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Levels of Immunoglobulins among iron deficiency anemic children in Sana'a City Yemen

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ABSTRACT

Iron deficiency (ID) is a common cause of anemia worldwide. The importance of iron deficiency as a public health problem is based ultimately on the seriousness of its consequences on health. This case-control study aimed to evaluate the levels of immunoglobulins (IgM and IgG), and their association with red cell indices, iron indices, total and differential leukocyte count among children with iron deficiency anaemia (IDA). This study was conducted during a period of six months; starting in December 2021 and ending in May 2022. During this period, 136 samples were collected from preschool-aged children (<5 years). Sixty IDA children were enrolled from outpatient pediatric clinics in Al-Sabeen hospital for maternity and childhood and other private pediatric clinics in Sana'a city, Yemen, and 68 age and sex-matched healthy children were enrolled and a complete history was obtained from all subjects. Clinical examination, C-reactive protein, albumin test, complete blood count, iron profile tests and immunoglobulins assays were performed. The results of the present study revealed that, serum levels of IgM and IgG in IDA group were significantly lower than those in control group (p= 0.001). Total leukocyte count and percentage of eosinophils were significantly increased (p= 0.01, 0.001, respectively), in contrast, percentages of lymphocytes and monocytes were significantly decreased (p= 0.002, p= 0.04, respectively) in IDA than control group. However, there were no statistically significant differences in percentages of neutrophils, basophils and platelets count between the two groups (p=0.47, 1.00, 0.07; respectively). Serum levels of IgM were correlated with levels of Hb, HCT, RBCs, MCV, MCH, RDW, iron indices and percentage of eosinophils (p<0.05). However, serum levels of IgG were correlated with levels of all red cell indices, iron indices and percentage of eosinophils (p<0.05). It can be concluded from these results that the IDA is associated with humoral immunity and may predict increased susceptibility to infections.

CONTENTS

1. Introduction:

Iron is dynamic for all living organisms because it is critical for multiple metabolic processes, involving DNA synthesis, oxygen and electron transport. Iron deficiency (ID) is defined as a decrease in the total content of iron in the body.

It is the main nutritional insufficiency complaint affecting large fractions of the world population and is a common cause of anemia. Iron deficiency anemia (IDA) occurs when ID is sufficiently to reduce erythropoiesis and is represented by a defect in hemoglobin synthesis, resulting in red blood cells that are microcytic and hypochromic [1]. The frequency of IDA varies between sex, age groups, and geography. Around half of anemia cases in developing countries are companied with ID. In Middle East region, the prevalence of IDA is high and about 63% of the preschool children are suffering IDA [2, 3].

Humoral and cell mediated immunity have been studied extensively in relation to ID in both humans and animals. Some studies suggest a link between ID and bloodied immune system function [4, 5]. Mullick *et al*. and Tang *et al*. showed association between the severity of hematological and immunological compromise [6, 7]. An increased vulnerability to infections has been detected in some ID Children, especially infants who live in developing countries, they are highly susceptible to infectious diseases due to impairment of their immunity by ID [8, 9]. Furthermore, it has been suggested that iron supplementation can ameliorate iron levels and reduce morbidity from upper respiratory tract infections in children with or without infection [10]. It is important to understand the effects of IDA on the immune system due to its high prevalence in the world [11, 12, 13], particularly in Yemen [14]. Therefore, the aim of this study was to display whether serum immunoglobulins (IgM and IgG) levels alter in children with IDA.

2. Methods

This case-control study was conducted in Medical Microbiology and Immunology department, Faculty of Medicine and Health Sciences, Sana'a University, Yemen. The study was carried out after obtaining the approval from the ethical committee of the institution and after getting the informed consent from parent of the child. Of total 136 preschool-aged children (<5 years), sixty-eight children with IDA were enrolled from outpatient pediatric clinics in Al-Sabeen hospital for maternity and childhood and other private pediatric clinics in Sana'a city, Yemen from December 2021 to May 2022. The diagnosis of IDA was based on the following; Hb <11 (g/dl), Mean corpuscular volume (MCV) < 80 femtolitrs (fl), Mean corpuscular Hemoglobin (MCH) < 27picograms (pg), serum ferritin < 14 ng/ml, serum iron (SI) < 25 µg/dl and TIBC > 428 µg/dl [15]. 68 healthy children of comparable age and sex fulfilling the inclusion criteria and normal **CBC, albumin, and CRP** were enrolled from different places and considered as control group.

