

# Neutropenia and Lymphocytopenia Among Arab Females with Iron Deficiency Anemia (IDA) and their Response to Iron therapy

Mohamed A. Yassin<sup>1</sup>, Hussam A. Almasri<sup>2</sup>, Mustafa A. Al-Tikrity<sup>2</sup>, Arwa E. Alsaud<sup>2</sup>, Rita W. Ahmad<sup>3</sup>, Mona M. Babikir<sup>2</sup>, Majd M. Aldwairi<sup>2</sup>, Mohammad N. Kloub<sup>2</sup>, Mahmoud S. Eisa<sup>2</sup>, Ruaa W. Attaa<sup>3</sup>, Shaima Ahmed<sup>2</sup>, Abdulqadir J. Nashwan<sup>4</sup>, Ashraf T. Soliman<sup>5</sup>

<sup>1</sup> Hematology-Oncology Department, National Centre for Cancer Care and Research, Doha, Qatar; <sup>2</sup> Department of Medicine, Hamad Medical Corporation, Doha, Qatar; <sup>3</sup> Department of Family Medicine, Primary Health Care Corporation, Doha, Qatar; <sup>4</sup> Nursing Department, Hazm Mebaireek General Hospital, Hamad Medical Corporation, Doha, Qatar; <sup>5</sup> Department of Pediatrics, Division of Pediatric Endocrinology, Hamad General Hospital, Doha, Qatar

**Abstract.** *Introduction:* The link between iron deficiency anemia (IDA) and neutropenia/ lymphocytopenia is not well established in the literature. This study aims at assessing the prevalence and clinical characteristics of neutropenia and lymphocytopenia in IDA patients considering the impact of iron replacement on the total and differential WBCs' count. *Subjects and Methods:* The records of all female patients with IDA who attended our hematology clinic (Jan 2018 to Jan 2020) were retrospectively reviewed. Patients with systemic or chronic diseases were excluded. Age, BMI, CBC, and iron parameters were collected before and after IV iron therapy. *Results:* Out of 1,567 adult females with IDA, 80 patients had leukopenia (5.1%), 64 had neutropenia (4.0%), and 20 had lymphocytopenia (1.2%). After iron therapy, their mean leukocytes, neutrophils, and lymphocytes increased significantly to  $4.38 \pm 1.82 \times 10^3/L$ ,  $2.3 \pm 1.56 \times 10^9/L$  and  $1.76 \pm 0.48 \times 10^3/L$ , respectively. About 67% of women with IDA and neutropenia had increased ANC in response to iron therapy. However, no significant correlation was found between leukocytes, ANC, or lymphocytes with TIBC or serum iron concentration. *Conclusions:* Neutropenia and/or lymphocytopenia may occur in patients with IDA and are reversible with iron therapy. Iron therapy led to the correction of anemia in 100% and increased ANC in 67%. Therefore, neutropenic women with IDA should be treated, initially only with iron, and observed for their Hb and ANC responses before starting any other treatment. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Iron Deficiency Anemia (IDA), leukopenia, neutropenia, lymphocytopenia, iron metabolism, iron treatment

## Introduction

Globally, iron deficiency accounts for the most common micronutrient deficiency causing Anemia. Iron is essential for erythropoiesis as well as mitochondrial function, DNA synthesis, DNA repair, redox reactions, and oxygen transportation. Additionally, it plays a central role in embryonic hematopoiesis and continues in adults to assist in all blood cells' production (1-3).

Iron deficiency is the main cause of anemia worldwide, where adult females (childbearing age) and children are the most affected groups. Iron is necessary for cellular immune responses, oxidative metabolism within the mitochondria and production of hemoglobin and myoglobin. Iron deficiency anemia (IDA) causes an extensive spectrum of signs and symptoms as well as short and long-term complications. The prevalence of IDA varies geographically,

socioeconomically, between age groups, races, and genders (4, 5).

