Hepatic and Renal Status of Patients with Sickle Cell-β Thalassemia in Thi-Qar Province/Iraq

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Abstract

The present study was designed to evaluate the biochemical parameters which related withthe hepatic and renal status in sickle cell /β thalassemia patients. Patients with Hb S/β- Thal (n=100) 53 males and 47 females were on follow up in the Thi-Qar Center for Hereditary Blood Disease, Thi-Qar province, Iraq who were included in this study and age and sex matched healthy persons (n=50) as controls. The results showed that non-significant difference in a spartate transaminase (AST), alkaline phosphate (ALP) and urea in sickle cell /β thalassemia patients compared with the control groups. Alanine transaminase (ALT) and creatinine level decreased in sickle cell /β thalassemia patients compared with control, while, Glomerular filtrate rate(GFR) increased in sickle cell /β thalassemia patients compared with the control. The result showed non-significant difference between male and female in AST, ALT, ALP, urea and creatinine while increased significant in male patients when compared with female patients. The study showed significant difference of AST, ALP, urea, creatinine and GFR among age groups in patients with sickle cell /β thalassemia, while, there was non-significant difference of ALT among age groups in patients with sickle cell /β thalassemia.

Keywords: Sickle Cell /β Thalassemia, ALT, AST, ALP Urea, Creatinine and GFR.

Introduction

Sickle cell disease (SCD) results from a single amino acid substitution in the gene encoding the β-globin subunit(β6Glu> Val) that produces the abnormal hemoglobin named HbS. SCD has different genotypes with substantial variations in presentation and clinical course The combination of the sickle cell mutation (Hb S) and beta-thalassemia mutation (β Thal) gives rise to a compound heterozygous condition known as sickle cell /β thalassemia (Hb S/ β Thal), which was first described in 1944 by Silvestroni and Bianco[1].The polymerization of deoxygenated Hb S (sickling) is the primary event in the molecular pathogenesis of SCD. However, this event is highly dependent on the concentration of Hb S, and type and concentration of the other typesof Hb. Therefore, the major primary genetic determinant ofthe severity of SCD is the genotype [2].Many different β-Thal mutations have been associated with Hb S, and the molecular basis of the thalassemia in HbS/ βThal individuals reflects the spectrum of β-Thal mutations observed in a particular population [3].

HbS/βThalleads to quantitatively different β-globin synthesis and consequently to different amounts of Hb A. This fact results in variable clinical manifestations, ranging fromnearly asymptomatic to a severe condition similar to sickle cellanemia (homozygous Hb S).There is no consensus about the classification of Hb S/ βThal, but it is usually classified in two types: Hb S/ β^0Thal and Hb S/ β^+Thal. Hb S/ β^0Thal, which β Globin production is zero, is often clinically indistinguishable from sickle cellanemia(SCA), Sickle cell β^+ thalassemia, where β globin production is less than normal and the milder form is designated as Sickle cell/β^{++} thal with high Hb A (20-30%)[4].

The thalassemia acts on sickled red blood cells, inducing microcytosis, hypochromia, and Hb F is elevated. This result is an improvement of the circulatory competence of these cells, a reduction of hemolysis, and a small increase in Hb concentration and in packed cell volume.

However, these effects are not accompanied by any reduction in vaso-occlusive events, probably due to the great number of Hb S-containing red blood cells resulting in increased blood viscosity which can affect any organ [5].

Clinical severity varies widely from sickle cell trait (heterozygous) to sickle cell anemia (homozygous). SCD patients suffer with varied clinical and physical problems including urinary tract infection, gross hematuria, exertional heat illness and idiopathic sudden death [6]. Our study intended to find out hepatic function and renal function status of patients with sickle cell-β thalassemia from Thi-Qar province, Iraq.

Methods

This study comprises of 100 Sickle cell/β thalassemia and 50 healthy individuals as control group who same sex and age range with patients. Intravenous blood was collected and centrifuged at 3000 rpm for separation of serum to perform biochemical parameters. Urea by Photometric method [7], Creatinine, by Kinetic method [8], standardized serum creatinine was used to calculate eGFR [9].The equation is as follows: **eGFR = 175 *(sCr)$^{\wedge -1.154}$ *(Age)$^{\wedge -0.203}$** Age and sCr = serum creatinine concentration was measured in years. This formula is for white males. For females was multiplied by 0.742,Aspartate transaminase, Alanine transaminase , by Colorimetric method[10] Alkaline phosphatase by Colorimetric method(11), were carried out by using commercially available kits.

Statistical Analysis

Statistical analysis was done using the software SPSS version 23.0; the results were expressed as mean± standard deviations (SD).T test and one way ANOVA test were used to compare parameters in different studied groups. P-values (P< 0.05) were considered statistically significant.