Exclusion criteria for subjects were: children with a history of administration of iron, other hematinic or multivitamins in the last 3 months; children with chronic illness, acute or chronic infection; children with chronic blood loss or recent acute blood loss; children with clinical features of malnutrition, children with serum albumin< 3.5 g/dl, children with a C-reactive protein (CRP)> 0.6 mg/dl; children with diseases that can alter levels of immunoglobulines such as immunodeficiencies, malignancy, autoimmune diseases. Venous blood sample was withdrawn from each participant and were divided into two tubes; EDTA tube for CBC test and blood film, and plain tube for CRP, albumin, iron profile and immunoglobulins assays. The hematological parameters were performed using Siemens Advia 2120 hematology analyzer. Levels of CRP, albumin, iron indices and immunoglobulins were determined by immunoturbidimetry method using Cobas Integra 400 systems analyzer. Data was analyzed using SPSS version 26 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov's test was used to detect the normal distribution. Results were expressed as mean±standard deviation (SD) for the normal distributed data and median for that were not normally distributed. Unpaired Student t-test was used for comparing between groups, and Pearson coefficient of correlation (r) were used for the correlation between the variables. All statistics tests were two-tailed and a probability

(p values) ≤ 0.05 qualify as significant results and those ≤ 0.001 as highly significant results.

3. Results

This study is the first one in Yemen that deals with this issue. In this study, the age of the 68 IDA children (37 of them were males and 31 were females) ranged from six months up to 59 months, with a median age of 23.5 (13.3-44.0) months. On other hand, the age of control group (36 of them were males and 32 were females) ranged from six to 58 months, with a median age of 22.1(14.5-40.8) months (Table 1).

The unpaired t test showed significant difference between these two groups (p< 0.05) for all red cell indices (Table 2) and iron indices (Table 3). Children with IDA had significantly lower IgM, and IgG levels, than control (p= 0.001). T. WBCs and percentage of eosinophils (p= 0.01, 0.001; respectively) were higher significantly, while percentages of lymphocytes and monocytes were significantly decreased (p= 0.002, 0.04; respectively) in IDA group compared to control group. However, there were no statistically significant differences in percentages of neutrophils and basophils between IDA group and control (p=0.47, 1.00, respectively). Although, the platelets count was higher in iron IDA group than control, it was without statistically significant (p= 0.07). (Table 4).

There were positive correlations between serum IgM and levels of almost red cell indices (Hb, HCT, RBCs, MCV and MCH) where p values were 0.03, 0.001, 0.02, 0.005, 0.02; respectively. And there were negative correlation between serum IgM and levels of RDW (p=0.004). In addition, there were highly positive correlations between serum IgG and all red cell indices (p= 0.001) except the correlation with levels of RDW was negative correlation (p=0.001) (Table 5). There were positive correlations between serum IgM, and serum levels of ferritin and iron (p= 0.03, 0.003; respectively) and a negative correlation with levels of TIBC (p= 0.02) (Table 6). Also, there were highly significant positive correlations between serum IgG and levels of serum ferritin and iron (p= 0.0001), but negative correlation with levels of TIBC (p= 0.0001) (Table 3.6). There was negative correlation between percentage of eosinophiles and serum IgM (p= 0.04) and IgG (p= 0.0001). However, there were no any correlations between serum IgM or IgG and the levels of other immune cells (p> 0.05) (Table 7).

