-30 years females ,5-20 years males.

Distribution of blood parameters in other study						
Parameters	Anemic Group(Mean ±S.D)		Non Anemic Group(Mean ± S.D)		p VALUE	
	Present study	Kavitha ukkirapandian etal	Present study	Kavitha ukkirapandian etal	Present study	Kavitha ukkirapandian etal
Hb (gm%)	10.28±1.71	10.37±0.12	14.16±1.70	12.61±0.10	<0.01	<0.001
MCV(fl)	87.56±12.28	81.15±0.96	98.03±10.62	90.39±0.79	<0.01	<0.001
MCH(pgm)	25.82±5.37	25.76±0.50	28.63±2.49	28.78±0.34	0.01	<0.001
MCHC (%)	28.95±3.12	30.29±0.40	30.08±1.31	31.74±0.19	0.017	0.002

In the present study , comparison to study by kavitha etal the values of various parameters like Hb% ,MCV,MCH,MCHC in Anemic and Non Anemic group are 10.28 gm %, 87.56 fl ,25.82pgm , 28.95%, and 14.16 gm %,,98.03 fl, 28.63 p gm, 30.08 % respectively with significant difference with p value of <0.01, <0.01, 0.01, 0.017. In kavitha etal the values of various parameters like Hb% ,MCV,MCH,MCHC in Anemic and Non Anemic group are 10.37 gm %,, 81.15±0.96 fl , 25.76±0.50 pgm , 30.29±0.40% and 12.61 gm %, 90.39±0.79 fl, 28.78±0.34 p gm , 31.74±0.19% respectively with significant difference with p value of <0.001, <0.001, <0.001, 0.002.

Correlation of cognitive impairment with IDA explained by three main mechanisms. Systemic effects of anemia lead to low oxygen delivery to the brain-cerebral hypoxia (Lena Hulthen et al. (2003).[25]Iron-dependent enzyme, aldehyde oxidase activity is reduced which may interfere with the degradation of serotonin (Lozoff B et al. [26]

As iron is an essential component of Heme needed for hemoglobin synthesis, iron deficiency itself leads to low hemoglobin levels.

Iron deficiency anemia is a common health problem which produces bad consequences in overall body health. Iron needs of the brain vary with the stage of the life cycle. Iron intake into the brain is maximal during the period of rapid brain growth, which coincides with the peak of myelinogenesis.

Iron is the component of the main enzymes that involve essential oxidation and reduction reactions, synthesis of neurotransmitters, catabolism of neurotransmitters and synthetic processes such as the production of myelin. By discussing the functions of iron on CNS, we surely can expect the cognitive dysfunction in IDA.

Several clinical studies suggest a significant influence of IDA on dynamic properties and functional features of the central nervous system activity.

Previous research showed that iron deficiency could exert a direct deleterious effect on learning and the brain. Researches in rodent models have found that highest brain concentrations of iron found in dopaminergic structures, and the dopaminergic neurons are co-localized with iron throughout the brain. In iron deficient rats, there was a reduction in the number and function of dopamine D2-receptor, elevation in the extracellular dopamine and nor epinephrine in brains and alteration in the density of D2 and D1 receptors and dopamine transporters. Intact dopaminergic systems are known to be important in attention and learning processes. Decreased iron content resulting from IDA may reduce the activity of neurotransmitters such as dopamine, serotonin, and nor adrenaline by interfering with the iron-dependent enzymes (Youdim MB et al. (1990)

[8].In this study above mechanisms would be taken as a reason for less cognitive performance in an anemic group when compared to control group. Performance in the reasoning test positively correlated with red blood cell hemoglobin. Its suggested that cognitive achievement is strongly related to hemoglobin (Hb) level in both anemic and non-anemic persons, i.e., higher Hb level results in better CNS function [27] Although several clinical studies demonstrated a significant positive correlation between Hb level and various aspects of cognitive function and intellectual performance between anemic and non-anemic children and adolescents[28,29,30], however, in adults, clear evidence of an association between anemia and cognitive function have not found. Jean- Luc Jougleux et al. (2011) mentioned that mild maternal IDA during gestation and altered the nervous system development of offspring.

