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Haptoglobin polymorphisms and their relationship to the activities of liver function enzymes in sickle cell anemia and hepatitis C patients

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The importance of the research lies in the fact that it aims to study the genetic polymorphisms of the haptoglobin (Hp) gene in patients with sickle cell anemia, hepatitis C, and sickle cell anemia with hepatitis C, as well as to study the relationship between the polymorphisms of the gene and the liver enzymes (alkaline phosphatase, aspartate aminotransferase, and alanine transaminase). Hp is a type of alpha-2 globulin found in human plasma. Its primary function is to bind to the globin portion of free hemoglobin in the bloodstream. Objectives: Determining the genotypes of the Hp gene in patients with sickle cell anemia and hepatitis C using allele-specific polymerase chain reaction and studying the relationship between genetic polymorphisms and increased liver enzymes (alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase). This study included 130 participants. They were classified to 4 groups: patients with sickle cell anemia (n = 40), patients with hepatitis C (n = 40), sickle cell patients with hepatitis C (n = 10), and a control group (n = 40). DNA was isolated and polymerase chain reaction was performed using genotype-specific primers for the three regions of the Hp gene. The genotypes were determined after electrophoresis on agarose gel and determination of the amplified fraction of each allele. Alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels were measured by colorimetric methods. The results showed that the Hp2-2 genotype was more frequent in all three patient groups than the Hp1-1 or Hp2-1 genotypes. The liver enzyme levels were also significantly higher in the Hp2-2 genotype group than in the other two groups. Hp2-2 was the most prevalent Hp phenotype among the patient groups and it may play a role in the pathogenesis of sickle cell anemia and hepatitis C. The study was approved by the Research Committee of the Thi-Qar Institutional Health Department in 2022.

Key words: *polymorphism, haptoglobin gene, sickle cell diseases, hepatitis C*

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Sickle cell disease (SCD) is an inherited disorder caused by a mutation (HBB; glu(E)6valA; GAG-GTG; rs334) that produces sickle hemoglobin (HbS) [1]. Homozygosity for HbS results in sickle cell anemia (SCA), a severe disease with variable clinical presentations. There are many hypotheses about the reasons for the phenotypic diversity observed in SCA, including environmental and socio-demographic factors [2].

Viral hepatitis primarily damages the liver [3], causing chronic inflammation, fibrosis, cirrhosis, and cancer [4]. During chronic liver infections, viruses persistently manipulate host antiviral defenses and cellular pathways that impact liver homeostasis and disease progression [5].

Haptoglobin (Hp) is an acute-phase protein that binds to hemoglobin and has a genetic polymorphism due to two different alleles encoding for the alpha chain of the protein [6]. There are three phenotypes: Hp1-1, Hp2-1, and Hp2-2. The latter two phenotypes have immunoglobulin-like properties and play a role in the immune response. The effectiveness of Hp in binding hemoglobin depends on the patient's genotype, and the Hp2-2 genotype has the lowest binding affinity, which is associated with increased cellular damage [1].

Studies have reported mixed results on the association between Hp polymorphisms and disease complications in SCA patients. Some studies suggest that the Hp1-1 genotype is protective against kidney injury and cardiovascular disease [7], while others suggest it is a risk factor for neurological or cardiovascular complications compared to the Hp2-2 genotype [1]. There is also mixed evidence on the association between Hp polymorphisms and disease complications in hepatitis C patients. Some studies suggest an association between the Hp1-1 phenotype and chronic hepatitis C [8]. Others found no significant association or even a protective effect for Hp phenotype [9].

Liver disease is a common complication of SCA and hepatitis C, caused by various factors such as intrahepatic sickling, bilirubin, gallstones, transfusion-related hepatitis infections, or excess iron deposition. There are several clinical chemistry tests that can help assess liver function, diagnose, monitor, and understand the prognosis of liver diseases.

MATERIALS AND METHODS

Patients and control groups

The study was carried out in the Labs of College of Science and Al-Hussein Teaching Hospital from June 2022 to January 2023. The samples of the patients included in this study (n = 130) were divided into four groups:

- the first group: 40 healthy controls;
- the second group: 40 patients with SCA;
- the third group: 40 patients with hepatitis C virus;
- the fourth group: 10 patients with SCA and with hepatitis C virus infection.