Result

Table 1 showed effect of sickle-βthal on hepatic function parameters revealed that non-significant difference of AST and ALP in sickle cell /β thalassemia patients compared with the control group, while ALT decreased significantly in sickle cell /β thalassemia patients compared with the control group.

Table- 1: Effect of sickle-βthal onhepatic function parameters

Parameter	Groups	N.	mean±SD	P
AST	control	50	12.540±5.617	0.068
	Sickle -thal	100	10.685±6.184	
ALT	control	50	9.740±4.034	0.00
	Sickle-thal	100	3.150±2.579	
ALP	control	50	100.814±22.747	0.503
	Sickle -thal	100	96.908±48.395	

Table 2 shows effect of sickle-β thal on hepatic function parameters of male revealed that nn-significant difference of AST and ALP in male patients compared to male control, while ALT decreased significantly in male patients compared with male control.

Table -2: Effect of sickle-βthal on hepatic function parameters of male patients.

Parameter	Groups	N	mean±SD	P
AST	Control	24	13.166±6.322	0.144
	Sickle –thal	53	10.858±6.247	
ALT	Control	24	10.583±4.781	0.000
	Sickle-thal	53	3.169±2.391	
ALP	Control	24	102.063±21.760	0.765
	Sickle –thal	53	99.858±42.669	

The present study showed non significant difference of AST and ALP level in female patients compared with female control, while ALT decreased significantly in female patients compared with female control(table 3).

Table- 3: Effect of sickle-βthal on hepatic function parameters of female patients.

Parameter	Groups	N.	mean±SD	P
AST	Control	26	11.961±4.935	0.270
	Sickle –thal	47	10.489±6.174	
ALT	Control	26	8.961±3.091	0.000
	Sickle-thal	47	3.127±2.802	
ALP	Control	26	103.583±24.653	0.571
	Sickle –thal	47	98.154±56.261	

Table 4 shows effect of gender on hepatic function parameters of sickle-βthal patients. The result showed non-significant difference of AST, ALT and ALP in male patients compared with female patients.

Table- 4: Effect of gender on hepatic function parameters of sickle-βthal patients

Parameters	Groups	N.	mean±SD	P
AST	Male	53	10.858±6.247	0.767
	Female	47	10.489±6.174	
ALT	Male	53	3.169±2.391	0.936
	Female `	47	3.127±2.802	
ALP	Male	53	99.858±42.669	0.526
	Female	47	93.580±54.415	

The results showed non-significant difference (p≤0.05) of AST level of patients with age groups (1-10, 11-20, 21-30 and 31-40 years) while, there was significant increase in age groups(11-20 years)when compared them with age group (>40 years).

The results showed non-significant difference (p≤0.05) of ALT level of patients among age groups.

There was non-significant difference (p≤0.05) of ALP level of patients with age groups(1-10, 11-20 and 31-40 years), also, non-significant difference (p≤0.05) of ALP level of patients with age groups(21-30 ,31-40 and >40 years)., while, there was a significant increase(p≤0.05) in age groups(1-10 and 11-20 years) compared with age groups (21-30 and >40 years) (table 5).

Table -5: Effect of age on hepatic function parameters of sickle-βthal patients

Age years	N.	Parameters(Mean±SD)		
		AST U/L	ALT U/L	ALP U/L
1-10	32	10.609±6.166^{ab}	2.468±1.684^{a}	106.846±46.657^{a}
11-20	41	12.000±7.348^{a}	3.682±3.297^{a}	107.457±56.836^{a}
21-30	15	8.933±3.195^{ab}	3.333±2.468^{a}	60.930±17.774^{b}
31-40	5	8.800±2.774^{ab}	3.600±1.673^{a}	79.100±7.802^{ab}
>40	7	8.428±4.157^{cb}	2.428±1.133^{a}	64.397±9.437^{b}
L.S.D		3.238	1.348	25.088

Note: non-identical superscript (a,b or c …etc). were considered significantly differences (P≤ 0.05), to compare vertically, LSD: Low significantly differences.

The results showed non-significant difference of urea in sickle cell /β thalassemia patients compared with the control group.

Creatinine decreased significantly ($p \leq 0.05$) in sickle cell /β thalassemia patients compared with the control group, while GFR increased significantly in patients with sickle cell /β thalassemia compared with the control group(table 6).

Table- 6: Effect of sickle-βthal on renal function parameters

Parameters	Groups	N.	Mean±SD	P
Urea Mg/dl	Control	50	26.354±9.369	0.157
	Patient	100	28.827±11.222	
Creatinine Mg/dl	control	50	0.951±0.280	0.00
	Patient	100	0.688±0.295	
GFR (ml/mim/1.73m²)	Control	50	104.090±36.907	0.00
	Patient	100	174.803±95.647	

The results showed non-significant difference of urea in male patients with sickle cell /β thalassemia compared with male control.