In developed countries, the most common causes of IDA are dietary choices (e.g., vegetarian, and vegan), altered iron absorption, and chronic blood loss, whereas inadequate iron intake and/or a parasitic infection are the most common causes in developing countries. During the reproductive years, women tend to have IDA due to physiologic demands, such as menstrual blood losses and pregnancy.

Around 14% of all women could experience excessive or irregular menstrual bleeding, which can lead to varying degrees of IDA (6). Furthermore, IDA might be associated with chronic conditions such as cancers, kidney, cardiovascular, and gastrointestinal diseases etc (4, 5).

The usual approach of assessing anemia by measuring only hemoglobin levels lacks both specificity and sensitivity. The World Health Organization (WHO) expert committee have come up with a more comprehensive definition which including several factors such as gender, age, ethnicity, altitude and based on statistical distribution considerations and cut-off points (4-7). It is advised that

“a Hb concentration below 13.7 g/dL in a white man, aged between 20 and 60 years, would have only an approximately 5% chance of being a normal value. For older men, this Hb value would be 13.2 g/dL. The corresponding value for women of all ages would be 12.2 g/dL” (8).

IDA is mainly assessed by transferrin saturation (TSAT) and serum ferritin where levels below 33.70 pmol/L (15 ng/mL) are consistent with a diagnosis of IDA, using a cut-off of 67.41 pmol/L (30 ng/mL) (9, 10). However, inflammation or infection and gender variations (naturally higher in men) jeopardize the capability of serum ferritin for determining IDA. Moreover, malnutrition and chronic illnesses many decrease transferrin synthesis and consequently low levels of transferrin. In addition, the diurnal fluctuations in TSAT levels (up to 70%), may affects the consistency of results (11-13). Non-hematological manifestations of IDA may give rise to unpleasant signs and symptoms which are proportional to anemia severity (14). Microcytic anemia and thrombocytosis are typically associated with iron deficiency but not lymphocyto-

penia (15-18). Few studies have been investigating the possible effect of IDA on white blood cells in particular (considering ethnicity) and the potential changes of WBCs' count in response to iron therapy.

This study aims at evaluating the possible association between IDA and leukopenia (neutropenia and/or lymphocytopenia) in adult females (non-pregnant) and the effect of iron therapy on WBC, ANC and lymphocyte counts. We also explored the association between abnormalities of white blood cells (WBC) and the occurrence of infections in these patients, before or during iron replacement therapy. To the best of our knowledge, this is the first study to address this association in the Arab population.

## Subjects and Methods

A retrospective cohort observational study has been conducted at Hamad Medical Corporation (HMC) (including a chain of 15 hospitals as the largest governmental healthcare provider in Qatar). All methods were performed in accordance with the relevant guidelines and regulations.

The electronic health records of all female patients attending the hematology outpatient clinic for the last 2 years (from January-2018 to January-2020) with a diagnosis of IDA have been reviewed. The diagnosis was established based on the hemoglobin (Hb) level (<12.0 g/dL), (serum iron <60 mcg/dL, transferrin saturation <19 %, Ferritin <30 ng/mL, and TIBC > 350 to < 400 mcg/dL for IDA with mild anemia (Hb = 9:12 g/dL) and >410 for IDA with severe anemia.

Inclusion criteria included females aged >18 years and <45 years (child-bearing period) with confirmed IDA. Exclusion criteria comprised all patients with other possible causes of anemia, such as hemoglobinopathies, folic acid or vitamin B12 deficiencies, pregnancy, chronic disease including (chronic kidney disease, heart failure, liver failure), and concurrent drug use that are known to cause leukopenia).

The following data were collected: age, body mass index (BMI), complete and differential blood counts, and iron parameters before and after intravenous (IV) iron therapy (all the 80 patients with leukopenia were treated with IV iron therapy). Associated infections

in patients who had IDA and leukopenia were noted, including the course of the infection and response to treatment. Severe cytopenia complications are defined as severe infections leading to sepsis or hospitalization.