Their ages ranged from 6 to 54 years. They were randomly selected for the study.

The study was approved by the Research Committee of the Thi-Qar Institutional Health Department in 2022

Blood samples

Five mL of venous blood were taken from each patient and healthy control. Three mL of blood were collected directly in an EDTA free plain tube and allowed to clot. Then serum was separated by centrifugation. After centrifugation, serum was separated and stored at –20°C, and we measured alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) serum concentration. Two mL of blood were collected in an EDTA tube for DNA extraction using Genomic DNA extraction mini kit (Geneaid, Thailand).

DNA extraction and haptoglobin genotyping

Genomic DNA was extracted from blood isolates using Geneaid Genomic DNA Eextraction Kit (Taiwan).

DNA template and polymerase chain reaction

Polymerase chain reaction (PCR) technique was used to amplify the Hp gene according to [1] and we used the following primers for the PCR technique. The primers (forward and reverse) are specified in *table 1*. The kit was provided by Geneaid Genomic DNA Extraction Kit company (Taiwan).

All samples were submitted to three reactions (1, 2, and 3) and the genotypes were defined after electrophoresis on a 1.5% agarose gel and identification of the amplified fragment for each allele.

Table 1
The product names, primers used, annealing temperature and the products size for the Hp gene

Name	Pb	AT	Primer name	Oligonucleotide sequence (5′-3′)
Hp2	935	58	F3	CAGGAGTATACACCTTAAATG
			C42	TTACACTGGTAGCGAACCGA
Hp1S	1200	58	C51	GCAATGATGTCACGGATATC
			S2	TTATCCACTGCTTCTCATTG
Hp1F	1400	58	F3	CAGGAGTATACACCTTAAATG
			C72	AATTTAAAATTGGCATTTCGCC

Estimation of activity and concentrations of enzymes

ALP in blood serum: serum ALP activity was estimated using ready-made assay kits from the French company (Biolabo).

AST activity in blood serum: serum AST activity was estimated using ready-made assay kits from the French company (Biolabo).

ALT activity in blood serum: serum ALT activity was estimated using ready-made assay kits from the French company (Biolabo).

Statistical analysis

Data were expressed as mean ± SD. The comparison between each patient group and the healthy control group was performed using one-way ANOVA along with a least significant difference (LSD) test to calculate the significant differences among the means of these groups. $p \leq 0.05$ was considered significant. All statistical analyses were done using a computer and the Statistical Package for Social Sciences (SPSS), version 20.

RESULTS

Molecular analysis

Frequency of Hp types in different groups

Table 2 shows the distribution of the Hp phenotypes among the patient groups and the control group. It was observed that the Hp2-2 phenotype was the most prevalent among all groups. We observed a significant increase ($p \leq 0.05$) compared with the rest of the phenotypes where the proportions were as follows: in the healthy controls - Hp1-1 (0.30), Hp2-2 (0.50), Hp2-1 (0.20), in the sickle cell patients – Hp1-1 (0.13), Hp2-2 (0.55), Hp2-1 (0.32), in the hepatitis C patients – Hp1-1 (0.13), Hp2-2 (0.63), Hp2-1 (0.24), in the sickle cell with hepatitis C patients – Hp1-1 (0.20), Hp2-2 (0.60), Hp2-1 (0.20). The results showed that there was no significant difference between the patients and healthy controls in the distribution patterns, and the Hp2-2 phenotype was the most prevalent among the cohorts.

The highest prevalence was in the group of patients with hepatitis C: Hp2-2 (0.63), compared to other groups of patients.

Biochemical study

Determination of ALP concentration and its association with haptoglobin genotypes

According to the groups

The results presented in *table 3* indicate a significant increase ($p \leq 0.05$) in the concentration

of ALP in all patients compared with the healthy control group and indicate a decrease ($p \leq 0.05$) in the concentration of ALP in the sickle cell patients with hepatitis C compared to the other patient groups.

