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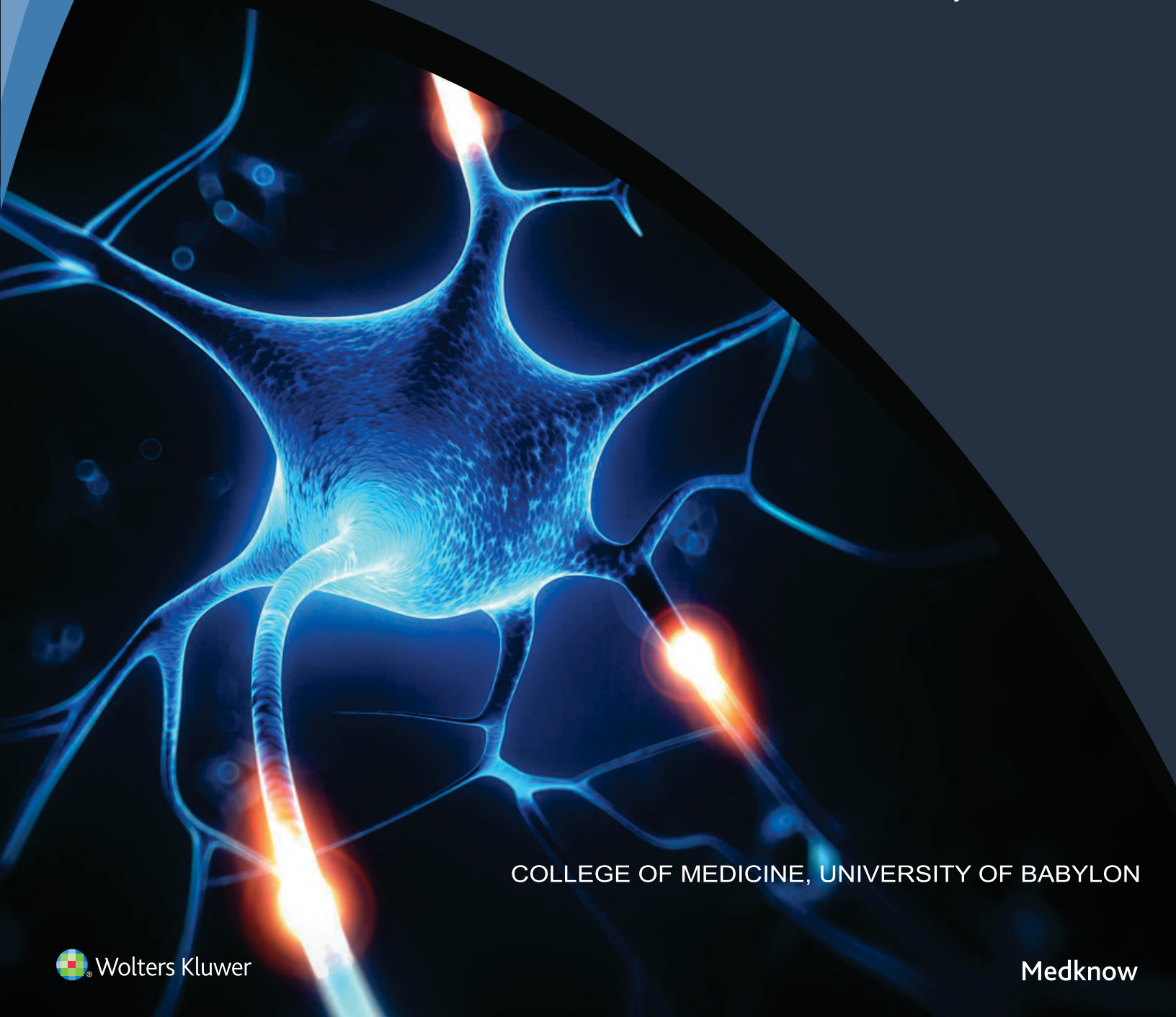

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Original Article

Serum Visfatin Level in Sickle/β Thalassemia in Correlation with Frequency of Vaso Occlusion Crises: A Comparative Study

