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The Impact of Genetic Polymorphisms in (STIM1 and ORAI1) on Erythropoietin Resistance in Patients with Chronic Renal Failure on Hemodialysis in Iraq

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Abstract
Objective: This study aims to investigate the correlation between genetic polymorphisms in store-operated calcium channels (SOCs) signaling and resistance to erythropoietin treatment in patients with chronic renal failure (CRF). Anemia is a significant complication of CRF, and understanding the genetic factors contributing to resistance could provide insights into potential mechanisms influencing treatment outcomes. Specifically, the focus is on exploring the relationship between SOCs, a pathway activated by erythropoietin, and resistance to address the challenges associated with anemia in CRF patients.
Methods: In this study, a single nucleotide polymorphism in each STIM1 and ORAI1 gene was selected. Genotyping was done by using allele specific polymerase chain reaction technique and the data was analyzed through the Statistical Package for the Social Sciences. 112 patients with CRF on hemodialysis were enrolled 58.9% of them were men and the mean age was 50.94 ± 13.42.
Results: We found that CC genotype of ORAI1 gene has a higher hemoglobin level, AA genotype of STIM1 has a higher EPO level, the interaction of the two genes showed that CCGG group has a higher Hb level and is considered good responder but represents only 4.5% of the patients.
Conclusion: After all the genetic polymorphisms of SOCs genes ORAI1 and STIM1 have no significant impact on erythropoietin resistance in patients with CRF on hemodialysis in Iraq.
Keywords: Genetic polymorphisms, STIM1, ORAI1, erythropoietin resistance, hemodialysis, chronic renal failure

Introduction

Chronic renal failure is a progressive incurable disease with considerably high rates of morbidity and mortality[1] one of the major complications of CRF is anemia that develops when the kidney has no more ability to produce the main hormone for hemoglobin production which is erythropoietin.[2] Several poor clinical outcomes are associated with anemia among them cognitive impairment, cardiovascular disease risk, and decreased quality of life.[3]

The foremost approach in treating anemia is epoetin alpha (recombinant human erythropoietin) which was approved by the Food and Drug Administration (FDA) in 1989, the use of epoetin results in increasing survival rates, ameliorating quality of life and lowering the chances of cardiovascular complications (like heart failure HF and left ventricular hypertrophy LVH)[4] although epoetin is the mainstay treatment of anemia in patients with CRF on hemodialysis, a common condition in those patients is resistance to recombinant human erythropoietin that resulted in increased hospitalization and mortality and the need for blood transfusion.[5] erythropoietin resistance is defined as the failure of hemoglobin (Hb) level to exceed 11 g/dl, even with an erythropoietin stimulating agent ESA dose of 500IU/kg/wk or 30000IU/wk.[6]

The main causes of the resistance are iron deficiency, malnutrition, chronic inflammation, hyperparathyroidism, and inadequate dialysis dose.[7] even when these causes of resistance were treated or handled the resistance persists which needs more explanations.

Genetic predisposition also has a role in erythropoietin resistance, several studies suggest an interrelation between erythropoietin resistance and genetic polymorphism.[8,9] A Korean cohort study showed that erythropoietin resistance index ERI considerably related to polymorphism in IL-1B and ACE genes.[10] In an Iraqi longitudinal study, ACE gene polymorphism had a significant effect on serum erythropoietin levels.[11]

ACE gene polymorphism plays an important role in determining the progression of chronic renal failure and the response to erythropoietin-stimulating agents.[12] Pharmacogenomic associations of polymorphisms in two genes STIM1 and ORAI1 with the risk of erythropoietin resistance was indicated by a study in Taiwan.[3]

Erythropoietin acts by increasing intracellular calcium signaling to induce proliferation and differentiation of erythroid cells.[13,14] The main calcium entry pathway in the non-excitable cells is store-operated calcium channel (SOC), which is activated by the loss of calcium from the endoplasmic reticulum ER.[15,16]

This study was designed to investigate the correlation between erythropoietin resistance and the genetic polymorphisms of two SOCs genes (STIM1 and ORAI1) in Iraqi patients with CRF on hemodialysis and the interaction of these two genes on Hb and EPO levels.

