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Selective immunoglobulin A deficiency in a sample of Iraqi blood donors in the National Blood Transfusion Center-Baghdad

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Abstract:

BACKGROUND: Selective immunoglobulin (Ig) A deficiency is the most common Ig deficiency in the world. Serum IgA level is reduced, 7 mg/dL (70 μg/mL), thus, associating with a wide range of clinical symptoms and signs that are related directly and indirectly to disturbances in the body immune system. Selective IgA deficiency patients are known to develop antibodies against lacking IgA. Whenever these antibodies are found in an individual's circulating blood, a severe allergic response and anaphylaxis can ensue upon receiving IgA containing blood or blood components. Hence, certain protocols are recommended in populations with increased prevalence of selective IgA deficiency including the use of red blood cell (RBC) washing machines or IgA-deficient blood components. Both measures are costly and require special maintenance procedures.

OBJECTIVES: The aim of this study was to screen for the presence of selective IgA deficiency in a group of blood donors and its probable role in the events of transfusion reactions that frequently occur which may necessitate the application of protocols that involve sophisticated procedures and highly-demanding machines.

SUBJECTS AND METHODS: This was a laboratory study that included 300 volunteer blood donors in the National Blood Transfusion Center. They were screened for their serum IgA levels. Related questionnaire was conducted and chemiluminescence immunoassay technique with MAGLUMI 600 series machine was used. This machine is already used by the National Center of Teaching Laboratories for variety of biochemical and immunological assays. Serum IgA levels then were plotted against age, blood group and smoking status.

RESULTS: No single case of Selective IgA deficiency was documented. Serum IgA levels showed increased levels with age and smoking demonstrated no significant effect on the Ig levels.

CONCLUSION: In light of these results, it does not seem urgent or necessary at this point of time to introduce the highly demanding and expensive RBC washing machines in blood banks in Iraq. We recommend conducting a larger study that is more comprehensive with wider involvement of population, considering age, gender, and ethnicity.

Keywords:

Anaphylaxis, blood transfusion, selective immunoglobulin A deficiency

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Introduction

Selective immunoglobulin A deficiency (SIgAD) is the most common primary Ig deficiency in the world, where serum immunoglobulin (Ig) A levels are <7 mg/dL (70 μg/mL) in conditions of absolute IgA deficiency, or 2 standard deviation (SD) below age-specific normal level in partial IgA deficiency.[1]

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Worldwide prevalence of SIgAD varies depending on ethnicity. In the Western world, selective IgA deficiency is considered the most common primary immunodeficiency, affecting around 1 in 20 people.[2] In 2014, Jeffrey Modell Centers Network has demonstrated that 8437 cases of SIgAD were diagnosed globally; they were distributed to 5492, 1704, 1050, 115, and 76 patients, in Europe, North America, Latin America, Asia, and Africa, respectively.[3] The prevalence of selective IgA deficiency was found to be 1:651 in Iran, 1:143 in the Arabian Peninsula, 1:188 in Turkey, 1:163 in Spain, 1:965 in Brazil, 1:252 in Nigeria, and 1:875 in England.[4-10]

SIgAD was first described in children with ataxia telangiectasia.[11] Consanguinity marriage has been associated with increased number of selective IgA deficiency in the same family, a condition defined as familial clustering.[12] It is more common in males.[13] Most selective IgA deficiency individuals are asymptomatic; nevertheless, a wide range of clinical features were noticed; most commonly those associated with respiratory infections, particularly extracellular noncapsulated bacteria as *Haemophilus influenzae* and *Streptococcus pneumoniae* infections.[14] Gastrointestinal disorders such as coeliac disease, recurrent infections, nodular lymphoid hyperplasia, inflammatory bowel disease, pernicious anemia, and gastric and colonic adenocarcinoma have also been documented.[15] Autoimmune diseases, on the other hand, are also not uncommon among SIgAD patients, like Immune thrombocytopenia, Hashimoto thyroiditis, autoimmune hemolytic anemia, and systemic lupus erythematosus.[16]