Table (1): Demographic data in iron deficiency anaemic and healthy children in Sana'a city, 2022

Demographic data	IDA Cases (n = 68)	Control (n = 68)
Age Median (IQR)	23.5 (13.3-44.0)	22.1 (14.5-40.8)
Sex Male No. (% Female No. (%)	37 (54.4) 31 (54.6)	36 (52.9) 32 (47.1)

Table (2): Comparison of hematological data between iron deficiency anaemic and healthy children in Sana'a city, 2022

Hematological Parameters	IDA Cases Mean±SD	Control Mean±SD	Independent t test	*p*
Hb (g/dL)	9.1±1.8	13.2±1.1	-15.9	0.001**
HCT (%)	30.1±2.1	39.8±2.9	-22.1	0.001**
RBC (10^{12}/L)	3.0±0.5	4.2±0.5	-13.5	0.001**
MCV (fl)	70.3±4.8	84.2±11.1	-9.5	0.001**
MCH (pg)	22.3±3.6	29.9±1.6	-15.7	0.001**
MCHC (g/L)	28.6±2.1	33.7±3.9	-9.4	0.001**
RDW (%)	18.6±2.5	13.7±0.5	15.9	0.001**

Hb: **H**emoglobin, HCT: hematocrit, RBC: Red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin, RDW: red blood cell distribution width, ***p***: Probability value ≤ 0.05 (significant)* (highly significant) **

Table (3): Comparison of iron indices between iron deficiency anaemic children and healthy children in Sana'a city, 2022

Iron indices	IDA cases Mean±SD	Controls Mean±SD	Independent t test	*P*
Ferritin (ng/mL)	8.5±3.2	74.1±33.9	-15.9	0.001**
Serum iron (µg/dl)	15.4±6.5	76.3±29.8	-16.5	0.001**
TIBC (µg/dl)	736.5±261.8	333.9±82.6	12.1	0.001**
TIBC: total iron binding capacity; ***p:*** Probability value ≤ 0.05 (significant)* (highly significant) **				

Table (4): Comparison of immunological data between iron deficiency anaemic and healthy children in Sana'a city, 2022

Immunological parameters	IDA cases Mean±SD	Controls Mean±SD	Independent t test	*P*
IgM (mg/dL)	66.5±27.5	84.1±35.3	-3.2	0.001**
IgG (mg/dL)	501.1±190.3	835.3±305.3	-7.7	0.001**
T.WBC (10^9/L)	7.4±3.5	6.2±1.8	2.6	0.01*
Neutrophils (%)	44.6±15.9	42.9±9.3	0.7	0.47
Lymphocytes (%)	37.9±13.9	44.3±8.9	-3.2	0.002**
Monocytes (%)	7.4±3.5	8.7±3.4	-2.1	0.04*
Eosinophils (%)	10.1±3.7	3.6±1.6	11.2	0.001**
Basophils	0.04±0.21	0.04±0.21	0.00	1.00
Platelets (10^9/L)	323.4±141.8	286.4±87.1	1.8	0.07
T. WBC: total white blood cells; *p:* Probability value ≤ 0.05 (significant)* (highly significant)**				

Table (5): Correlation between immunoglobulin levels and hematological parameters

Hematological parameters	**Pearson correlation**	**IgM**	**IgG**
Hb (g/dl)	***R***	0.19	0.61
	P	**0.03***	**0.001****
HCT (%)	***R***	0.30	0.49
	P	**0.001****	**0.001****
RBC (10^{12} /L)	***R***	0.20	0.46
	P	**0.02***	**0.001****
MCV (fl)	***R***	0.24	0.47
	P	**0.005****	**0.001****
MCH (pg)	***R***	0.20	0.52
	P	**0.02***	**0.001****
MCHC (g/L)	***R***	0.14	0.35
	P	0.10	**0.001****
RDW (%)	***R***	-0.25	-0.46
	P	**0.004****	**0.001****

Hb: **H**emoglobin, HCT: hematocrit, RBC: Red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin, RDW: red blood cell distribution width; ***p:*** Probability value ≤ 0.05 (significant)* (highly significant) **

Table (6): Correlation between serum immunoglobulin levels and iron indices

Iron indices	**Pearson correlation**	**IgM**	**IgG**
Ferritin (ng/mL)	***R***	0.31	0.50
	P	0.03*	0.0001**
Serum iron (µg/dl)	***R***	0.25	0.51
	P	0.003**	0.0001**
TIBC (µg/dl)	***R***	-0.20	-0.62
	P	0.02*	0.0001**

TIBC: total iron binding capacity; ***p:*** Probability value ≤ 0.05 (significant)* (highly significant) **

Table 7: The correlation between serum immunoglobulin levels and immune cells.