Materials and Methods

Patients Constant and Enrollment

This study was a cross-sectional observational study that was carried out at Imam Al-Hussain Medical City/Doctor Adel Al Sabbah Center for Hemodialysis in Karbala, during the period from November 2022 to April 2023. The protocol of the study was approved by the Scientific and Ethical Committee

of Pharmacy College/Kerbela University, and an informed signed consent form was given by each subject after explaining the nature and purpose of the study.

112 patients (66 male and 46 female) were enrolled in this study with age range from 20 to 79 years, being on hemodialysis for at least 4 months, taking erythropoietin vial for injection recommended weekly dose for more than 4 months. Blood samples and clinical data were collected from the patients at the enrollment.

Patient's socio-demographic and clinical data including; gender, age, weight, medical history, family history, and biochemistry data. Sixty-two healthy subjects were enrolled in the study (30 males and 32 females) as a reference for biochemical tests results.

Molecular Analysis

Genomic DNA was extracted from blood samples as stated by the protocol of gSYNC for blood genomic DNA extraction kit. DNA concentration and purity were measured by using a Nano-spectrophotometer nanodrop. The DNA purity was measured at A260/A280 ratio.

The SNP rs1561876 of STIM1 gene and the SNP rs6486795 of ORAI1 gene were selected (Tables 1 and 2).

Allele-specific PCR technique was used to detect the two SNPs, after several trials of PCR to obtain the best concentration of primers and best annealing temperature, the optimization of PCR was performed. Bioneer PCR Premix was used.

Statistical Analysis

The data of the present study was entered and analyzed through the Statistical Package for the Social Sciences (SPSS version 22).

The data were presented as frequencies and percentages or mean and standard deviation in appropriate tables and graphs or mean differences in others. Chi-square test, one-way and two-way ANOVA test, and post hoc analysis were used where is appropriate to find out the possible association between the related variables of the current study as LSD were used when equal variances are assumed while Dunnett's T3 were used when equal variances are not assumed depending on levene's test for homogeneity of variances.

Besides, Hardy Weinberg equilibrium was used to detect the prediction of alleles distribution. Statistical association was considered significant when p value equal or less than 0.05 (P value ≤ 0.05).

Table 1. **Primers of rs6486795 SNP of ORAI1 gene-Snv allele T > C, A**

Sequence (5′–3′)	Template strand	Product size
Forward primer	GCTCCAGACGTTTCCAGTGA Plus	462
R-allele T	ATGCCCACAGTGGATGGCA Minus	
R-allele C	ATGCCCACAGTGGATGGCG	
R-allele A	ATGCCCACAGTGGATGGCT	

The primers were designated by Dr. Hassan Mahmood Musa a participant in this study.

Table 2. **Primers of rs1561876 SNP of STIM1 genes-non-coding transcript variant [G/A/C/T]**

Sequence (5′–>3′)	Template strand	Product size
F-allele G	TGTTTCTGTCTCTTGCTTTCG Plus	328
F-allele A	TGTTTCTGTCTCTTGCTTTCA	
F-allele C	TGTTTCTGTCTCTTGCTTTCC	
F-allele T	TGTTTCTGTCTCTTGCTTTCT	
Reverse primer	ATGCCTCTCCCAACCCATTC Minus	

The primers were designated by Dr. Hassan Mahmood Musa a participant in this study.

Results

Socio-demographic data of the studied population. The studied population included 112 patients (46 females and 66 males) with CRF on hemodialysis. The mean age involved in this study was 50.94 ± 13.42 at the time of enrollment. 45.5% of the patients were responders while 54.5% of them were resistant to erythropoietin. The socio-demographic parameters are illustrated in Table 3 presented as numbers and percentages.

Biochemical parameters between genetic groups of patients are summarized in Table 4 presented as mean ± SD showed that CC group is statistically significant over TT group and control group is statistically significant over the three genetic groups.