Of particular interest, in SIgAD, there is a tendency to develop specific antibodies to IgA, which may result in anaphylactic reactions when the patient receives an IgA containing blood or blood component.[14] This is thought to be due to naturally occurring anti-IgA antibodies (IgG or possibly IgE).[17]

Whenever anti-IgA antibody is found to be involved in events of allergic transfusion reactions IgA deficient plasma and IgA deficient/washed cellular products should be given for any future transfusion.[18] So as the case with patients developing anaphylactic responses to blood transfusion with no previous history of IgA deficiency, yet with high suspicion to be. This study aimed to screen for the frequency of selective IgA deficiency in a group of Iraqi blood donors, and thereby providing a basic answer for the frequently asked question about the cost-effectiveness of providing highly sophisticated RBC-washing machines in blood banks in Iraq.

Subjects and Methods

This was a laboratory study in which 300 randomly selected volunteer blood donors were enrolled. They were subjected to routine detailed history-taking and general examinations. Basic routine predonation laboratory investigations were done. Association for the Advancement of Blood and Biotherapies (AABB) guidelines are followed in the National Center of Blood Transfusion in Baghdad. This study was approved by review ethical committee of medical city complex. Each participant was signed written informed consent explaining the nature of study.

A questionnaire was directed verbally to each of the 300 participants, and it included information about participants age, gender, ethnic group, blood group, history of smoking, history of recurrent infections and their sites, history of allergy like allergic rhinitis, allergic conjunctivitis and atopic dermatitis, food allergy, family history of selective IgA deficiency, family history of chronic illnesses as autoimmune diseases, and malignancy and any family history of hereditary immunological disorders.

Recurrent reparatory infections were defined generally as 2 or more severe infections per year with at least 2 symptom-free weeks apart.[19] Recurrent respiratory illnesses are those associated with fever ≥37.5°C, with one or more of the following: runny nose, nasal congestion, sore throat, earache, cough, wheezing, and/or dyspnea lasting minimally 2–3 days.[20] Recurrent urinary tract infections (UTIs) were defined as complicated or uncomplicated UTI that occurs in the absence of structural or functional abnormalities of the urinary tract, 3 or more episodes a year.[21] Severe infections were primarily considered as any episode of infections fulfilling 2 or more SIRS criteria.[22] They also included infections with persistent fever, being bed-ridden for 1 week duration or more, unresponsiveness to oral antibiotics &/or the need for hospital admissions. Also, we took into consideration any infections with unusual pathogens, occurrence of unusual complications like pleural effusion and mastoiditis, or persistent abnormal investigations like elevated WBC count, ESR &/or CRP or abnormal imaging studies results.

A sample of 5 ml of venous blood was aseptically collected from each donor, along with the beginning of the donation process, from the blood bag pouch. The drawn sample was placed into a gel tube and allowed to stand for 20–30 min at room temperature, for clotting to occur. Then, the samples were centrifugated, for 15 min at 3000 rpm. Serum was collected in Eppendorf tubes in 2 aliquots a sample. Aliquots were stored at −20°C. Samples were run using MAGLUMI 600 series- fully automated chemiluminescence immunoassay analyzer. Before analysis, samples were thawed and thoroughly

mixed to remove bubbles by disposable applicator sticks. Disposable pipettes were also used along the procedure, all to avoid cross contamination.

Statistical analysis

Statistical package of the Social Science version 26 program, (IBM, Chicago, Illinois, US), program was used to assess the effect of different Parameters. Independent *t*-test was used to compare serum IgA levels of smoker and nonsmoker donors, Kruskal–Wallis test was used to analyze levels of serum IgA in relation to ABO/Rh blood grouping, and Pearson's correlation coefficient was used to estimate the correlation between IgA concentration and age of donors. The data were presented as the mean ± SD or number and percentage (*n* and %) as appropriate. For all tests, $P < 0.05$ was considered statistically significant.

Results

Enrolled donors were healthy adult individuals, fulfilling AABB criteria of blood donation, which is conducted at the national center of blood transfusion in Baghdad. Data has been subjected normality tests and has shown normal (Gaussian) distribution.

