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Research article

The resistance to methoxy polyethylene glycol-epoetin beta in anemic patients of end-stage renal disease

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ABSTRACT

Background: Chronic kidney disease (CKD) is a global disease, and the number of people affected is increasing due to driving factors such as diabetes, obesity, and hypertension, as well as increased life expectancy. Many patients with CKD suffer anemia throughout the period of their disease.

Aim: This research aimed to investigate the relation between resistance to the methoxy polyethylene glycol-epoetin beta (ME-β) and angiotensin-converting enzyme (ACE) gene polymorphism.

Methods: Seventy Iraqi patients with CKD on hemodialysis treatment for at least six months and receiving a subcutaneous injection of ME-β were selected to enroll in this current study. In addition to these patients, the control group of 20 healthy subjects. Baseline samples (Three blood samples) were obtained and withdrawn from each participant, then 3 and 6 months following the starting sample. In addition, a unique blood sample was taken from each participant in the control group in the early morning hours following 8 h of fasting and before dialysis (for the patients' group).

Results: ACE polymorphism did not demonstrate a significant ($p > 0.05$) relation with changing the dose of ME-β. Furthermore, there was a negative relationship between ME-β dose and hemoglobin (Hb) in CKD patients. Comparing ACE polymorphism between good and hypo-response groups shows no significant effect ($p > 0.05$) on ME-β therapy. Moreover, the erythropoietin resistance index (ERI) was significantly ($p < 0.001$) lower in good responders to ME-β therapy compared to the hypo-response group. Finally, comparing the ERI of the patient, the good response group to the hypo-response group showed no significant association ($p > 0.05$) with ACE gene polymorphism in response to ME-β therapy.

Conclusion: No relation was determined between the polymorphism ACE gene and the resistance to the ME-β administration in CKD Iraqi patients.

1. Introduction

Chronic kidney disease represents a worldwide disease, and the number of people affected is increasing due to driving factors such as diabetes, obesity, hypertension, and increased life expectancy. Many patients with CKD suffer anemia throughout the period of their disease [1]. The insufficient erythropoietin (EP) produced by the kidney represents the primary cause of anemia. Additionally,

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erythropoietin is involved in the maturity of erythrocytes, proliferation, and its lifetime in interstitial renal peritubular cells and hepatocytes [2,3]. The optimum Hb goal range for CKD patients is 100.0–120.0 g/L. Patients with renal impairment utilizing erythropoiesis-stimulating agent (ESA) and iron should have a Hb goal of no less than 90.0 g/L and no more than 130 g/L [4]. Besides, anemia affects around half of these individuals before dialysis and over 90% of those on hemodialysis. ESAs are the usual treatment for renal anemia; however, managing anemia in CKD is still a problem from a medical standpoint [5,6]. Epoetin alfa, epoetin beta, darbepoetin alfa, and ME-β are the four types of ESAs available for clinical usage. In accordance with the most recent recommendations of the KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease, a doctor evaluated the criteria determining whether to use short- or long-acting EPO [7]. In addition, using ESAs to treat hemodialysis patients has been a significant step forward in treating renal anemia [4]. ME- β is the sole ESA produced by the chemical change of glycosylated erythropoietin via incorporating a single long, linear chain of polyethylene glycol. This ESA has a lengthy half-life and produces persistent erythropoietin receptor activation [8].

ME-β has been given intravenously or subcutaneously once every two weeks or monthly, leading to a high hemoglobin (Hb) response rate in people with CKD anemia, independent of whether the patient was on dialysis. When a patient fails to obtain the required serum Hb levels after utilizing ESA at higher doses, this is known as resistance or hyporesponsiveness to ESA [4]. Nevertheless, erythropoietin resistance represents a significant reason for anemia in CKD people. Up to 10% of individuals using erythropoietin are hyporesponsive and require high medication dosages. The pathophysiological mechanisms underlying this syndrome are not completely understood; nevertheless, the processes that produce chronic anemia play a significant role [8].

Moreover, the erythrocytic progenitor cell response to EP is inversely correlated to the intensity of chronic illness and the quantity of distributing cytokines. When TNF-β or IFN-γ are present in high doses, more EP is necessary to restore the creation of erythrocyte colony-forming units. Moreover, inflammatory diseases have been correlated with EP resistance in hemodialysis patients, primarily because inflammation reduces the bone marrow's response to ESA, alters iron regulation by hepcidin overexpression, and produces red blood cells (erythrocyte hemolysis) [9]. Furthermore, the hypo-responsiveness to EP in these patients can be attributed to iron inadequacy [10,11].