According to haptoglobin types

According to the statistical analysis of data provided in *table 3*, the highest ($p \leq 0.05$) ALP concentration was observed in healthy controls with the Hp1-1 type.

Biochemical study

Determination of ALP concentration and its association with haptoglobin genotypes

According to the groups

The results presented in *table 3* indicate a significant increase ($p \leq 0.05$) in the concentration of ALP in all patients compared with the healthy control group and indicate a decrease ($p \leq 0.05$) in the concentration of ALP in the sickle cell patients with hepatitis C compared to the other patient groups.

According to haptoglobin types

According to the statistical analysis of data provided in *table 3*, the highest ($p \leq 0.05$) ALP concentration was observed in healthy controls with the Hp1-1 type.

Determination of AST concentration and its association with haptoglobin genotypes

According to the groups

The results presented in *table 4* indicate a significant increase ($p \leq 0.05$) in AST concentration in all patients for three types of Hp compared to the control group, and the highest significant increase was observed ($p \leq 0.05$) in the sickle cell patients with hepatitis C compared with other patient groups.

Table 2
The distribution of the Hp types and their frequency

Group	Type	Type frequency
Sickle cell patient	Hp1-1	0.13
	Hp2-2	0.55
	Hp2-1	0.32
Hepatitis C patient	Hp1-1	0.13
	Hp2-2	0.63
	Hp2-1	0.24
Sickle cell with hepatitis C patient	Hp1-1	0.20
	Hp2-2	0.60
	Hp2-1	0.20
Healthy control	Hp1-1	0.30
	Hp2-2	0.50
	Hp2-1	0.20
p value = 0.61		

According to haptoglobin types

The results in *table 4* indicate an increase in AST concentration in the Hp2-2 type group among all participating groups compared to the rest of the Hp type groups, but it is not significant.

Determination of ALT concentration and its association with haptoglobin genotypes

According to the groups

The results presented in *table 5* indicate a significant increase ($p \leq 0.05$) in the ALT concentration in all patients for three types of Hp compared to the control group, and the highest significant increase was observed ($p \leq 0.05$) in the sickle cell patients with hepatitis C compared to other patient groups.

According to haptoglobin types

The statistical analysis of data provided in *table 5* shows the highest ($p \leq 0.05$) ALT concentration in the patients with the Hp2-2 type (all patient groups).

Table 3
A comparison of serum ALP concentrations in the sickle cell, hepatitis C, sickle cell with hepatitis C patients and healthy controls

Type of Hp group	Hp1-1 (M ± SD)	Hp2-2 (M ± SD)	Hp2-1 (M ± SD)	LSD
SCA	289.40 ± 36.27 Ab	314.77 ± 21.27 Aa	273.69 ± 29.99 Ac	15.88
HCV	276.20 ± 22.83 Ab	310.48 ± 15.14 Aa	274.10 ± 39.30 Ab	16.18
SCA and HCV	281.00 ± 11.41 Ab	299.00 ± 25.50 Ba	282.10 ± 21.00 Ab	13.00
Control	134.66 ± 18.228 Ba	124.80 ± 28.145 Bb	133.25 ± 20.90 Ba	5.86
LSD	15.32	17.14	9.44	

Notes. Values are expressed as mean ± SD. Different capital letters denote significant differences ($p \leq 0.05$) between the groups. Different small letters denote significant differences ($p \leq 0.05$) between the Hp types.

Table 4
A comparison of serum AST concentration in the sickle cell, hepatitis C, sickle cell with hepatitis C patients and healthy controls

Type of Hp group	Hp1-1 (M ± SD)	Hp2-2 (M ± SD)	Hp2-1 (M ± SD)	LSD
SCA	56.80 ± 4.38 Aa	57.72 ± 9.95 Aa	56.07 ± 2.60 Aa	3.92
HCV	55.40 ± 11.19 Aa	56.24 ± 12.73 Aa	54.40 ± 10.87 Aa	3.163
SCA and HCV	55.50 ± 9.19 Aa	59.00 ± 6.41 Aa	56.66 ± 8.11 Aa	4.51
Control	12.50 ± 1.87 Ca	15.60 ± 4.53 Ba	13.81 ± 2.98 Ba	2.50
LSD	3.60	5.51	7.4	