Ethnicity

Most donors were Arabs. The remaining were Kurds and Turkmen [Table 1].

Donors age: 300 healthy blood donors whose age- range was 18-59 years. Mean of age was 34.84 years [Table 2].

Serum immunoglobulin A concentration

In the present study, CLIA method was used to estimate the concentration of IgA in the sera of donors. The results are shown in Table 3. The mean and minimum IgA concentration values were within the reference range (already included in the kit leaflet; [200–3000 µg/mL]), but the maximum value exceeded the upper normal limit. Data seemed to fall into normal distribution.

Age grouping

The participants were divided into 4 categories depending on a 10-year age interval for each category. This categorization aimed to determine the effect of age on IgA concentration within the same decade.

The present study demonstrated that there was a nonsignificant correlation between serum IgA concentration and age within each age group.

Blood groups

The distribution of donor blood groups was studied and showed that most donors had to blood group O. AB-ve blood group was not found. A nonsignificant difference was found in IgA concentration in relation to blood groups of donors.

Table 1: Distribution of donors according to ethnicity

Ethnicity	*n* (%)
Arabs	294 (98)
Kurds	4 (1.33)
Turkmen	2 (0.66)
Total	300 (100)

Table 2: Participants age parameters

Parameter	*n*	Mean±SD	Median	Minimum-maximum	Range
Value	300	34.84±9.05	34.00	18.00-59.00	40.00

SD=Standard deviation

Table 3: Concentration of serum immunoglobulin A in sera of donors

Serum IgA levels (ug/mL)	*n*	Mean±SD	Median	Minimum-maximum	Range
All donors	300	2080.08±811.48	2091.60	220.59-4158.70	3938.11

SD=Standard deviation, IgA=Immunoglobulin A

Table 4: Correlation between serum immunoglobulin A and age in donors

Correlation test	Results
IgA (µg/mL)	
Pearson correlation	0.32
P	<0.01*
R^2	0.10

*Significant correlation, IgA=Immunoglobulin A

Table 5: Statistical analysis of donors age groups

Age group (years)	*n* (%)	Mean±SD	Median
18-28	78 (26.00)	23.85±2.35	24.00
29-38	130 (43.33)	33.67±2.72	34.00
39-48	72 (24.00)	43.62±3.04	44.00
≥49	20 (6.67)	53.65±3.64	53.00
Total	300 (100)		

SD=Standard deviation

Table 6: Immunoglobulin A concentration in sera of donors for each age group

IgA (ug/mL)	*n*	Mean±SD	Median	Minimum-maximum	Range
Age group 1	78	1592.07±663.60	1530.60	606.40-3328.30	2721.90
Age group 2	130	2210.10±767.75	2216.70	394.80-4158.70	3763.90
Age group 3	72	2262.48±736.07	2362.30	220.59-4158.70	3938.11
Age group 4	20	2481.53±817.69	2518.05	1006.06-3993.8	2987.74

SD=Standard deviation, IgA=Immunoglobulin A

Discussion

Diagnosing SIgAD requires the presence of 4 major

criteria: IgA concentration below 7 mg/dL, or 70 ug/mL, age more than 4 years, normal serum levels of IgG and IgM, and other causes of hypogammaglobulinemia being excluded. T cell defects need also to be excluded and individuals must exhibit normal response to vaccination in the form of normal levels of IgG production.[15] If serum IgA concentration is higher than & mg/dL but is still lower than 2 SD of normal range for age, it's called partial or probable IgA deficiency.[14]

Directed questions of this study's survey was extremely beneficial in terms of ability to simplify otherwise complex points to the participants and putting their immediate responses into words. Jones *et al*.[23] demonstrated a simplified way to design and implement a research questionnaire, and we adhered to it.

This study subjects were randomly selected blood donors the majority of whom were Arabs, with age range of 40 years [Tables 1 and 2]. Under-representation of women is attributed to many factors, particularly lower Hb levels, pregnancy, breastfeeding, and more adverse effects as described by Marco Bani *et al*.[24] The major variation of IgA deficiency among populations 1:3000 to 1:150[13,14] could not be well-represented in this study as well, as number of participants other than Arabs could not be statistically analyzed [Table 1]. Age distribution of donors demonstrated clustering into 4 main groups, with the second group (age 29-38) representing the largest one [Figure 1].