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Abstract

Background: Hemoglobinopathies are the most common heritable disorders of erythrocytes, with sickle cell diseases (SCDs) and thalassemia being the most common. SCDs are characterized by the presence of sickle hemoglobin within red blood cell (RBC) as a result of point mutation (β6glu→val). SCDs include sickle cell anemia, hemoglobin C disease (HbSC), and sickle/β thalassemia. The latter is caused by coinheritance of two different mutations in β globin gene, one from each parent: one for sickle hemoglobin and the other for β thalassemia. Vaso occlusion is a key feature of this disease that occurs due to a series of interactions leading to painful crisis. Visfatin is a pro-inflammatory adipocytokine that contributes to vaso occlusive crises (VOC) through its role in the inflammatory process. Visfatin can directly promote endothelial dysfunction and stimulates vascular smooth muscle cells proliferation. **Objectives:** The primary aim of this study was to assess serum visfatin level in sickle/β thalassemia patients and evaluate the possible association between serum visfatin level in sickle/β thalassemia patients and the frequency of VOC, serum ferritin level, complete blood count (CBC) and high-performance liquid chromatography (HPLC) parameters. The secondary aim of this study was to compare the findings in two centers (Al-Karama Teaching Hospital, in Baghdad and Babylon Teaching Hospital for Maternity and Children, in Babylon). **Materials and Methods:** This was a cross-sectional study conducted from December 2018 until the end of August 2019 and included 77 individuals. Among them, 57 were sickle/β thalassemia patients (Group I): 28 from Al-Karama Teaching Hospital (Group IA) and 29 from Babylon Teaching Hospital for Maternity and Children (Group IB). The remaining 20 individuals act as a healthy control group (Group II). Clinical data were gathered, with collection of 5 mL of peripheral blood in order to examine CBC, C-reactive protein (CRP), serum ferritin, and serum visfatin. **Results:** Mean age was (13.14 ± 5.40) years. Males formed (59.74%), whereas females formed the remaining (40.26%). The mean number of annual frequency of VOC events was (3.05 ± 0.95) with no significant difference between the two subgroups. White blood cells count was significantly higher among cases compared to controls ($P = 0.004$). Hemoglobin was significantly lower among cases compared to controls ($P < 0.001$). Also, hemoglobin was significantly higher in cases of group IA compared to group IB with $P = 0.022$. Similarly, hemoglobin A2 (HbA2) was significantly higher in cases of group IA compared to group IB with $P = 0.013$. Serum ferritin was markedly higher among cases compared to controls with $P < 0.001$. Serum visfatin was significantly higher among cases compared to controls with $P < 0.001$. No significant difference was observed between the two subgroups regarding serum ferritin and visfatin. There was positive correlation between visfatin and annual frequency of VOC ($r = 0.821$, $P < 0.001$), moderate negative correlation between visfatin and HbA ($r = –0.46$, $P < 0.001$), moderate positive correlation between visfatin and HbS ($r = 0.54$ and $P < 0.001$), and strong positive correlation between visfatin and ferritin among cases group ($r = 0.60$ and $P < 0.001$) but not in control group. **Conclusions:** Serum visfatin level is significantly higher among patients with sickle/β thalassemia compared to healthy individuals with positive correlation exists between visfatin level and the annual frequency of VOC, ferritin level, and HbS; negative correlation with HbA, among those patients with sickle/β thalassemia. Hemoglobin level and HbA2 percentage significantly higher among Al-Karama hospital patients compared with those in Babylon hospital.

Keywords: Sickle, thalassemia, vaso occlusion crises, visfatin

Introduction

Hemoglobinopathies are the most common inherited diseases of red blood cell (RBC) worldwide. Of these, sickle cell diseases (SCDs) and thalassemia account for most of cases, with 7% carrier rate among the world population.[1,2]

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SCD is an umbrella term that refers to a group of related hemoglobin disorders, which is characterized by the predominance of hemoglobin S within erythrocytes. This includes sickle cell anemia (HbSS), sickle hemoglobin C disease (HbSC), sickle/β thalassemia disease (S/β thal), and many other compound heterozygous conditions. However, the sickle cell trait (HbAS), the carrier state, is not regarded as an SCD.[3]

Sickle/β thalassemia is a type of compound heterozygous hemoglobin disorder, in which the patient inherits two different mutations in the β globin gene, one from each parent. One mutation produces hemoglobin S (sickle hemoglobin) and the other mutation results in production of functional hemoglobin in reduced levels (β thalassemia).[4] Sickle/β thalassemia accounts for less than 10% of patients with SCD. Most of cases have the β^+ phenotype, which is mild in general, and the clinical severity of disease is related to the amount of hemoglobin A present. However, the clinical severity of less frequent β^0 phenotype is closely similar to that of sickle cell anemia.[5]

Vaso occlusion, the key feature of sickle/β thalassemia, is the end result of a series of red cell, endothelial, leukocyte, and platelet interactions, in which the cytokines play a vital role.[6] The severity of sickle/β thalassemia disease in the form of vaso occlusive crises (VOC) frequency may be affected by many factors. Clarification of these factors is essential for prompt and effective management of patients with frequent crises.[7] Of those visfatin, which is a pro-inflammatory adipocytokine, predominantly expressed in visceral adipose tissue, structurally identical to preB-cell colony-enhancing factor (PBEF). It has the ability to exert different deleterious effects on vascular cells, including endothelial inflammation and smooth muscle proliferation.[8] Many studies have indicated its role in inflammatory processes and chronic inflammatory disorders.[9] Visfatin can directly promote inflammation through the activation of the extracellular signal-regulated kinase (ERK)–nuclear factor kappa light chain enhancer of activated B cells (NF-κB)–inducible nitric oxide synthase (iNOS) axis.[10] This feature makes it as a target for development of novel therapeutic strategies in treatment of many inflammatory and metabolic disorders.[8]