Table 3. **Descriptive statistics of the socio-demographic parameters**

Variables		No.	Percent
Age (year)	20–39	25	22.3
	40–59	50	44.6
	60–79	37	33.0
Gender	Female	46	41.1
	Male	66	58.9
Weight (kg)	30–50	14	12.5
	51–70	69	61.6
	71–90	22	19.6
	91–130	7	6.3
Duration of disease (months)	4–60	90	80.4
	61–120	15	13.4
	121–180	7	6.3
Duration of dialysis (months)	4–60	102	91.1
	61–120	8	7.1
	121–180	2	1.8
Duration of treatment (months)	4–50	90	80.4
	51–90	16	14.3
	91–156	6	5.4
Family history	Yes	14	12.5
	No	98	87.5
Response	Responders	51	45.5
	Non-responders	61	54.5

Table 4. **Mean ± SD of biochemical parameters between groups of ORAI1 gene (rs6486795)**

Parameters	Groups								*P*-value
	control		TT		TC		CC		
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		
Epo	13.04	3.10	13.52	4.07	14.30	4.70	14.15	4.77	0.362 NS
Hb	13.48	1.03	9.13	1.69	9.74	1.83	10.23	1.73	0.001 S 0.005 S
BU	25.48	7.79	112.97	34.15	112.74	33.63	126.84	35.15	0.001 S
S.Cr	0.86	0.16	7.81	2.21	7.78	2.22	7.48	1.69	0.01 S

Epo, erythropoietin serum level; Hb, hemoglobin level; BU, blood urea; S.Cr, serum creatinine; S, Significant; NS, Non significant.

Table 5. **Effect of age on Epo level**

Dependent variable: Epo				
Age (year)		**Mean ± SD**		***P*-value**
20–39*	25	11.87	3.75	
40–59	50	13.88	4.62	0.004
60–79	37	15.16	4.31	
	112			

Epo, erythropoietin level.

Table 6. **Distribution of ORAI1 gene polymorphism (rs6486795) different genotype in patients**

Variable		Frequency	Percent
Genotype ORAI1 rs6486795	TT wild	44	39.3
	TC hetero	43	38.4
	CC homo	25	22.3
	Total	112	100.0

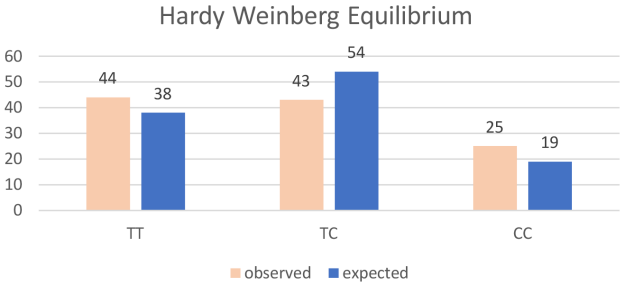

Fig. 1 **Hardy-Weinberg equilibrium for ORAI1 gene (rs6486795).**

Patients in the age group of (60–79) had a statistically significant raise in erythropoietin levels on the patients in the age group of (20–39) as presented in Table 5.

The distribution of ORAI1 gene polymorphism (rs6486795) different genotypes in the 112 enrolled patients is represented in percent and frequency in Table 6.

The Hardy-Weinberg equilibrium test (Figure 1) was used to show the expected frequency and percent of genotype groups, and the expected predominant group will be the hetero TC group based on this study shown in Tables 7 and 8 showed that there is an association between response and genetic variation.

Biochemical parameters between genetic groups of patients are summarized in Table 9 presented as mean ± SD showed that only control group is statistically significant over the genetic groups but there was no statistically significant difference between the genetic groups. The distribution of STIM1 gene polymorphism (rs1561876) different genotypes in the 112 enrolled patients is represented in percent and frequency in Table 10.

The result in Table 11 showed that there was an association between gender and genetic variation.