Table 7: Correlation between age and immunoglobulin A in age-groups

IgA (µg/mL)	Correlation test	Result
Age group number 1	Pearson correlation	0.05
	P	0.60 (NS)
	R^2	0.004
Age group number 2	Pearson correlation	−0.07
	P	0.40 (NS)
	R^2	0.006
Age group number 3	Pearson correlation	0.18
	P	0.11 (NS)
	R^2	0.03
Age group number 4	Pearson correlation	0.14
	P	0.55 (NS)
	R^2	0.02

NS=Nonsignificant, IgA=immunoglobulin A

On the other hand, the present study has demonstrated that IgA concentration in sera of blood donors showed a normal distribution with a mean of 2080.08 ug/mL [Table 3] with a gradual increase in serum IgA levels with increasing age [Figure 2], [Table 4]. ($P < 0.01$). This agrees with another study conducted at Duke University Center in 1970, which included 811 health individuals where effect of aging was assessed on human serum Ig concentration. Approximating adult ranges of IgA concentration occurs by puberty and continues to increase slowly through the third decade with increasing variation throughout life.[25]

Our results have demonstrated normally distributed data with mean of 2080.08 ug/mL. Donors were divided into 4 groups [Figure 1], [Table 5]. depending on age. This categorization helped to assess the effect of other possible factors on IgA levels wit the effect of age is minimal or absent [Figure 3], [Tables 6]. Moreover, Within the same age group, non-significant impact could be demonstrated of age on the serum level of IgA [Table 7]. The manufacturer reference level of serum IgA concentration (200-3000 µg/mL or 20-300 mg/dL) was subjected to verification according to CLSI guidelines.[26] 20 values were selected randomly, and no more than 2 values were out of the reference range. So, this range was considered verified to evaluate our results according to. However, this range could not be considered valid as a reference range for our target population, because more than 10% of our data values have fallen outside it. According, validation of a new reference range obtained from our data was conducted. We have included the values falling within the central 95th percentile and our

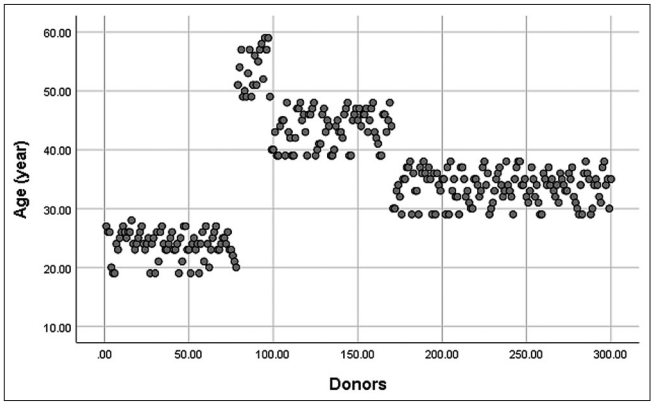

Figure 1: Age distribution of donors. Clustering into 4 main groups with the largest group is between 29 and 38 years of age

Table 8: ABO/Rh blood group distribution in age group

	A+	A−	B+	B−	AB+	O+	O−
Age group number 1, *n* (%)	14 (17.94)	0	15 (19.23)	2 (2.57)	5 (6.41)	36 (46.15)	6 (7.70)
Age group number 2, *n* (%)	36 (27.69)	3 (2.30)	25 (19.23)	3 (2.30)	18 (13.84)	37 (28.46)	8 (6.15)
Age group number 3, *n* (%)	8 (11.11)	1 (1.40)	15 (20.84)	3 (4.16)	7 (9.72)	34 (47.22)	4 (5.55)
Age group number 4, *n* (%)	5 (19.05)	1 (4.76)	5 (23.80)	2 (9.53)	5 (23.80)	2 (9.53)	0 (9.53)
Total (*n*)	63	5	60	10	35	109	18

reference range was found to be [658.177-3693.08] ug/mL for males, in this geographic region.