Iron overload is another problem in sickle/β thalassemia, because the patient may require regular blood transfusions to prevent or manage disease-related complications especially during VOC. So iron overload is an inevitable consequence of ongoing transfusion.[11,12] Serum ferritin is a noninvasive method widely used for monitoring iron overload. But because of being an acute phase reactant, its level disproportionately increased in relation to true iron load for several weeks after a VOC.[13]

Patients, Materials, and Methods

Study design, sample, and setting

This was an analytical cross-sectional study performed on 77 individuals divided into two groups: Group I and Group II. Group I comprised 57 patients with sickle/β thalassemia. The individuals of Group I were further divided into two subgroups: Group IA comprising 28 patients registered at Hereditary Blood Disease Center, Al-Karama Teaching Hospital, in Baghdad and Group IB comprising 29 patients registered at Hereditary Blood Disease Center, Babylon Teaching Hospital for Maternity and Children, in Babylon, Iraq. Group II comprised 20 age- and sex-matched apparently healthy individuals, served as a control group.

The study was performed over the course of 9 months period from the first of December 2018 until the end of August 2019.

Exclusion criteria

Any patients who had fever, acute illness, malignant, hepatic, renal, autoimmune disorder, surgery or blood transfusion within 30 days before the study, and pregnant ladies were excluded from the study.

Data collection and blood sampling

Patients were interviewed for about 10–15 min after stabilization of their condition by using a predesigned questionnaire. The gathered data included the following: name, age, gender, transfusion history, chelation therapy, numbers and types of painful crises per a year, history of splenectomy, and any other complications.

From each participant in this study, a volume of 5 mL of venous blood sample was collected by venipuncture under an aseptic technique just before blood transfusion. Two mL of blood was poured into the EDTA tube and the residual blood was collected into a gel tube. The blood in the EDTA tube was used for complete blood count (CBC), whereas blood in the gel tube was allowed to clot in water bath at 37°C then centrifuged at 2000× *g* for 5 min to get the serum that was used to measure serum ferritin by using VIDAS (bioMerieux, Marcy-l'Étoile, France); the blood was then separated in small aliquots and kept in deep freezer (below –40°C) until serum visfatin assay was done by sandwich enzyme-linked immunosorbent assay (ELISA) using Human PBEF/visfatin Duo Set ELISA Kit (R&D System, Minneapolis, MN, USA). The high-performance liquid chromatography (HPLC) results were obtained from their records at the center.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software program was used to perform the statistical analysis for this study. Qualitative data were represented as numbers and percentages, whereas continuous numerical data were represented as mean ± standard deviation (SD). Numerical variables were compared

between study groups using the Student's *t* test, whereas categorical variables were compared using the chi-square test. Correlations were assessed using Pearson's product–moment correlation coefficient and Spearman's rank-order correlation coefficient. A value of $P < 0.05$ was considered statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 4 (including the number and the date in 15/7/2017) to get this approval.

Results

This study included a total of 77 individuals comprising 57 patients with sickle/β thalassemia (Group I) and 20 controls (Group II). The patients' group was further divided into two subgroups: Group IA composed of 28 patients registered at Al-Karama Teaching Hospital and Group IB composed of 29 patients registered at Babylon Teaching Hospital for Maternity and Children.

Age of participants ranged from 2 to 20 years with a mean of 13.14 ± 5.40 years and a median of 13 years. Figure 1 shows age group distribution among study groups. No statistically significant difference of age was observed between patients (13.16 ± 5.37) and controls (13.10 ± 5.60) [Table 1]. Similarly, there was no statistically significant difference of age between Group IA (12.25 ± 5.44) and Group IB (14.03 ± 5.25) [Table 2].

Men comprised 59.74% (45/77) of the total study population, whereas women formed the remaining 40.26% (31/77) of them. Chi-square test was used to assess the difference in gender distribution among study groups. No statistically significant difference in gender distribution was observed neither between patients and controls [Table 1] nor between the patients of Group IA and Group IB [Table 2].

The annual frequency of VOC (painful crises) was compared between patients in Group IA and Group IB using Student's *t* test. No significant difference was observed between the two groups [Table 2]. Types of VOC in the study groups are shown in Figure 2.

Regarding splenectomy, patients in Group IA and Group IB were compared. No statistically significant difference was observed between the two groups [Table 2]. Other complications are shown in Figure 3.

Comparisons of CBC parameters (white blood cells (WBC), hemoglobin (Hb), and platelet (Plt) count) were performed twice: first between patients and controls, then between patients of Group IA and Group IB. Student's *t* test was used for those comparisons.