The Hardy-Weinberg equilibrium test (Figure 2) was used to show the expected frequency and percent of genotype groups, the hetero GA group will increase in frequency and percent while both the homo wild GG group and the homo mutant AA group will decrease in frequency and percent based on this study these results summarized in Table 12.

Table 13 showed that there was no association between response and genetic variation.

Table 14 represent cross-tabulation of rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene and the percent of each group of patients regarding the two SNPs at the same time (Figure 3), the AATT (homo wild of ORAI1 gene and homo mutant of STIM1 gene) group was the highest group in percent in this study Two-way ANOVA test was used to show the interaction of the two SNPs (rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene) on the hemoglobin level in Table 15 and Figure 4 and on erythropoietin level in Table 16 and Figure 5.

Discussion

Anemia is widespread in patients with chronic renal failure and those on hemodialysis this is associated with decreased quality of life and increased morbidity and mortality.[17,18] Before the development of erythropoietin stimulating agent ESA anemia in patients with CRF on hemodialysis was treated by blood transfusion and the main adverse outcomes were sensitization and infections, ESA lowers the need for blood transfusion and enhances the quality of life besides cardiovascular risk increase.[19] However, erythropoietin resistance can raise the risk of adverse outcomes in patients with CRF.[20]

This cross-sectional study was done in an endeavor to give some evidence of the correlation between genetic polymorphism in ORAI1 and STIM1 genes and erythropoietin

Table 7. **Hardy–Weinberg equilibrium for ORAI1 gene (rs6486795) in patients**

Variable			Frequency	Percent	Alleles		Hardy–Weinberg equilibrium X2 test
Genotype	TT wild	Observed Expected	44 38.31	39.3 34.2	T	C	
	TC hetero	Observed Expected	43 54.39	38.4 48.56	131 (58.48%)	93 (41.52%)	$P < 0.0267$ (S)
	CC homo	Observed Expected	25 19.31	22.3 17.24			

Table 8. **Association between response and genetic variation in ORAI1 gene**

variable		Responder (no.)	Non-Responders (no.)	*P* value
Genotype	TT	14	30	0.031 S
	TC	21	22	
	CC	16	9	

Table 9. **Mean ± SD of biochemical parameters between groups of STIM1 gene (rs1561876)**

Parameters	Groups								*P*-value
	Control		GG		GA		AA		
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		
Epo	13.04	3.10	13.89	4.35	13.48	5.06	14.04	4.21	0.574 NS
Hb	13.48	1.03	9.78	1.83	9.47	1.85	9.63	1.78	0.001 S control
BU	25.48	7.79	114.27	25.5	117.56	42.06	115.66	32.56	0.001 S control
S. Cr	0.86	0.16	7.61	2.19	7.86	2.18	7.69	2.05	0.001 S control

Epo, erythropoietin serum level; Hb, hemoglobin level; BU, blood urea; S. Cr, serum creatinine; S, Significant; NS, Non significant.

Table 10. **Distribution of STIM1 gene polymorphism (rs1561876) different genotype in patients**

Variable		Frequency	Percent
Genotype STIM1 gene rs1561876	GG wild	19	17
	GA hetero	33	29.5
	AA homo	60	53.6
	Total	112	100.0

Table 11. **Association between gender and genetic variation in STIM1 gene**

Demographic parameters		Patient genotype (N = 112)			*P* Value
		GG N (19)	GA N (33)	AA N (60)	
Gender	Male	16	16	34	0.036 (S)
	Female	3	17	26	