Immune cells	Pearson correlation	IgM	IgG
T. WBC (10^9/L)	***r***	0.04	-0.07
	p	0.68	0.44
Neutrophiles (%)	***r***	0.04	0.002
	p	0.63	0.98
Lymphocytes (%)	***r***	-0.005	0.12
	p	0.96	0.20
Monocytes (%)	***r***	0.02	0.10
	p	0.84	0.23
Eosinophiles (%)	***r***	-0.17	-0.41
	p	**0.04***	**0.001****
Basophils (%)	***r***	0.04	-0.01
	p	0.65	0.89
Platelets (10^9/L)	***r***	-0.09	-0.07
	p	0.25	0.42

T. WBC: total white blood cells; *p*: Probability value ≤ 0.05 (significant)* (highly significant) **

4. Discussion

The present study provides a case-control analysis which investigated the levels of serum IgM and IgG among IDA and healthy children in Sana'a city. The effects of IDA on humoral immunity remain controversial. Some studies investigate that IDA may be responsible for the defect in humoral response while others did not find any change in the levels of Ig in IDA [7, 8, 16]. In our study, IgM levels were significantly lower in children with IDA than control group (p= 0.001). A study in adult by Sadaghan *et. al.* [17] found lower levels of serum IgM in ten patients (premenopausal adult females) with moderate to severe IDA in comparison to control. However, our result disagreed with other studies [9, 18, 19] in which their results revealed that there was no statistically significant difference in serum levels of IgM between children with IDA group and non-IDA group (p> 0.05).

In addition, our results showed that there was statistically significant decreasing in serum IgG levels (p= 0.001) which was similar to that reported by previous studies [7,18] where their results revealed highly statistically significant decreasing in serum IgG levels. Moreover, Feng *et al.* found that the mean concentration of serum IgG4 and IgG1, and pneumococcal polysaccharides specific IgG1, IgG2 antibodies were decreased in children with iron-deficient children compared with age-matched healthy children [20]. Also, a decrease levels of serum IgG were found by Guzikowska [21]. On the other hand, our finding disagreed with result of Das and co-workers [19], who reported that there was no significant difference of serum IgG levels between children with IDA and non-IDA.

While a study done by Ekiz and co-workers reported that there was no significant difference of serum IgG levels between children with IDA and non-IDA group except IgG4 that was significantly lower in IDA group than control group [8].

A relationship between IDA and the count of immune cells was studied in this work, the results showed that the T. WBCs count was significantly higher among children with IDA than control group (p= 0.01). This result was similar to that reported by Ekiz and co-workers [8], in contrast, Rhamani reported that there was statistically significant decreasing in T. WBCs count in IDA group [9]. On other hand, other study reported that there was no statistically significant difference in T. WBCs count between children with IDA and control group [19]. Our result may explain that the susceptibility to infection in IDA may lead to increased levels of T. WBCs [22].

As regard differential count, the current study demonstrated that there was no statistically significant difference in percentage of

neutrophils between the two studied groups (p= 0.47). This result agreed with what reported by Aly and co-workers [23], however, disagreed with other studies [24, 25], who found a significant decrease in percentage of neutrophils in children with IDA comparing to control group. On the other hand, a study on premenopausal adult females by Sadeghian and co-workers [17] reported that there was no difference between percentage of neutrophils in the studied groups.

The percentage of lymphocytes in this study was significantly lower in IDA group than in control group (p= 0.002), this result agreed with studies conducted by Mullick and co-workers [6], Das and co-workers [19], Aly *et al.* [23], OMS/UNICEF [26] who reported decreasing in total lymphocyte count. Moreover, many studies showed that the levels of T lymphocytes were improved following iron supplementation [6, 27]. On the other hand, this study result disagreed with a study conducted by Rahmani and Demmouche, where percentage of lymphocytes was significantly higher in IDA group [9], and with other studies which reported that there was not any change in lymphocytes count in IDA group [8, 18]. The decreasing in percentage of lymphocytes in IDA group may due to that the proliferative phase of lymphocyte activation is a Fe−demanding phase for enzymes such as ribonucleotide reductase [28], thereby it can be weakened during IDA. Kuvibidila and Porretta found a decrease in DNA synthesis in the activated lymphocytes with purified protein derivatives (PPD) and in the formation of 'macrophage migration inhibition factor' and in delayed type of immune reaction after stimulation with PPD and Candida antigens in patients with IDA [29]. This may result in altered expression of cell markers that may contribute to the reduced T-cell proliferation.