Major blood groups of donors were also documented [Table 8]. Blood group O+ was most prevalent.

No significant effect of smoking on IgA levels was observed, [Figures 4 and 5], [Tables 9 and 10]. a finding that is agreeable with 2 other studies. In 2008, Gonzalez-Quintela *et al*.[27] investigated serum Ig concentration in 460 adult smokers and despite being demonstrating a negative impact on IgG levels, no effect was pronounced on IgA levels. Furthermore, Bell *et al*.[28] had studied the impact of smoking on certain proteins levels in bronchoalveolar lavage fluid and serum, among which was the IgA level. No significant correlation between the two was established. On the other hand, a study conducted by Tabriah *et al.*, has compared the serum

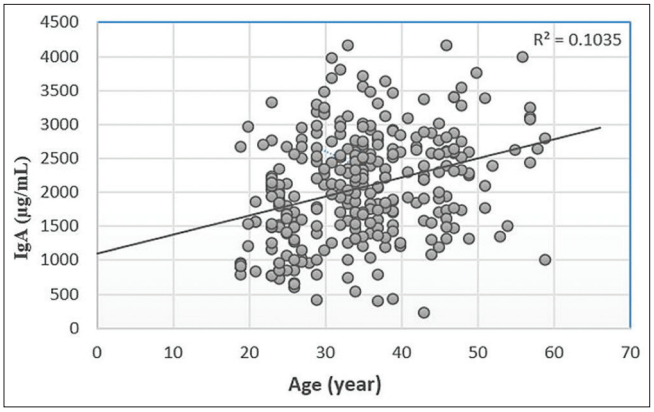

Figure 2: Correlation between serum IgA levels and age. This figure demonstrates the distribution of IgA levels of all donors in relation to age. There is a gradual increase of IgA with increasing age. IgA: Immunoglobulin A

Table 9: Comparison between serum immunoglobulin A levels between smokers and nonsmokers

Serum IgA levels (ug/mL)	*n*	Mean±SD	Median	Minimum-maximum	Range
Smokers	51	2263.99±697.27	2297.70	220.59-3635.39	3414.71
Nonsmokers	249	2043±806.52	1964.40	394.80-4158.70	3763.90

NS difference. SD=Standard deviation, IgA=Immunoglobulin A, NS=Nonsignificant

Table 10: Comparison between concentration of immunoglobulin A in smoker and nonsmoker donors

Parameter IgA (µg/mL)	Smokers, *n* (mean±SD)	Nonsmokers, *n* (mean±SD)	*t*	*P*
Age group number 1	5 (2366.72±502.74)	73 (1539.01±642.17)	-	-
Age group number 2	33 (2194.81±676.09)	97 (2218.40±800.32)	−0.16	0.88 (NS)
Age group number 3	12 (2396.47±864.44)	60 (2235.68±712.95)	-	-
Age group number 4	1	19 (2483.85±840.03)	-	-