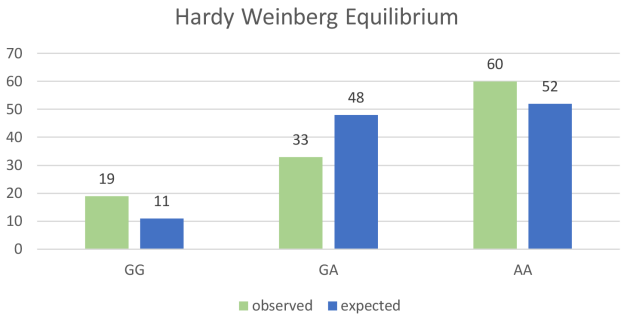

Fig. 2 **Hardy-Weinberg equilibrium for STIM1 gene (rs15161876).**

resistance in Iraqi patients with CRF on hemodialysis. The results in this study showed that regarding STIM1 gene AA genotype was the most frequent (53.6%) followed by GA (29.5%) and GG (17%) these results are approximately consistent with a 2020 Chinese study in the frequencies of AA, GA, and GG of 300 healthy Chinese Han individuals (54.0%), (36.33%), (9.67%) respectively.[21] while regarding ORAI1 gene TT and TC genotypes were almost similar in frequencies (39.3% and 38.4% respectively) and CC group was lower in frequency at 22.3% some similarity can be found when these results were compared with the results of a Taiwanese study in 2011 in which they represent that the frequency of TT, TC, and CC were 39.6%, 46.1%, 14.3% respectively.[22] In this study, elderly patients have higher erythropoietin serum levels than young patients, in 2017 a study in Canada showed that in

Table 12. **Hardy–Weinberg equilibrium for STIM1 gene (rs1561876) in patients**

Variable			Frequency	Percent	Alleles		Hardy–Weinberg equilibrium X^2 test
Genotype	GG wild	Observed Expected	19 11.25	17 10.05	G	A	
	GA hetero	Observed Expected	33 48.5	29.5 43.3	71(31.7)	153(68.3)	*P*<0.0007 (S)
	AA homo	Observed Expected	60 52.25	53.6 46.65			

Table 13. **Association between response and genetic variation in STIM1 gene**

Variable		Responder (no.)	Non-responders (no.)	*P* value
Genotype	GG	10	9	
	GA	14	19	0.770 NS
	AA	27	33	

Table 14. **rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene cross-tabulation**

Groups		GG	GA	AA	Percent
TT	Count % of Total	5 4.5%	13 11.6%	26 23.2%	44 39.3%
TC	Count % of Total	9 8.0%	10 8.9%	24 21.4%	43 38.4%
CC	Count % of Total	5 4.5%	10 8.9%	10 8.9%	25 22.3%
Total	Count % of Total	19 17.0%	33 29.5%	60 53.6%	112 100.0%

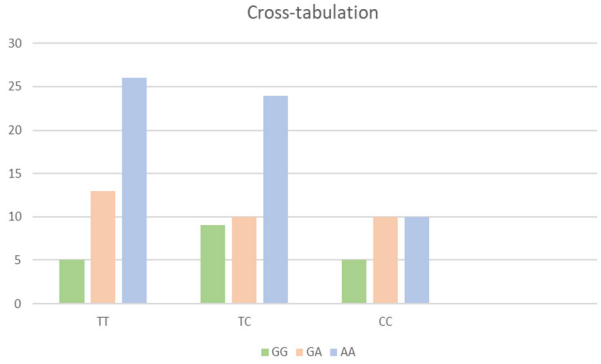

Fig. 3 **Cross-tabulation of ORAI1 rs6486795 and STIM1 rs1561876.**

Table 15. **Interaction of rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene on the Hb level**

SNP1	SNP2	Mean	SE	*P* value
TT	GA	8.785	0.499	0.677 NS
CC	GG	10.700	0.805	0.431 NS

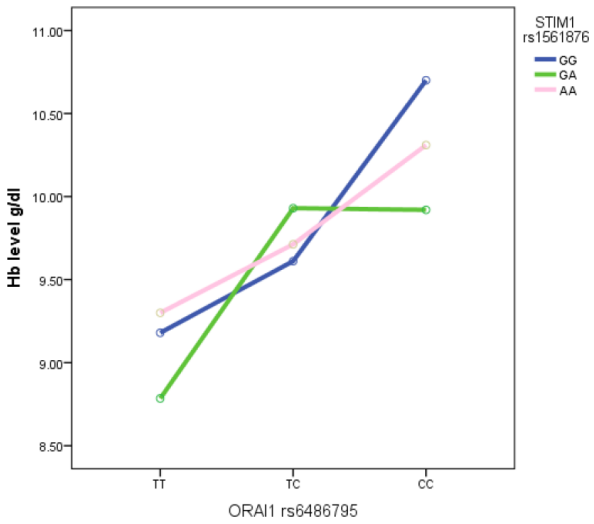

Fig. 4 **Interaction of rs6486795 and rs1561876 on Hb level.**

Table 16. **Interaction of rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene on Epo level**