WBC count was significantly higher among patients as compared with controls. On the contrary, hemoglobin level was significantly lower among patients as compared with controls. No significant difference was observed between patients and controls regarding platelet count. Table 1 details the findings.

Hemoglobin level in patients of Group IA was found to be significantly higher than those of Group IB. No significant difference was observed between the two groups regarding WBC or platelet count. Table 2 summarizes the findings.

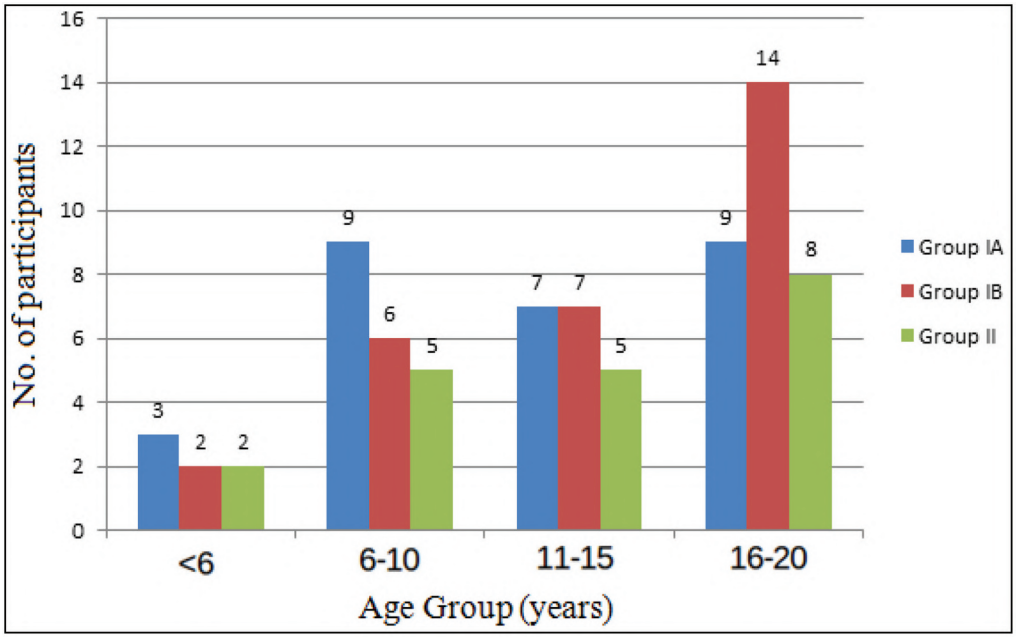

Figure 1: Age group distributions among study groups

HPLC parameters (HbA, HbA2, HbF, and HbS) were compared between patients of Group IA and Group IB using Student's *t* test. There was a statistically significant difference in HbA2 between the two groups. No other significant differences were found. Table 2 describes the findings.

Serum ferritin level was significantly higher in the patients' group compared to the control group [Table 1]. Regarding the two patients' subgroups, no significant difference was observed regarding serum ferritin level, as detailed in Table 2.

Serum visfatin level was also found to be significantly higher in patients' group as compared with control group, as detailed in Table 1. On the contrary, no significant difference in visfatin level was observed between Group IA and Group IB [Table 2].

Spearman's rank-order correlation coefficient was calculated to assess the correlation between visfatin level among patients and the number of VOC per year. There was a strong positive correlation between the two variables: correlation coefficient (r) = 0.821 and $P < 0.001$. Figure 4 shows the finding.

Student's *t* test was used to assess the correlation between visfatin level and splenectomy. No significant correlation was observed between the two variables, as described in Table 3.

Correlations of visfatin level to CBC parameters (WBC, Hb, and Plt count) were assessed by calculating Pearson product–moment correlation coefficient: once within the patients' group, then with the controls group. No significant correlation was observed in either patients [Table 4].

Correlations between visfatin level and each of HPLC parameters (HbA, HbA2, HbF, and HbS) within the case group were also assessed using Pearson product–moment correlation coefficient. There was a moderate positive correlation between HbS and visfatin level, with $r = 0.54$ and $P < 0.001$ [Figure 5]. On the contrary, there was a moderate negative correlation between HbA and visfatin level, with $r = –0.46$ and $P < 0.001$ [Figure 6]. Table 5 summarizes the findings.