Table 5
A comparison of serum ALT concentrations in the sickle cell, hepatitis C, sickle cell with hepatitis C patients and healthy controls

Type of Hp group	Hp1-1 (M ± SD)	Hp2-2 (M ± SD)	Hp2-1 (M ± SD)	LSD
SCA	15.33 ± 7.607 Ca	17.40 ± 2.61 Ca	15.50 ± 4.041 Ca	1.92
HCV	48.20 ± 7.293 Bb	62.63 ± 13.26 Ba	47.00 ± 11.902 Bb	5.73
SCA and HCV	50.0 ± 7.582 Bb	61.64 ± 5.55 Ba	49.20 ± 14.140 Bb	4.43
Control	55.20 ± 11.41 Ab	68.00 ± 7.00 Aa	59.33 ± 17.09 Ab	5.00
LSD	3.78	5.00	4.80	

DISCUSSION

The current study is the first study showing the Hp genotype distribution among SCA, hepatitis C and SCA with hepatitis C patients in Iraq.

It revealed that the Hp2-2 genotype was the most common: it was found in 55% of SCA patients, in 63% of hepatitis C patients, and in 60% of SCA and hepatitis C patients. There were no significant differences in the distribution of the three Hp genotypes between the patients and healthy controls (*table 2*).

The findings are consistent with those reported by [10], who observed a higher frequency of the Hp2 genotype in SCA patients compared to the control group. Their study showed a significant difference ($p < 0.05$) in the Hp2-2 genotype frequency, with SCA patients having a higher frequency (54%) compared to sickle cell trait (42%) and healthy individuals (38%).

These results are like those obtained by [11] in Kuwaiti patients. However, these are different from those of [1] in Nigeria, they found that Hp genotype distribution among the patients and controls were Hp1-1, 43 (42.6%); Hp2-1, 40 (39.6%); Hp2-2, 18 (17.8%) and Hp1-1, 35 (54.7%); Hp2-1, 24 (37.5%); Hp2-2, 5 (7.8%), respectively, with no difference between the SCA patients and a control group ($p < 0.05$).

Hp allele frequencies exhibit notable variations across different geographical regions and ethnic groups. The Hp-1 allele frequency is found to be the lowest in Southeast Asia and the highest in Africa and South America, as reported in previous studies [12, 13]. In this study, the analysis of the Hp genotypes was performed by processing PCR products containing single nucleotide polymorphisms, which were then visualized under UV light after staining with ethidium bromide.

Hp is a protein present in both mammals and humans. In humans, Hp polymorphism results in two dominant alleles (Hp1 and Hp2) located on chromosome 16q22, leading to three genotypes: HP1-1, HP2-1, and HP2-2. The HP1-1 genotype is prevalent in Africa and Latin America but rare in Southeast Asia. Despite this, it has the highest efficiency and biological activity in terms of binding free plasma hemoglobin and suppressing inflammation [7]. In contrast, the Hp2-2 variant has the lowest capacity to perform these functions. The Hp2-1 variant has intermediate biological and anti-inflammatory abilities compared to Hp1-1 and Hp2-2. These conclusions are supported by previous studies [11].

Hp polymorphism is recognized as a significant marker in vascular diseases and can provide protection against the development of certain complications. Although the lower antioxidant capacity and higher inflammatory response of Hp2-2 do not appear to have a significant impact on the clinical course of sickle cell disease in the patients studied, Hp polymorphism may contribute to the diverse range of clinical manifestations that are characteristic of this disease when combined with other genetic and environmental factors [4].

In this study, liver function tests in sickle cell disease patients compared to controls revealed a statistically significant difference in the activities of serum enzymes such as ALP, AST, and ALT ($p < 0.05$). These findings are consistent with previous studies conducted by [14–16].

The high activities of serum ALP observed in sickle cell patients can be due to both bone and liver complications typically associated with SCA. This finding is consistent with previous studies conducted by [9, 17] which suggest that the increased serum ALP could be due to liver ischemia, cholestasis, or vaso-occlusive crisis involving the bone.