NS=Nonsignificant, SD=Standard deviation, IgA=Immunoglobulin A

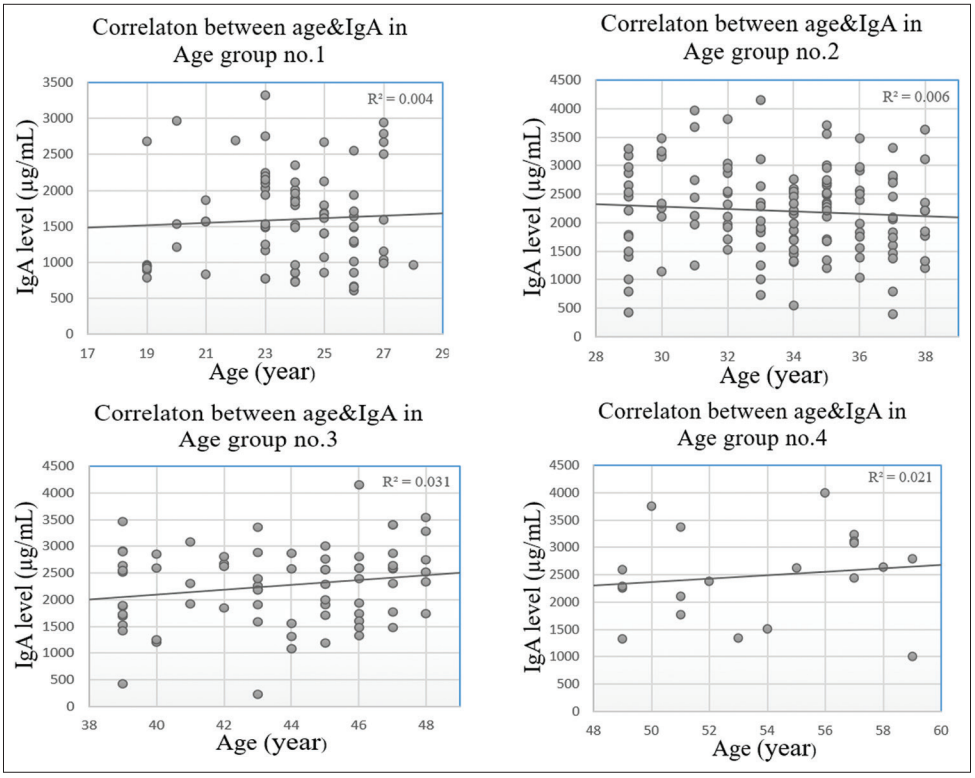

Figure 3: Correlation between IgA concentration and age within a single age group. No significant variation of IgA levels within the same age decade could be observed. IgA: Immunoglobulin A

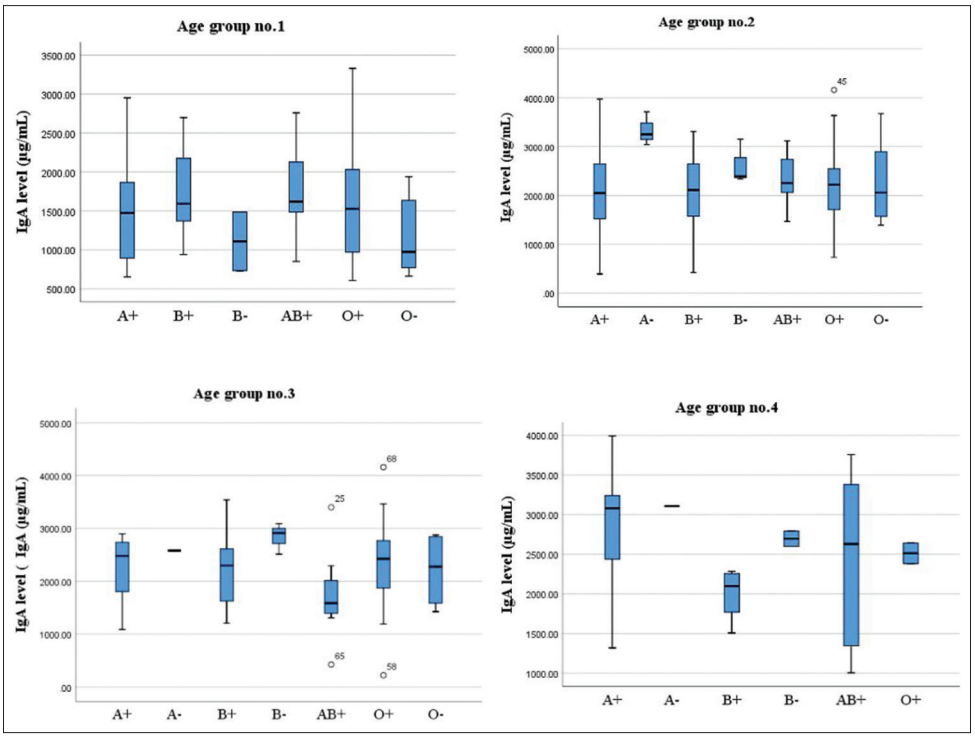

Figure 4: Serum IgA level for each age group is demonstrated in relation to ABO/Rh blood grouping. Serum IgA level distribution is variable from normal to positively and negatively skewed distribution (blue boxes represent interquartile range, black lines in the middle of each box represent the median). Outliers are seen in age groups 2 and 3 (small squares in O+, AB+ and O+ respectively). IgA: Immunoglobulin A