Leukopenia was defined as WBCs count below 4,000/ $\mu$ L, and neutropenia as neutrophils count to be less than 1,500/ $\mu$ L. Neutropenia was classified as severe if absolute neutrophils count (ANC) was less than 500/ $\mu$ L and profound if ANC was less than 100/ $\mu$ L (16,17). Lymphocytopenia was diagnosed when lymphocytes count was less than 1,000/ $\mu$ L.

The iron requirements were calculated according to the following equation: "Total iron deficiency in mg = [body weight (kg) x (normal Hb - actual Hb in g/L) x 0.24] + 500" (19) Marif et al. Parental Ferric Hydroxide Saccharate Therapy for Iron Deficiency Anemia: Safety and Efficacy. American Society of Hematology. 2004. The indications for parenteral iron therapy were bleeding, severe symptomatic anemia, and non-adherence to oral therapy. Intravenous iron therapy of ferric carboxy-maltose (1,000 mg) or ferric hydroxide saccharate complex was given as an initial dose (100 mg) on the first day and the following days as divided doses of 200 mg.

Ethical approval for the study was obtained from the institutional review board (IRB) at the Medical Research Center (MRC), Hamad Medical Corporation, Doha, Qatar (MRC-01-20-142).

## Statistical analysis

Paired "t-test" and Wilcoxon test were used to compare variables after versus before iron therapy. A linear regression was used to investigate possible relationships between variables. Excel 2010 statistical pack was used for analysis. Differences were considered statistically significant at ( $p \leq 0.05$ ).

## Results

Out of 1,567 females with IDA (mean age: 38.3  $\pm$  5.2 years, and mean BMI: 28.2  $\pm$  3.8 Kg/m<sup>2</sup>), 80 had leukopenia (5.1%) and 64 had neutropenia (4%). Their mean leukocyte count was 3.35  $\pm$  0.48  $\times 10^9$  before iron replacement therapy. After the correction of Anemia, the leukocyte count increased significantly to 4.38  $\pm$  1.82  $\times 10^9$ /L ( $P < 0.05$ ) (Table 1).

Eight out of the 64 patients with neutropenia had an infection at the time of presentation: 5 with upper respiratory tract infections, 1 with gastroenteritis, 1 with lymphadenitis, 1 with urinary tract infections. Five of these patients received antibiotics, with no reported complications.

After iron therapy, 43/64 patients increased their ANC. The rest of the patients had no change (4/64) or decreased ANC (17/64). The mean neutrophils count was 1.18  $\pm$  0.28  $\times 10^9$ /L before iron replacement and significantly increased to 2.33  $\pm$  1  $\times 10^9$ /L after iron therapy ( $P < 0.05$ ).

**Table 1.** Blood parameters in adult females with IDA and leukopenia before and after iron therapy

Before treatment	WBC	Hb	MCV	PLT	ANC	Lymphocyte	Serum iron	TS	TIBC	Transferrin	Serum ferritin
Mean	3.35	9.08	72.8	290*	1.46	1.54	7.10	13.40	70.9*	3.17	9.94
SD	0.48	1.92	9.85	149.00	0.41	0.44	12.02	20.68	16.4	1.03	20.30
After treatment											
Mean	4.38*	11.7*	87.3*	233.00	2.3*	1.56	15.45*	30.23*	46.2	8.4*	157*
SD	1.82	1.55	16.50	86.60	1.76	0.48	10.72	22.45	23.98	14.76	81.60