In addition to these, Faux et al. [31] found lower hemoglobin and differences in blood measures for mean cell hemoglobin, packed cell volume and higher erythrocyte sedimentation rates in people with AD, while Ferrer et al. [32] found that levels of neuronal hemoglobin reduced in AD. The findings in our study concur with the done research by Khedr E et al.[33] He demonstrated low score of cognitive function test (MMSE, WMS) in anemic adults when compared to the control group (2008).

In contrary to the present study, after adjusting for age, co morbid disease, and chronic inflammation, hemoglobin levels were not significantly associated with cognitive function in men or women. Similar patterns found in the subgroup of middle-aged and older adults who were HIV positive. The reason may be the content of the cognitive tests they focused was on verbal memory and orientation. They did not have direct measures of Executive function, Attention and Processing speed which are part of our study.

Halterman JS et al.[34] demonstrated lower standardized math scores not only among iron-deficient school-aged children and also in adolescents, with iron deficiency. The results of the present study also revealed a significant decrease in cognitive function in patients with IDA with the MoCA test.

Engin Kelkitli et al. (2013)[35] concluded from their study that MoCA test scores were significantly lower in patients with IDA.

Murray Kolb and Beard [36] evaluated cognitive abilities in a group of Women in their reproductive age are having iron deficiency (anemic and 61 non-anemic). The authors found that the severity of iron deficiency is proportionately adversely affects processing speed and accuracy of cognitive function over a broad range of tasks. The authors observed that iron supplementation resulted in improvement by 5–7 folds in cognitive performance assessed by Detterman's Cognitive Abilities Test. Performance by reasoning test, positively correlated with hemoglobin.

In complementary analyses in Add Neuro Med, a cohort study of dementia, we similarly find that red blood cell indices including red cell count, PCV and Hb are associated with AD and with a decline in cognitive function measures

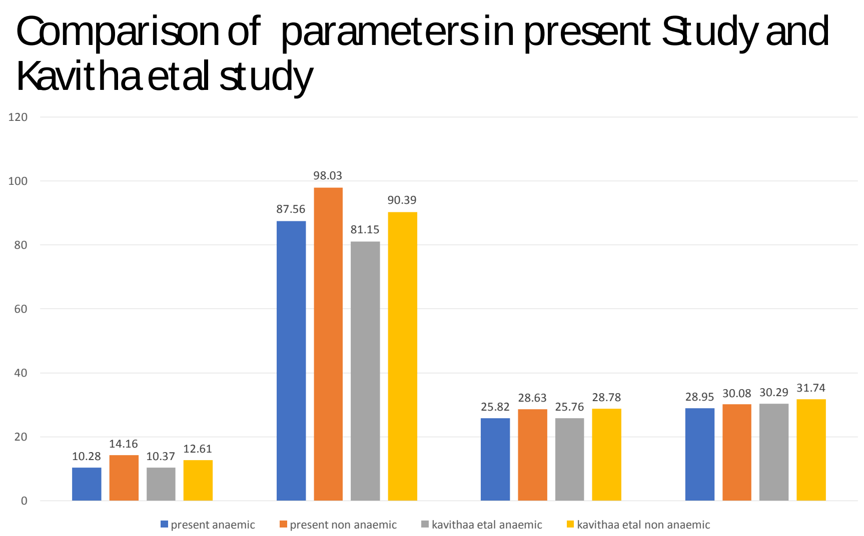
It proved that non-anemic children performed significantly better in cognitive function tests than mildly and moderately anemic children. It has also found that higher hemoglobin levels result in better CNS functions.
In general, several mechanisms by which iron deficiency may contribute to cognitive impairment discussed