Correlation of visfatin level to serum ferritin level was also assessed using Pearson product–moment correlation

Table 1: Comparison of age characteristics between patients and controls

Parameters		Group		*P* Value
		Patients (mean ± SD) or number (%)	Controls (mean ± SD) or number (%)	
Age (years)		13.16 ± 5.37	13.10 ± 5.60	0.967
Gender	Male	34 (59.65%)	12 (60%)	0.978
	Female	23 (40.35%)	8 (40%)	
WBC ($\times 10^9$ /L)		9.79 ± 3.62	8.01 ± 1.58	0.004*
Hemoglobin (g/dL)		8.72 ± 1.34	13.39 ± 1.00	<0.001*
Platelet ($\times 10^9$ /L)		268 ± 153	254 ± 56	0.564
Serum ferritin level (ng/mL)		3358.1 ± 1731.1	134.6 ± 68.1	<0.001*
Serum visfatin level (ng/mL)		5.43 ± 2.41	2.71 ± 0.98	<0.001*

*Significant at $P < 0.05$

Table 2: Comparison of age characteristics between Group IA and IB

Parameters		Group		*P* Value
		Group IA (mean ± SD) or number (%)	Group IB (mean ± SD) or number (%)	
Age (years)		12.25 ± 5.44	14.03 ± 5.25	0.213
Gender	Male	15 (53.57%)	19 (65.52%)	0.358
	Female	13 (46.43%)	10 (34.48%)	
VOC/years		3.11 ± 0.92	3.00 ± 1.00	0.675
Splenectomy	Yes	3 (10.71%)	6 (20.69%)	0.470
	No	25 (89.29%)	23 (79.31%)	
WBC ($\times 10^9$ /L)		10.17 ± 3.52	9.43 ± 3.74	0.442
Hemoglobin (g/dL)		9.13 ± 1.34	8.32 ± 1.23	0.022*
Platelet ($\times 10^9$ /L)		306 ± 137	231 ± 160	0.062
HbA		11.33 ± 11.43	11.47 ± 10.69	0.963
HbA2		4.63 ± 1.00	4.02 ± 0.76	0.013*
HbF		17.39 ± 6.30	18.11 ± 5.82	0.652
HbS		66.65 ± 9.98	66.39 ± 10.46	0.924
Serum ferritin level (ng/mL)		3514.8 ± 1388.6	3206.8 ± 2021.5	0.507
Serum visfatin level (ng/mL)		5.24 ± 2.03	5.61 ± 2.75	0.575

*Significant at $P < 0.05$

coefficient. There was a strong positive correlation between the two variable within the cases group, with $r = 0.60$ and $P < 0.001$ [Figure 7]. However, no significant correlation was observed between the two variables within the control group, with $r = 0.21$ and $P = 0.377$.

Discussion

The study groups and subgroups were confirmed to be statistically comparable regarding age and gender. Overall patients' age range was 2–20 years with a mean of 13.16 ± 5.37 years and a median of 13 years. Men comprised 59.65% of the total patients, whereas women formed the remaining (40.35%) of them. These results were comparable to other Iraqi studies done by Al-Momen[14] and Abbas *et al*.,[15] respectively.

The mean number of VOC events per year in this study was 3.05 ± 0.95, which was higher than the finding by Habashy *et al*.,[8] whereas in the study done by Mukherjee *et al.*[16] in western India, VOC events per year in tribal groups were lower than that in this study but in nontribal groups were higher. The authors explained these results by differences in the underlying disease mutations in different ethnic groups. However, the finding of this study was consistent with that reached by Bitoungui *et al.*[17] in their study of