**Legend** = \* $P < 0.05$ ; White blood cell count (WBC): 4.0 – 11.0  $\times 10^9$ /L; Haemoglobin (Hb): 12.0 – 15.6 g/L; Mean cell volume (MCV): 80 – 100 fL; Platelet count (PLT): 150 – 450  $\times 10^9$ /L; Absolute Neutrophil Count (ANC):  $> 1.5 \times 10^9$ /L; Lymphocytes: 1.5 – 4.5  $\times 10^9$ /L; Total serum iron: 4.6 – 30.4  $\mu$ mol/L; Iron (transferrin) saturation (TS): 20.8 – 41 %; Total iron binding capacity (TIBC): 45 – 81  $\mu$ mol/L; Transferrin: 2.0 – 3.6 g/L; Serum ferritin: 10 – 200 ng/mL (10<sup>th</sup> percentile: 3.0–6.0 ng/mL; 90<sup>th</sup> percentile: 201–243; ng/mL).

Table 2 compares patients with neutropenia who had increased ANC after iron therapy versus those who had no change or decreased ANC after iron therapy. Both received an equivalent dose of iron. Hb concentration and ferritin levels did not differ significantly between the two groups (Table 3). Twenty out of the 1,567 patients had lymphocytopenia (1.2%). Their mean lymphocytes count increased from  $0.73 \pm 0.15 \times 10^9/L$  before iron replacement to  $1.79 \pm 0.74 \times 10^9/L$  after iron treatment ( $P: < 0.05$ ). Four out of the 20 patients with lymphocytopenia had mild infections (2 with upper respiratory tract infections, 1 with urinary tract infection, and one with gastroenteritis) (Table 4).

## Discussion

In the Arabian Gulf region (Saudi Arabia (KSA), Kuwait, Bahrain, Oman, Qatar, Iraq, and the United Arab Emirates (UAE)), the prevalence of IDA in women appears to be considerably high and ranges between 26.7% and 64%. In Qatar, a cross-sectional study in 2016 reported ID in 35.4% and IDA in 15.9% of pregnant women. In the UAE, IDA was reported in 22% of married (healthy) women and 16% before marriage. In KSA, 40% of female adults and 34.2% of female adolescents were diagnosed with IDA and less in university female students (20-23).

In our study, 4% of the IDA women had neutropenia. The findings of our study confirm and extend previous reports on the high prevalence of neutrope-

**Table 2:** Comparison between the group of women who improved their ANC after iron therapy with those who had no improvement of ANC.

ANC no change	Number	Baseline										After treatment							
		Fe dose mg	Age	BMI	WBC	Hb	MCV	Platelet	ANC	Lymph	ferritin	WBC2	Hb2	delta Hb	MCV2	Plat2	ANC2	ferritin 2	
mean	17.00	1011	37.3	28.9	3.51	9.2	71.0	293.3	1.57	1.47	9.91	3.27	12.8	2.5	79.86	240	1.47	167.1	
SD		333	9.9	4.9	0.33	1.5	9.41	74.88	0.31	0.33	21.5	0.57	1.3	1.2	7.44	46.4	0.31	115.3	
<b>ANC increased</b>																			
mean	43.00	1079	36.9	28.3	3.17	9.0	73.5	276.1	1.23	1.68	4.17	5.75*	12.3	2	81.3	252	3.13*	129.3	
SD		442	9.8	6.3	0.56	2.2	8.84	86.70	0.35	0.58	1.56	2.51	2.0	1.1	7.55	75.0	1.16	163.1	

**Legend =** \* $P: < 0.05$ ; White blood cell count (WBC):  $4.0 - 11.0 \times 10^9/L$ ; Haemoglobin (Hb):  $12.0 - 15.6$  g/L; Mean cell volume (MCV):  $80 - 100$  fL; Platelet count (PLT):  $150 - 450 \times 10^9/L$ ; Absolute Neutrophil Count (ANC):  $> 1.5 \times 10^9/L$ ; Lymphocytes:  $1.5 - 4.5 \times 10^9/L$ ; Total serum iron:  $4.6 - 30.4$   $\mu\text{mol/L}$ ; Iron (transferrin) saturation (TS):  $20.8 - 41$  %; Total iron binding capacity (TIBC):  $45 - 81$   $\mu\text{mol/L}$ ; Transferrin:  $2.0 - 3.6$  g/L; Serum ferritin:  $10 - 200$  ng/mL (10<sup>th</sup> percentile:  $3.0 - 6.0$  ng/mL; 90<sup>th</sup> percentile:  $201 - 243$ : ng/mL).