Creatinine decreased significantly ($p \leq 0.05$), while GFR increased significantly in male patients with sickle cell /β thalassemia compared with the male control group(table 7).

Table- 7: Effect of sickle-βthal on renal function parameters of male patients

Parameters	Male	N.	Mean±SD	P
Urea Mg/dl	Control	24	27.997±10.762	0.899
	Patient	53	27.658±10.989	
Creatinine Mg/dl	Control	24	1.058±0.339	0.00
	Patient	53	0.715±0.334	
GFR (ml/mim/1.73m²)	Control	24	110.089±48.618	0.00
	Patient	53	197.904±108.265	

Table 8explained theeffect of sickle-β thal on renal function parameters of female revealed that urea and GFR increased significantly in female patients as compared to healthy female while Creatinine decreased significantly in female patients when compared to healthy female.

Table -8: Effect of sickle-βthal on renal function parameters of female

Parameters	Female	N.	Mean±SD	P
Urea Mg/dl	Control	26	24.837±7.780	0.022
	Patient	47	30.145±11.453	
Creatinine Mg/dl	Control	26	0.852±0.162	0.00
	Patient	47	0.658±0.244	
GFR (ml/mim/1.73m²)	Control	26	98.55±20.706	0.00
	Patient	47	148.739±71.600	

Table 9 showed effect of gender on renal function parameters of sickle-βthal patients. There was non-significant difference ($p \leq 0.05$) in urea and Creatinine levels of patients compares with the control group, while, GFR increased significantly in in male patients compared with female patients.

Table- 9: Effect of gender on renal function parameters of sickle-βthal patients

Parameters	Groups	N.	Mean ±SD	P
Urea Mg/dl	Male	53	27.658±10.989	0. 272
	Female	47	30.145±11.453	
Creatinine Mg/dl	Male	53	0.715±0.334	0.511
	Female	47	0.658±0.244	
GFR (ml/mim/1.73m²)	Male	53	197.919±108.254	0.034
	Female	47	148.739±71.600	

The results showed non-significant difference ($p \leq 0.05$) of urea level of patients with age groups (1-10, 11-20 & 21-30 years) ,also non-significant difference($p \leq 0.05$) of urea level with age groups(31-40 and >40 years) while, these significant decrease in age groups(1-10, 11-20 & 21-30 years)when compared them with age groups (31-40 and >40 years).

The results showed non-significant difference ($p \leq 0.05$) of creatinine level of patients with age groups (1-10, 11-20, 21-30 and >40 years).while there was a significant increase ($p \leq 0.05$) in age groups (21-30 and >40 years) compared with age group (31-40).

The results showed non-significant difference ($p \leq 0.05$) of GFR of patients with age groups(1-10, 11-20 and 31-40 years), also, non-significant difference ($p \leq 0.05$) of GFR of patients with age groups(21-30 and 31-40).In addition The results showed non-significant difference ($p \leq 0.05$) of GFR of patients with age groups(21-30 and >40 years), while, there was a significant increase($p \leq 0.05$) in age groups(1-10 and 11-20 years) compared with age groups (21-30 and >40 years) (table 10).

Table -10: Effect of age on renal function parameters of sickle-βthal patients

Age (years)	N.	Parameters (Mean±SD)		
		Urea Mg/dl	Creatinine Mg/dl	GFR (ml/mim/1.73m²)
1-10	32	28.461±10.244[b]	0.667±0.292[ab]	200.370±81.724[a]
11-20	41	29.025±10.767[b]	0.663±0.298[ab]	192.041±114.997[a]
21-30	15	23.496±7.396[b]	0.808±0.330[a]	115.704±39.003[bc]
31-40	5	34.416±7.704[a]	0.568±0.196[b]	151.774±44.661[ab]
>40	7	36.780±20.585[a]	0.773±0.241[a]	100.057±46.798[c]
L.S.D		5.760	0.155	47.575

Note: Legend as in table 5

Discussion

Our results showed non-significant difference of AST and ALP in sickle cell-β thalassemia patients compared to control group, while ALT decreased significantly in sickle cell-β thalassemia patients when compared to control group although all three enzymes within normal range . This agree with other studies

conducted by[12,13] who reported that 25% and 31% respectively of the patients with SCD had normal enzymes(AST,ALT and ALP) [14]. revealed AST, ALT and ALP in HbS/β thal lower than SCA, also they revealed no significant difference in mean ALT between HbS/β thal patients and control [15]. revealed no significant difference in means ALT and ALP in SCD when compared them with control, also they revealed mean ALT in patients lower than control [16]. revealed no significant difference in means ALT and AST in SCD when compared them with control. Also our result showed same result in both male and female patients with sickle-thalassemia as compared with their healthy counterparts.