In this study, percentage of monocytes was significantly lower in IDA group than in non-IDA group (p= 0.04). Many **i**nvestigators found an impaired cellular immune functions in IDA [8, 25, 27, 30]. Interestingly, there was a previous study on phagocytic activity of monocytes in children reported that the phagocytic activity of monocytes was significantly decreased in IDA group [8]. The decrease in monocytes count in IDA could be due to defects in iron dependent enzymes. However, our result disagreed with previous study which reported that percentage of monocytes was significantly higher in IDA group than control group [8].

As regard that percentage of eosinophils, it was significantly higher in IDA group than in non-IDA group (p= 0.001), while in Rahmani and Demmouche study, there was no statistically significant difference in percentage of eosinophils between the two studied groups [9]. This variation may be attributed due to increasing the prevalence of parasitic infection in Yemen (51.8% among children and immunocompromised patients) [31], which is one of the most risk factors causing IDA among children in Yemen [14]. As regard basophils, our result (p= 1.00) is matched with those of Rahmani and Demmouche who reported no change in the in percentage of basophils between the children with IDA and control groups [9].

Although, platelets count was higher in this study among IDA group than non-IDA group, this increase was not statistically significant (p= 0.07). This result agreed with what reported by Aly and co-workers who found that there is no significant difference in platelets count between the two groups [23]. However, our result was in contrast to previous results in which there was significant high platelets count in children with IDA comparing to control [6, 18, 19].

As regard correlation study, this study showed that there were positive correlations between serum levels of Ig (IgM and IgG) and levels of Hb, HCT, RBCs, MCV, MCH and negative correlations with RDW (p< 0.05), however, MCHC had a significant positive correlation only with serum IgG (p= 0.001) but not with IgM (p= 0.10). In general, these correlations indicate that there is a relation between serum Ig levels (IgM and IgG) and levels of red cell indices, moreover, the levels of IgG is more correlated to

the decrease levels of red cell indices in this study. Unfortunately, these correlations were not discussed in any other studies to compared with this study results, except the correlations that were reported by Rahmani and Demmouche who found positive correlations between serum levels of IgG, and levels of Hb and HCT [8]. Also, there was a study in pregnant women reported that there was a positive correlation between levels of IgG and Hb concentration [7, 32].

In addition, this study showed that there were positive correlations between levels of IgM and levels of ferritin, SI and a negative correlation with levels of TIBC (p= 0.03, 0.003, 0.02; respectively). Also, there were high positive correlations (p= 0.0001) between levels of IgG and levels of ferritin, SI and a negative correlation with TIBC. These results were similar to the results of previous study where there were positive correlations between levels of IgG and ferritin and SI [9]. On the contrary, these results were not similar to what reported by Hassan and co-workers in which there were no correlations between the levels of Ig (IgM & IgG), and serum levels of iron indices [18]. In our study, this correlation between levels of serum Ig and iron indices explains the essential role of iron in humoral immune response.

Interestingly, serum levels of IgM and IgG had negative correlations with percentage of eosinophils (p= 0.04; p= 0.001, respectively), while they were no any correlations with rest of differential count of WBCs, T. WBCs count or platelets count (p> 0.05). To our knowledge these correlations were not reported in any previous studies to be compared with our results. The reverse correlation between levels of Ig and levels of eosinophils may be explained due to the common cause of eosinophilia and the prevalence of IDA that is parasitic infections [14, 31] which may be affect the levels of Ig (IgM, IgG) especially IgG.

Finally, it seems that the differences between this study results and some results of previous studies to the heterogeneity of different studies in aspects including age groups, number of samples, different types of infection in different places, and experimental errors that can affect the results of various studies and thereby create different and divergent results.

5. Conclusion

We concluded that IDA in children is associated to humoral immunity which may predict increased susceptibility to infections of children. We needed future studies for specific defects of immunity in IDA before and after supplementation.

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6. References

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