**Table 3.** Blood parameters of patients with IDA and neutropenia before and after iron therapy

Before treatment	WBC	Hb	MCV	PLT	ANC	Lymphocyte	Serum iron	TS	TIBC	Transferrin	Serum ferritin
mean	3.56	9.12	72.98	292.15*	1.18	1.91*	6.47	9.39	72.8*	3.15	13.96
SD	1.06	2.06	12.53	98.84	0.28	0.76	10.49	12.59	14.01	0.85	48.84
<b>After treatment</b>											
Mean	4.58*	12.8*	89.5*	235.70	2.33*	1.72	17.9*	31.43*	45.20	8.7*	138*
SD	2.11	8.66	42.35	89.80	2.07	0.59	12.64	20.72	24.12	16.05	174.48

**Legend =** \* $P: < 0.05$ ; White blood cell count (WBC):  $4.0 - 11.0 \times 10^9/L$ ; Haemoglobin (Hb):  $12.0 - 15.6$  g/L; Mean cell volume (MCV):  $80 - 100$  fL; Platelet count (PLT):  $150 - 450 \times 10^9/L$ ; Absolute Neutrophil Count (ANC):  $> 1.5 \times 10^9/L$ ; Lymphocytes:  $1.5 - 4.5 \times 10^9/L$ ; Total serum iron:  $4.6 - 30.4$   $\mu\text{mol/L}$ ; Iron (transferrin) saturation (TS):  $20.8 - 41$  %; Total iron binding capacity (TIBC):  $45 - 81$   $\mu\text{mol/L}$ ; Transferrin:  $2.0 - 3.6$  g/L; Serum ferritin:  $10 - 200$  ng/mL (10<sup>th</sup> percentile:  $3.0 - 6.0$  ng/mL; 90<sup>th</sup> percentile:  $201 - 243$ : ng/mL).

**Table 4.** Blood parameters of patients with IDA and lymphocytopenia before and after iron therapy

Before Treatment	WBC	Hb	MCV	PLT	ANC	Lymphocyte	Serum iron	TS	TIBC	Transferrin	Serum ferritin
Mean	5.77	7.15	68.18	272.05	4.54*	0.73	3.69	10.85	68.41	2.86	7.87
SD	2.66	1.63	12.00	69.82	2.68	0.15	1.68	21.17	20.85	0.48	6.88
After treatment											
Mean	5.73	11.27*	80.2*	260.79	3.38	1.79*	10.29*	20.8*	59.40	5.2*	158*
SD	2.39	2.06	8.16	68.90	2.02	0.74	5.67	13.21	9.76	8.07	217.61

**Legend** = \*P: <0.05; White blood cell count (WBC): 4.0 – 11.0 x 10<sup>9</sup>/L; Haemoglobin (Hb): 12.0 – 15.6 g/L; Mean cell volume (MCV): 80 – 100 fL; Platelet count (PLT): 150 – 450 x10<sup>9</sup>/L; Absolute Neutrophil Count (ANC): > 1.5 x 10<sup>9</sup>/L; Lymphocytes: 1.5 – 4.5 x 10<sup>9</sup>/L; Total serum iron: 4.6 – 30.4 µmol/L; Iron (transferrin) saturation (TS): 20.8 – 41 %; Total iron binding capacity (TIBC): 45 – 81 µmol/L; Transferrin: 2.0 – 3.6 g/L; Serum ferritin: 10 – 200 ng/mL (10<sup>th</sup> percentile:3.0-6.0 ng/mL; 90<sup>th</sup> percentile:201-243: ng/mL).

nia in the Arab Peninsula. Denic S et al, studied 1032 adult Arab participants in Saudi Arabia and reported that 10.7% had neutropenia <1.5 × 10<sup>9</sup>/L. On the other hand, Benign neutropenia (BN) has been previously reported KSA, Jordan, Kuwait, Yemeni and Ethiopian Jews, and an Arab tribe of Sudanese origin. These studies reported a high prevalence of BN in many populations in the Arabian Gulf region (24-28).