According to the results of our study, there was a high enzyme activity of ALT in sickle cell patients, which is consistent with previous studies conducted by [18, 19]. These studies suggested that liver enlargement seen in sickle cell patients is not solely due to hepatic disease, as ALT abnormality is specific for hepatic injury. Additionally, our study found a high activity of AST in SCA patients, which may be due to the presence of sickled red blood cells in the lobular parenchyma of the liver, as suggested by [20].

Based on the results of our study, there was a statistically significant increase ($p \leq 0.05$) in ALP activity in both hepatitis C patients and SCA patients with HCV compared to the control group. This finding

is consistent with previous studies conducted by [21, 22], which also found that the high level of this enzyme in the blood may be a result of a defect or damage in the liver that leads to an increase in the enzyme in the blood or it may increase due to oxidative stress and the formation of free radicals.

The increased levels of ALP in the blood may lead to harmful structural and functional changes in liver cells, which can affect the permeability of the cell membrane and disrupt the transport of metabolites. The damage to liver cells causes the release of this enzyme into the bloodstream. Previous studies conducted by [23, 24] have shown that alkaline phosphatase is primarily associated with the plasma membrane of liver cells.

Our study found a statistically significant increase ($p \leq 0.05$) in the efficacy of AST and ALT in the patients infected with hepatitis C compared to the control group. These findings are consistent with previous studies conducted by [17, 25].

The increase in AST and ALT levels in patients infected with hepatitis C may be due to the formation of free radicals that cause peroxidation of fats in the cell membrane, resulting in changes in its permeability and destruction. This leads to the leakage of these enzymes into the bloodstream and an increase in their levels in the serum [26].

As for the other side of the study, the current results showed differences in the concentrations of liver enzymes in relation to the patient groups, distributed among the Hp patterns. Our study results support the hypothesis that individuals with certain Hp genotypes, such as Hp2-2, which are associated with very poor biological activities, may have a higher risk of complications from certain health conditions.

The results obtained from our study indicate that there were variations in the concentration of liver enzymes between different Hp types, with type 2-2 showing a greater increase in enzyme levels compared to other types.

Our study findings support previous research that suggests a link between genotype 2-2 and an increase in clinical complications, including elevated levels of liver enzymes. For instance, studies conducted by [27] found that SCA patients with the Hp2-2 genotype had significantly higher levels of ALP, ALT, and AST compared to individuals with the Hp1-1 or 2-1 genotype.

Similarly, studies have shown that patients with the Hp2-2 genotype may be more likely to experience clinical complications than those with other Hp genotypes. For example, a study by [26] found that patients with sickle cell disease who had the Hp2-2 genotype had higher levels of ALP, ALT, and AST, which are liver enzymes that can be elevated in people with liver damage. Similarly, a study by [28] found that patients with hepatitis C who had the Hp2-2 genotype were more likely to experience clinical complications, such as liver failure. And a study by [7, 29] found that patients with non-alcoholic steatohepatitis who had the Hp2-2 genotype were also more likely to experience clinical complications, such as liver fibrosis.

It is important to note that there are also studies that report results that are contrary to our findings. For instance, studies conducted by [1, 11, 30] found no significant association between Hp genotype and liver enzyme levels in SCA patients. Additionally, a study by [31] on hepatitis C patients suggested that the Hp1-1 genotype is most strongly associated with clinical complications.

The exact mechanism by which the Hp2-2 genotype may increase the risk of clinical complications is not fully understood. However, it is thought that the Hp2-2 genotype may be associated with impaired clearance of free hemoglobin, which can lead to inflammation and oxidative stress. This can damage cells and tissues and may increase the risk of developing clinical complications.

CONCLUSION

The study found that the Hp2-2 genotype is more common in SCA, hepatitis C, and SCA with hepatitis C patients than in healthy controls. This suggests that the Hp2-2 genotype may be a risk factor for liver complications in patients with these diseases. However, more research is needed to confirm these findings and to determine the underlying mechanisms by which the Hp2-2 genotype may increase the risk of liver complications.

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The author declares that there is no conflict of interest.

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