In addition the result showed non-significant difference between male and female patients ofAST, ALT and ALP. This same result with study conducted by [13].This is due to the fact that hemoglobinpathies are an autosomal recessive disease caused by abnormalities in the β-globin gene located on chromosome 11. Since this disease is unaffected by sex variable, both sex are equally affected with sickle cell/β thalassemia.

The biochemical abnormalities vary and in most cases do not correlate with the severity of insult or even histological findings [17]. Serum transaminases - alanine transaminase (ALT), aspartate transaminase (AST) are usually elevated from the normal. The transaminase levels also fall rapidly followed by resolution of crisis [18].

When compared hepatic function parameters according age of sickle-thal patients, the result revealed, the highest mean AST in 11-20 age groups. There was no significant difference ($p \leq 0.05$) in mean ALT among age groups .In addition the result showed the highest mean ALP in 1-10 and 11-20 age groups in comparison with other age groups. The clinical features of HbS- βthal are extremely variable, ranging from a completely asymptomatic state to a severe disorder similar to homozygous sickle cell disease [19] .In addition our result showed the highest mean ALP in 1-10 and 11-20 age groups in comparison with other age groups.Average values of alkaline phosphatase vary with age and are relatively high in childhood and puberty and lower in middle age and higher again in old age [20].

Many studies confirm increase significant in AST, ALT and ALP activity in patients with hemoglobinpathy when compared them with control [21-24]but our study showed means AST,ALT and ALP in patients within normal range and lower than control. Variation between our study and previous studies may be explained by different locality, different number of studied patients, variations in ages of studied patients, variations in severity of disease, variations in degree of iron overload and compliance with iron chelating agents. Sickle cell hepatopathy is a spectrum of disease manifestations with varying levels of severity due acute or chronic changes within the hepatobiliary system in patients with sickle cell hemoglobinopathy [25].

The degree and rate of enzymes alteration may provide minor and nonspecific clues to diagnosis, but the presence of symptoms and the patient's history, with particular emphasis on comorbid conditions, may provide fundamental clues. Liver ultrasound may reveal the presence of bile duct dilation, demonstrate signs of chronic liver disease or even liver cirrhosis, and identify hepatic masses [26].

The result showed non-significant difference of urea in sickle-thalassemia patients compared to control group. This agrees with study conducted by [27]. Who reported means Urea were similar in the sickle homozygous and sickle β-thalassemia patients as well as controls. Also resent study showed same result conducted by [28] but in contrast to that of [29] who found a significant difference in the mean serum urea. However, consideration must be given to the fact that diet influences plasma urea and creatinine levels [30]. Also the result show not significant difference between male patients and male control in urea but there was increase significant between female patients and female control this may be related to GFR which lower in female control than in female patient. Although not significant difference in means urea between male and female patients .The value of urea as a test of renal function depends on the observation that serum/plasma urea concentration reflects GFR: as GFR declines, plasma/serum urea rises [31].

Our study showed urea is increased significantly in younger patients with sickle cell but it is typically reduced in older patients. Mean urea showed increase with age specially which mostly indicates permanent involvement after repeated insult to kidney [32].

The result showed significant decreased of creatinine in sickle-thalassemia patients compared to control group while GFR increased significant in sickle-thalassemia patients compared to control group. Also, creatinine was observed to be significantly lowered when male and female sickle cell disease patients were compared with their respective controls. There was no gender difference between the male and female patients.

This result is quite identical to the other study conducted by [33]. This reduced levels of creatinine observed in sickle cell patients may be attributed to reduced muscle mass seen in Sickle cell anemia patients. In SCD, there are several abnormalities in proximal tubular function with increased rate of creatinine secretion [34] .

The result show that GFR increased significantly in sickle-thalassemia patients when compared to control group. This agreement with other studies conducted by [35,36] .SCD patients have Hb S content, which leads to sickling of the red blood cells and the acidic, hypoxic and hypertonic environment of the renal medulla leads to vaso-occlusion and consequently to injuries of the vasa recta. To avoid renal injuries, the levels of vasodilation agents such as prostaglandins and nitric oxide increase and augment the blood flow to the glomerulus resulting in hyper filtration[37,38].

There result showed that GFR increased significantly in male patients compared with female patients, .this may be reflect the mean urea was lower in male than in female patients .The value of urea as a test of renal function depends on the observation that serum/plasma urea concentration reflects GFR: as GFR declines, plasma/serum urea rises [31].

Our result showed GFR is usually increased in younger patients with sickle cell disease but it is typically reduced in older patients. This agree with other study conducted by [39] .A reversible renal concentrating defect in younger age groups can become irreversible in older patients [40].

Conclusion

Although specific biomarkers related to these different events needs to understand for assessment of pathogenesis, the ones we have studied can be useful to assess the status of hepatic and renal function to follow the effectiveness of therapeutic interventions.

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