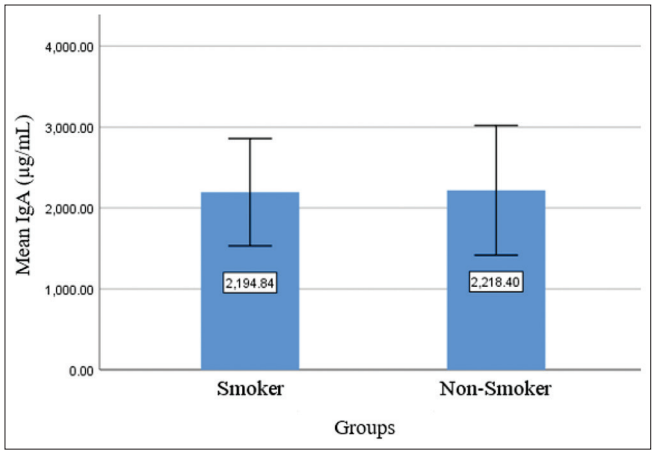

Figure 5: Comparison between smokers and nonsmokers serum IgA levels. Mean serum IgA levels of the two groups are close to each other (written inside the white boxes). The upper limit of nonsmokers seems to be higher than smokers. IgA: Immunoglobulin A

and saliva levels of IgG, IgA, IgM and IgD, in 48 smoking and 48 nonsmoking age-matched participants, has demonstrated increased levels of serum IgA in smokers.[29]

Different commercial assays for measuring serum IgA levels exist with different levels of detection and undesirable drawbacks, among which are nephelometry, radial immunodiffusion, hemagglutination inhibition, and the immunoassays: RIA, and EIA.[30-32] In 1989, M Haun *et al*. used the EIA to detect serum IgA levels. It was capable of detecting low levels of the immunoglobulin concentration by using anti-IgA antibody linked to micron-sized polyacrylamide beads. This test reaction resulted in anti-IgA horseradish peroxidase conjugate. 3 levels of dilution have been assayed. These results, which had been obtained practically directly from the machine, were compared to the calculated results from WHO Ig reference and had showed a difference of 6% at the least dilution. Besides, Haun and Wasi study had demonstrated a linear standard curve in the region between 25 and 2000 ng/mL IgA. In the same study, EIA and RIA have demonstrated similar results in IgA values. RIA measure of serum IgA level had a difference of 25% from the calculated value at the least dilutional level.

Cinquanta *et al*. discussed the role of CLIA technology in antibody detection. In this technique, the indicator is the luminescent molecule. Energy is released from the atom in the form of light. When adopting the spectrophotometric principle of measurement luminescence methods, which give absolute measurements of the target, has proved to be superior to absorbance methods where results are relative. According to this, in this research, the CLIA technology was used. Moreover, CLIA has other benefits of employing a wide dynamic range, high signal intensity and high specificity. Its reagents are relatively stable and incubation time is in minutes. This assay has been fully compatible with immunological assays protocols and recommendations. Its limitations reside mainly in its high

costs and closed-analytical system.[31] This study could not demonstrate any significant correlation between ABO/RhD blood grouping and IgA levels. Another side finding from this study results data can be mentioned here about the frequency of major blood groups ABO/RhD. O+ blood group was the most common, followed by A+ and B+ blood groups respectively. This agrees with a cross-sectional study conducted in Al-Najaf governorate,[33] where 1628 young adult individuals were included, both males and females.

Conclusion

Serum IgA levels were within the reference range in this study population and no single case of selective IgA deficiency has been detected. Accordingly, it does not seem too urgent to provide highly demanding and costly RBC washing machines in the national blood transfusion center in Baghdad at this time point. On the other hand, this study has its own limitations particularly related to sample size and variety of participants in terms of gender and ethnicity, and we recommend conducting another study with a wider range.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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