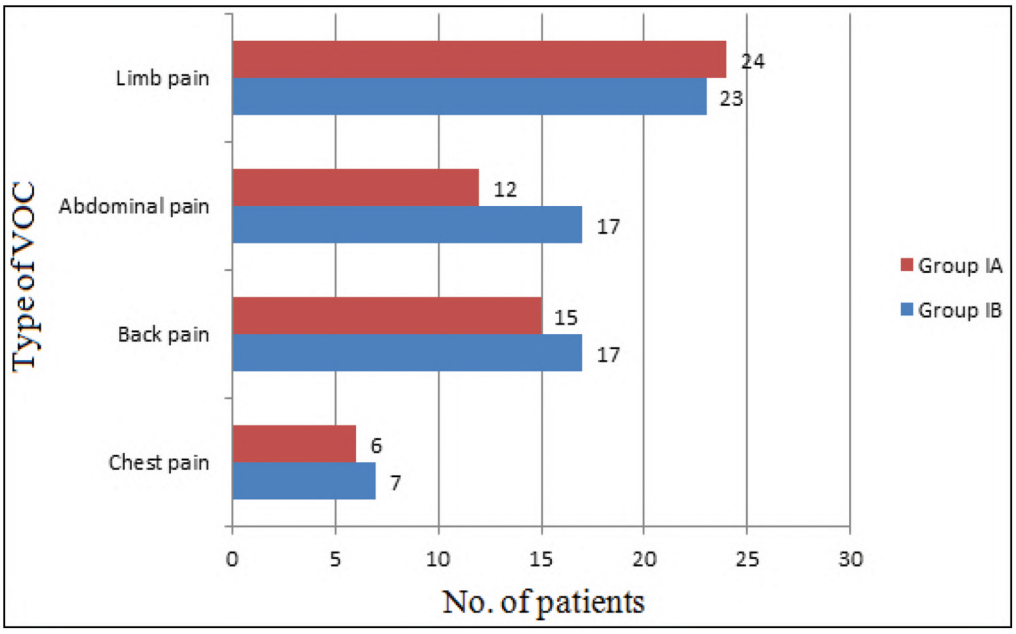

Figure 2: Types of vaso occlusion crises in the study groups

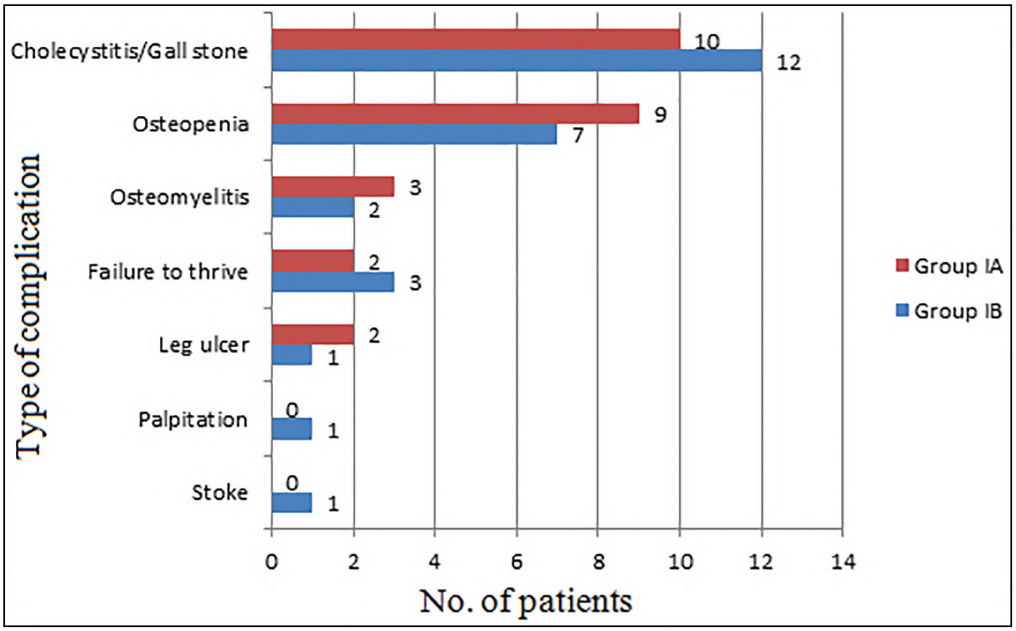

Figure 3: Other complications in patient's subgroups

SCD in Africa. Therefore, the difference in disease clinical severity in different population groups can be explained by variation in the underlying disease mutations.

The majority of patients enrolled in this study had suffered from limb pain during vaso occlusion (painful) crisis, which was similar to the findings reported by Abbas *et al.*[15] and Niscola *et al.*[18] The next most common site of pain was abdominal pain, followed by back pain and chest pain.

Cholecystitis/gallstone was present in more than one-third of the cases. This result was comparable to that obtained by Martins *et al.*[19]

Hemoglobin level was significantly lower among cases compared to controls, with a mean hemoglobin level of 8.72 ± 1.34 g/dL. This finding was closely similar to the finding reported by Jain *et al.*[20] in their study conducted in India in 2015, which included 91 patients with SCD, among which are 36 patients with sickle/β thalassemia. This is in agreement with the study done by Jha *et al.*[21] and Habashy *et al.*[8] This study had also showed a significant difference in hemoglobin levels between Baghdad patients and Babylon patients, with a higher level among Baghdad patients. This might be attributed to several factors including the difference in socioeconomic status, access and use of the health-care services, type of automated hematological analyzer, genetic background (type of β thalassemia mutation and/or co-inheritance of α thalassemia) as well as social and cultural attitudes toward consanguinity. A similar significant difference was observed by Jha *et al.*,[21] in which there was a significant difference in mean hemoglobin level among 10 different geographical locations in India, ranging from 7.92 g/dL in one region up to 8.99 g/dL in another one. The researchers attributed these differences mainly to the variation in the genetic architecture of those ethnic groups, followed by the tradition of limiting marriage within the local communities.

It is worth noting that WBC count was significantly elevated among cases compared to controls, with a mean of 9.79 ± 3.62 ×10^9 /L. This finding was in agreement with the study done by Mishra *et al.*[22]

No significant effect was observed regarding platelet count between cases and controls, with a mean of 268 ± 153 ×10^9 /L. This mean value was comparable to that observed by Shabbir *et al.*[23]

Regarding HPLC parameters, HbA2 was found to be significantly higher among Al-Karama (Baghdad) patients with a mean of 4.63 ± 1.00, compared to Babylon hospital patients with a mean of 4.02 ± 0.76. This value was slightly lower than the value observed by Jain *et al.*,[20] which was 4.86. Similarly, Banerjee *et al.*[24] and Adekile *et al.*[25] found higher values of HbA2 in their studies, but the opposite result was obtained by Jha *et al.*,[21] which was lower than that of this study. The significant difference in HbA2 level between the two geographical regions in this study was supported by the finding of Jha *et al.*[21] who described a highly significant variation in HbA2 among different geographical and ethnic groups.