SNP1	SNP2	Mean	SE	*P* value
TT	GA	12.585	1.269	0.747 NS
CC	AA	15.303	1.447	0.386 NS

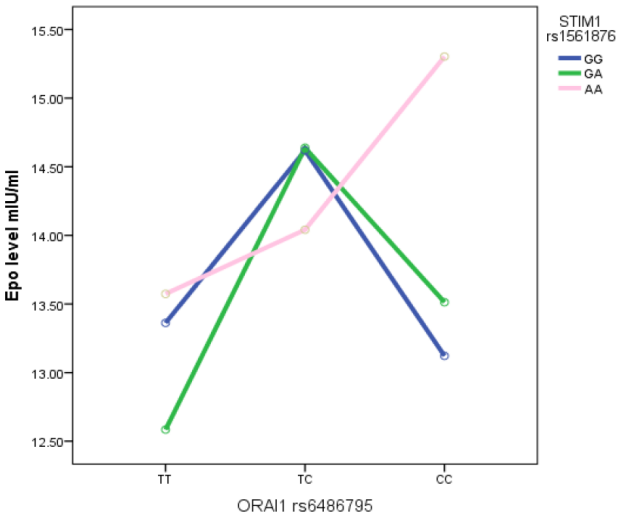

Fig. 5 **Interaction of rs6486795 and rs1561876 on Epo level.**

ESA therapy with higher Hb targets the adverse outcomes are restricted to sick elderly patients, and the healthier younger patients without resistance to the treatment may benefit from the health-related quality of life perspective[19] which may explain the higher EPO level in elderly patients.

In STIM1 gene the genetic variation has no association with erythropoietin resistance based on this study but there is an association between gender and genetic variation, this is controversially disagreeing with the 2021 Taiwan study in which AA genotype has increased risk of EPO resistance, the same study showed that CC/CT genotype has higher risk of EPO resistance while in this study CC group of ORA1 gene has statistically significant raise over TT group with Hb level but also has a negative outcome represented by higher BU level.[3]

Hardy-Weinberg equilibrium test showed that the expected results will be an increase in hetero groups and a decrease in homo groups compering with the observed groups in both ORAI1 and STIM1 genes.

A cross-tabulation of rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene showed that the predominant group is the AATT genotype (23.2%) while the lower group in frequency are GGTT and GGCC with the same percentage (4.5%).

Depending on the interaction of rs6486795 in ORAI1 gene and rs1561876 of STIM1 gene and their impact on Hb level and EPO level, TTGA genotype has the lower Hb level and EPO level among other groups, CCGG genotype has the higher Hb level while CCAA genotype has the higher EPO level.

CCGG group who have the higher Hb level and are considered good responders represent only 4.5% of the patients' population based on this study, this might explain the commonness of erythropoietin resistance in these patients.

Conclusion

In patients with CRF on hemodialysis the genetic polymorphism of SOCs genes ORAI1 and STIM1 have no significant effect on erythropoietin resistance. Although CC group of ORAI1 gene has higher Hb level and AA group of STIM1 has higher EPO level, CCGG group the good responder represents 4.5% of these patients.

Ethical Approval

This study was approved by the Ethics Committee of the College of Pharmacy/University of Karbala on 3rd November 2022 (Ref:2022HU7). All patients provided informed consent before being enrolled in the study. The study was performed in accordance with the Declaration of Helsinki.

Conflict of Interest

None.

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