1. Iron has actions on brain receptors and interferes with brain neurotransmission mechanisms that lead to cognitive impairment, attention and memory processing [37,38].
2. In advanced stages of ID, the Hb% has compromised with systemic effects that may impair cognition, e.g., brain hypoxia. Anemia via cerebral hypoxia and other possible mechanisms have been suggested to have great influence on perception [39]. Also, a combination of the mechanisms mentioned above may be a possible mechanism for cognitive deficits caused by iron deficiency anemia.
3. Systemic effects of anemia lead to low oxygen delivery to the brain-cerebral hypoxia (Lena Hulthen et al. (2003)[40]
4. Iron-dependent enzyme aldehyde oxidase activity is reduced which may interfere with the degradation of serotonin (Lozoff B et al. (1996)[41].
5. Decreased iron content resulting from IDA may reduce the activity of neurotransmitters such as dopamine, serotonin, and noradrenaline by interfering with the iron-dependent enzymes (Youdim MB et al. (1990)[42].

In this study above mechanisms would be taken as a reason for less cognitive performance in an anemic group when compared to control group.

Pollitt [43] described several studies in Indonesia and Thailand in which iron supplementation for adolescents with poor iron status resulted in significant improvements in tests related to specific components of cognition, for example, simple figures test or general tests of academic ability.

In the study of Bruner et al. [44] on 81 non-anemic iron deficient adolescent girls in high school, iron supplementation was found to improve verbal learning and memory but did not effect on measures of attention.
In the present study, as the severity of Anemia increases, as measured by lowering the Hemoglobin concentration, the cognitive performance is impaired as measured by reducing cognitive scores. The difference between Hb%, MMSE and MOCA is statistically significant.



Cognitive scores in comparison with other study

Cognitive Parameter	Anemic Group(Mean ±S.D)		Non Anemic Group(Mean ± S.D		p VALUE	
	Present study	Kavitha ukkirapandian etal	Present study	Kavitha ukkirapandian etal	Present study	Kavitha ukkirapandian etal
MMSE	25.76±0.59	26.23±0.54	27.07±0.86	27.83±0.43	< 0.01	0.02

In the present study, the cognitive scores assessed by MMSE in Anemic and Non Anemic group as compared to Kavita etal study are 25.76±0.59 ,26.23±0.54 and 27.07±0.86, 27.83±0.43 respectively .

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Cognitive scores in comparison with other study

Cognitive Parameter	Anemic Group(Mean ±S.D)	
	Present study	Engin Kelkitli study
MOCA	20.49 ±1.38	23.75 ±4.00

in the present study, the cognitive scores assessed by MoCA in anemic group is 20.49 ±1.38 as against 23.75 ±4.00 in engin kelkitli study.

SUMMARY

In the present study, the total prevalence of iron deficiency anemia in our study is 75%.Sex distribution shows more females (53.85%) being anemic than males (21.7%).

There is statistically significant difference in various parameters of iron deficiency anemia and cognitive scores between Anemic and Non Anemic groups.

There is statistically significant negative correlation between severity of anemia and cognitive scores.

V. Conclusion

Even in well-educated group prevalence of anemia is noted.

Microcytic hypochromic anemia secondary to iron deficiency is the most common type of anemia.

Anemia has a significant effect on cognition.

Screening for Anemia at the time of academic admission in young medical students helps to prevent complications of anemia like easy fatigability, reduction in physical work capacity, cold intolerance and problems in concentration.

A strategy is essential to monitor the nutrition of young adults to improve health.

Early intervention by treating anemia in these economically productive group helps in avoiding lassitude and impairment in mood and ability to concentrate.

LIMITATIONS OF THE STUDY

1.Small sample size.

2. Follow up is required.

3. The prevalence of Anemia in this younger group may not be representative of the General population

4. The cognitive scores measured in this younger group may not be representative of the General population.

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