Interestingly, the proportions of HbA, HbF, and HbS were found to have no significant difference between the two subgroups of cases, which contrasts with the study of Jha *et al.*[21] who confirmed that HbF proportion is also significantly variable among various geographical

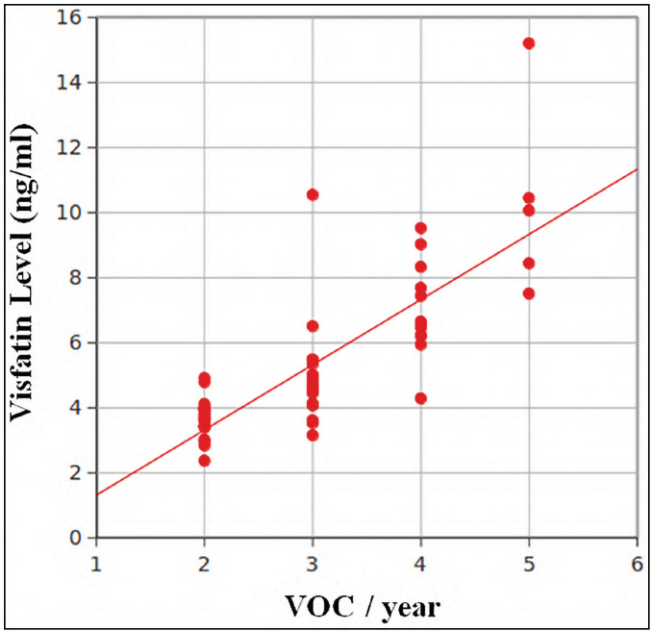

Figure 4: Scatter plot diagram showing the correlation between visfatin level and vaso occlusion crisis per year

Table 3: Correlation of serum visfatin level with splenectomy status

Serum visfatin level (ng/mL)	Splenectomy status		*P* Value
	Splenectomy (*n* = 9)	No splenectomy (*n* = 48)	
Mean	4.55	5.59	0.237
SD	1.11	2.55	
Range	3.42–6.46	2.37–15.20	

Table 4: Correlations of visfatin level with CBC parameters

Parameters		Correlation with visfatin level	
		With patients group (*n* = 57)	With control group (*n* = 20)
WBC (×10^9 /L)	*r*	–0.16	–0.19
	P Value	0.225	0.420
Hemoglobin (g/dL)	*r*	0.02	0.27
	P Value	0.867	0.254
Platelet (×10^9 /L)	r	–0.05	0.38
	P Value	0.710	0.096

regions. This could be due to the difference of the genetic characteristics of Iraqi patients compared to Indian patients.

The values of HbF and HbS in this study are consistent with that reported by Banerjee *et al.*[24] However, HbF values in this study were lower than those shown by Jain *et al.*[20] and the levels of HbS were higher than that observed by Habashy *et al.*[8] Similarly, HbA values were higher than those obtained by Jain *et al.*[20] and Banerjee *et al.*,[24] again these differences might be explained by variation in the underlying disease mutations in different populations.