The impact of iron deficiency and its relationship with the occurrence of leukopenia, neutropenia, and or lymphocytopenia has not been well studied. Previous case reports suggested the possible association between IDA and leukopenia, neutropenia and lymphocytopenia (15-18).

In our large cohort with IDA, leukopenia and neutropenia was present in 5.1% and 4% of patients, respectively. The iron replacement was associated with a significant increase of ANC counts in 67% and Hb in 100% of them. In addition, the ferritin level and Hb concentration were significantly correlated with ANC. Both groups with improved ANC and without improvement in ANC had a similar increase in Hb concentration and serum ferritin after iron therapy. In support of our findings, one study found that more than 2% of patients who had incidental adulthood neutropenia also had IDA. Typically, the neutrophil count for these patients will be improving when treated with iron replacement therapy (29).

Iron is an important factor in many pathways and the effects of iron deficiency on bone marrow functions other than erythropoiesis are not well defined. It was suggested that iron deficiency could impair enzymes that are involved in leukopoiesis. In the iron-deficient mouse model, iron deficiency has been shown to affect

erythro-myeloid progenitors significantly which could lead to iron deficiency (2, 16, 30, 31).

Iron is also an essential element of the immune cell function. Iron deficiency may suppress the immunological response to pathogens and increase the susceptibility to infection (32, 33).

Several reports have shown a correlation between immune cell function and iron concentration. Low iron levels may lead to macrophage and neutrophil dysfunction. “Iron levels have also been shown to alter the proliferation of T<sub>H1</sub> and T<sub>H2</sub> subsets, likely related to the difference independence of cells on transferrin-related iron uptake” (34-36). Furthermore, iron is an essential nutrient for the growth of various pathogens (37, 38). During infections, the availability of iron affects both the pathogen proliferation and efficacy of antimicrobial immune pathways (37, 38). Longitudinal studies of iron therapy are inconclusive; either showed beneficial effects (39), no effect (40), or a worsening (41). In our study, 7 out of 80 (8.75%) patients with IDA and leukopenia, 8 out of 64 (12.5%) of patients with IDA and neutropenia, and 4 out of 20 (20%) of patients with IDA and lymphocytopenia presented an infection (respiratory tract infections, urinary tract infection, gastroenteritis, lymphadenitis at the time of presentation) at first examination. All were commonly treatable and did not result in serious complications.

Our study presents some limitations because it included only females, which can impair the generalizability of the results. However, IDA affects mainly women and it would be difficult to perform a balanced analysis if males are included as their sample size would be smaller.

In addition, this is an observational study that would limit the causality addressing the given clinical question. Therefore, further studies, especially controlled ones, are required to confirm our findings. Specific patterns can be found if flow-cytometry is done to those patients with IDA and cytopenia.

## Conclusion

In our study, neutropenia occurred in 4% of patients with IDA. Iron therapies led to the correction of anemia in 100% and increased ANC in 67% of them. Therefore, neutropenic women with iron deficiency should be treated, initially only with iron, and observed for their Hb and ANC responses before starting any other treatment.

**Conflict of Interest Statement.** The authors declare that they have no competing interests.

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Correspondence:  
Mohamed A Yassin  
Department of Hematology Oncology,  
National Cancer Institute, Hamad Medical Center  
Doha, Qatar  
E-mail: yassinmoha@gmail.com