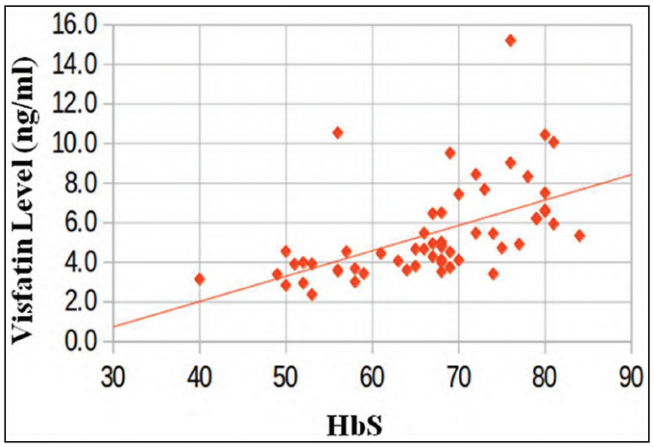

Figure 5: Scatter plot diagram showing correlation between visfatin and HbS

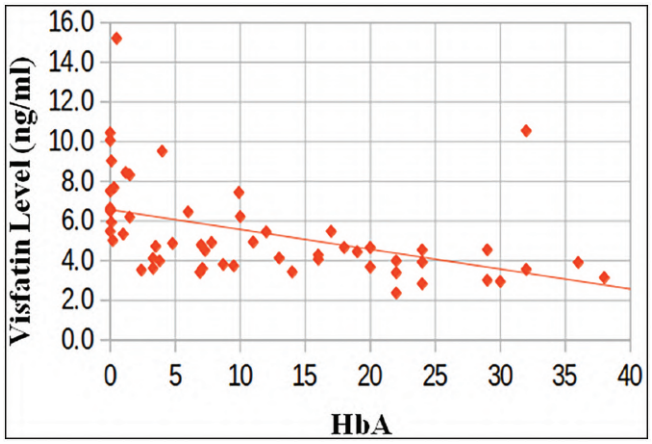

Figure 6: Scatter plot diagram showing correlation between visfatin and HbA

Table 5: Correlations of visfatin level to HPLC parameters within cases group

Parameters	Correlation coefficient	*P* Value
HbA	–0.46	<0.001*
HbA2	–0.12	0.391
HbF	–0.05	0.685
HbS	0.54	<0.001*

*Significant at $P < 0.05$

Serum ferritin level was markedly elevated among cases compared to controls with a mean of 3358.1 ± 1731.1 ng/mL, reaching up to 25 times the value seen in apparently healthy individuals, with no significant difference between the cases subgroups. This finding was much higher that obtained by Al-Momen,[14] Habashy *et al.*,[8] Mishra *et al.*,[22] and Voskaridou *et al.*[26] Patients in this study from both Baghdad and Babylon Hereditary Blood Disease Centers were suffered from inadequate chelation, because of shortage in chelation agents supply, use of agents from non-authentic companies, or frequent shifting from one agent to another depending on availability. This might explain the very high serum ferritin level in this study.

Serum visfatin level was found to be significantly higher in the case group with a mean of 5.43 ± 2.41 ng/mL, with no significant difference between the cases subgroups. The mean value among cases was slightly lower than that described by the study done by Habashy *et al.*[8], with a median of 6.5 ng/mL. This slight difference may be explained by different ELISA kit supplier, underlying genetic mutation, and sample size between the two studies.

Visfatin level was positively correlated with the number of VOC events per a year. This finding shows the possible link between the expression of visfatin in patients with sickle/β thalassemia and the increased frequency of VOC events among them, and suggests the possible use of visfatin level as a predictor for the possible occurrence of VOC events.

The study by Habashy *et al.*[8] showed similar correlation within sickle cell anemia patients, but failed to show such a strong correlation within the sickle/β thalassemia patients. This may be related to the difference in sample size between this study, which enrolled a total of 57 sickle/β thalassemia patients, and the study by Habashy *et al.*, which enrolled a total of 30 SCD patients, of them only 14 sickle/β thalassemia patients.

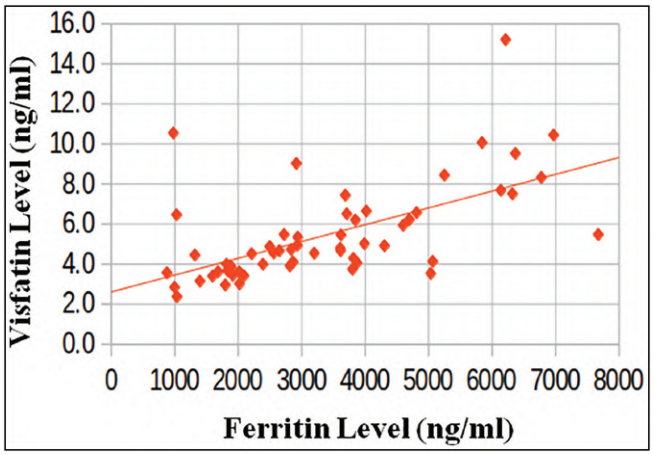

Figure 7: Scatter plot diagram showing correlation between visfatin and ferritin within the cases group

HbA and HbS were shown to have a significant correlation with visfatin level, whereas HbF and HbA2 failed to show such correlation. HbA negatively correlated to visfatin level. On the contrary, HbS and visfatin level showed a positive correlation. This can be explained by the underlying disease pathophysiology, the higher HbS and lower HbA, associated with more disease severity, so higher visfatin level. However, the study by Habashy *et al.*[8] failed to show such statistical correlation.

Regarding CBC parameters, no significant correlation with visfatin level was observed in this study. This finding was consistent with that obtained by Habashy *et al.*[8] in sickle/β thalassemia group. Similarly, no significant correlation was found between serum visfatin level and splenectomy.

Serum ferritin showed a strong correlation with serum visfatin level. The study conducted by Habashy *et al.*[8] showed such correlation within sickle cell anemia patients, but not in sickle/β thalassemia.

Conclusions

The study concludes that serum visfatin level is significantly higher among patients with sickle/β thalassemia compared to healthy individuals, with a positive correlation between serum visfatin level and the annual frequency of VOC, ferritin level, and HbS; negative correlation with HbA, among those patients with sickle/β thalassemia. Hemoglobin level and HbA2 percentage are significantly higher among Al-Karama hospital patients compared with those in Babylon hospital.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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