Nevertheless, many patients do not improve with treatment, even when intravenous iron is used, indicating other significant resistance causes. Infection, malnutrition, insufficient dialysis, and hyperparathyroidism all have a role in CKD patients' anemia [12]. The gene of ACE was detected at 17q23. It includes 25 introns and 26 exons [13]. The ACE enzyme serum concentration is significantly influenced by the ACE gene insertion/deletion (I/D) polymorphism. One of the elements most in charge of the significant interindividual variation in serum ACE concentration is this polymorphism. Compared to subjects with the I allele, those with the D allele have much greater ACE levels in their serum [13]. Some studies39–42 found a correlation between erythropoietin resistance and ACE gene I/D polymorphism, whereas other studies could not demonstrate this association [14].

Recently, studies showed the critical effect of angiotensin-converting enzyme (ACE) gene polymorphisms on individual response variations to ESAs [15]. As a result, in this study, the effects of ACE gene polymorphisms II, ID, and DD on ME-β effectiveness in CKD individuals receiving hemodialysis were evaluated.

2. Methods

Seventy Iraqi patients with CKD on hemodialysis treatment for at least six months and receiving a subcutaneous injection of ME-β for renal anemia attending the Iraqi center of kidney dialysis in Baghdad, Iraq, from November 2020 until June 2021 were recruited. In addition to these patients, a control group of 20 healthy subjects was also enrolled for comparison. The participants provided informed consent. The local ethics committee of Pharmacy College, Al Farahidi University, approved the study protocol (FCP 3102021).

The inclusion criteria included the following: age 18 years or above, patients on hemodialysis for three months or more, and injections of ME- β for renal anemia.

The exclusion criteria included the following: bleeding, cancer patients, hypothyroidism, and acute infectious disease. Utilization of angiotensin receptor blockers (ARB) or ACE inhibitors, Age, body weight, and primary cause of renal disease were all considered in the study.

Three blood samples were taken from each individual: one at the start of the trial (baseline sample), three months later (follow-up sample), and six months later (follow-up sample). In addition, each participant in the control group had a single blood sample taken in the morning following an overnight fast and before dialysis for the patients' group. The dose of ME-β was individualized every week to achieve and maintain hemoglobin levels between 100 and 120 g/L. All patients were distributed into good-responsive and hypo-responsive groups based on hemoglobin variation (elevation exceeded 30% of baseline value or did not exceed 15% of baseline value for three consecutive months) and whether or not the target hemoglobin level (between 100 and 120 g/L) was achieved. In other words, the good-responsive group involved patients who showed an adequate response to EP therapy that increased and maintained their hemoglobin level above that recorded at baseline or any patient who reached the target hemoglobin level throughout the study. In contrast, the hypo-responsive group involved patients who failed to increase or maintain their hemoglobin concentration above that recorded at baseline.

The average weekly erythropoietin dose ([IU] per kg body weight divided by hemoglobin [g/dl]) in each quarter was determined for each participant at the end of the study to account for a more reliable indicator of response to EP treatment (3-month period).

A genomic DNA extraction kit was utilized to separate the genomic DNA from whole blood samples (ReliaprepTM Blood gDNA Miniprep System, Promega, USA). Agarose gel electrophoresis was used to assess the DNA's purity (AgaroPowerTM, Bioneer, Republic of Korea). The ACE gene was molecularly genotyped via the standard polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique with a few minor modifications (MyGenie™ 96 Thermal Block, Bioneer, Republic of Korea). The PCR amplification process used these primers:

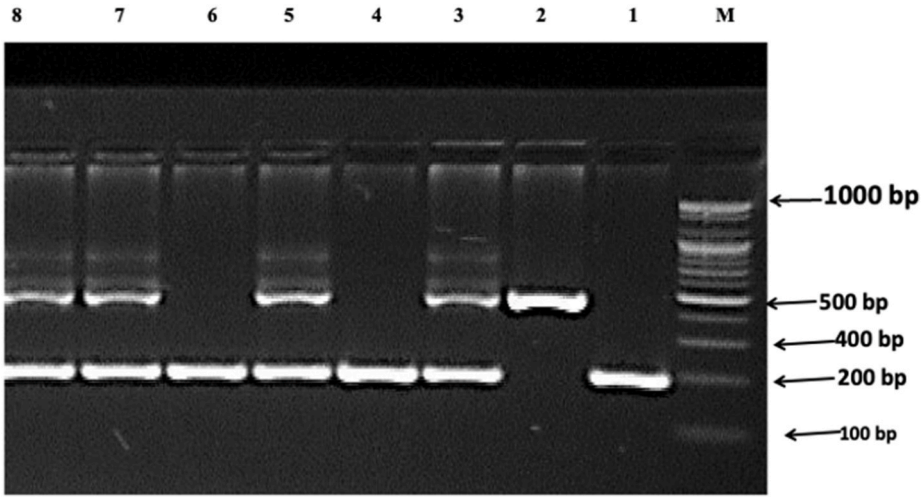

Fig. 1. PCR results exhibiting ACE gene polymorphism on a 2% agarose gel electrophoresis.

Table 1
ACE gene polymorphism distribution according to the need to change ME-β dose between 3 and 6 months.

Polymorphism	No. (%)	No change	Decrease	Increase	P-value
DD	(n)	23	2	1	0.331
	%	39.0%	33.3%	20.0%	
II	(n)	7	0	2	
	%	11.9%	0.0%	40.0%	
ID	(n)	29	4	2	
	%	49.2%	66.7%	40.0%	
Chi-square test					

Forward: 5′CTG GAG ACC ACT CCC ATC CTT TCT 3’
Reverse: 5′ GAT GTG GCC ATC ACA TTC GTC AGA T 3’

The SPSS program (edition 22) was used to do statistical calculations. The continuous variables with a normal distribution were examined using the Anderson-Darling test. Discrete variables’ numbers and percentages were used to present the data.

To compare discrete variables between study groups, the chi-square test was used. Direct counting was used to determine the ACE gene genotype frequencies. The link between ME-β and Hb was studied using linear regression analysis. A p-value <0.05 was significant.

3. Results

3.1. Demographic data

The patients’ age was 49.3 ± 7.4 years (mean ± SD); of them, 30 patients (42.9%) were female, and 40 patients (57.1%) were male. On the other hand, the age of the control group was 46.2 ± 6.3 years (mean ± SD); of them, ten patients (50%) were male, and ten patients (50%) were female.

3.2. ACE gene polymorphism

The PCR-RFLP detection system is demonstrated in Fig. 1 for the ACE gene polymorphism.

3.3. Association between ME-β dose change and ACE gene polymorphism

This study found that the dose of ME-β was only increased in five patients with ACE polymorphism, with the DD allele having the lowest percentage needed to increase the dose and the II and ID alleles having similar percentages required to increase the dose. On the other hand, a high percentage of ID alleles is needed to decrease the dose of ESA. However, ACE polymorphism did not show a significant ($p > 0.05$) association with changing the dose of ME-β (Table 1).

Table 2
Correlation between ME-β dose and hemoglobin using Linear regression analysis.

Intervals	Correlation coefficient	P-value
3 months	−0.368	0.002
6 months	−0.44	<0.001

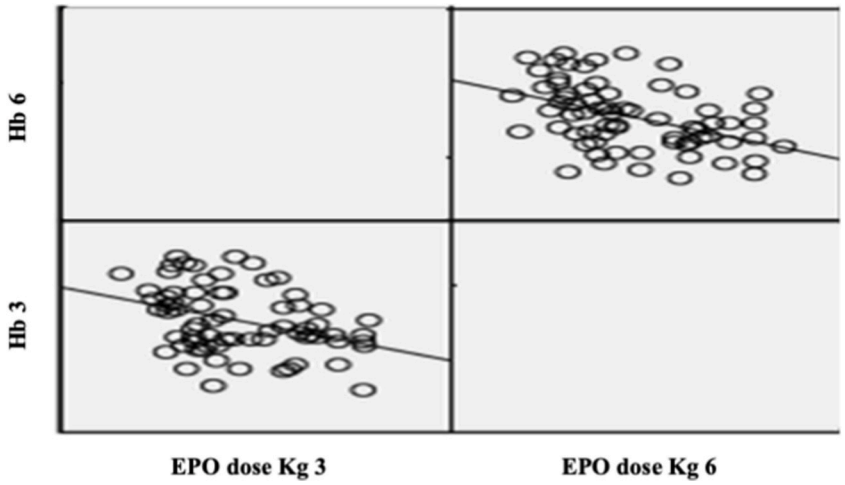

Fig. 2. Scatter plot of ME-β dose per kg per month versus hemoglobin in patients.
Hb3 and Hb6: represent 3 and 6 months, respectively.

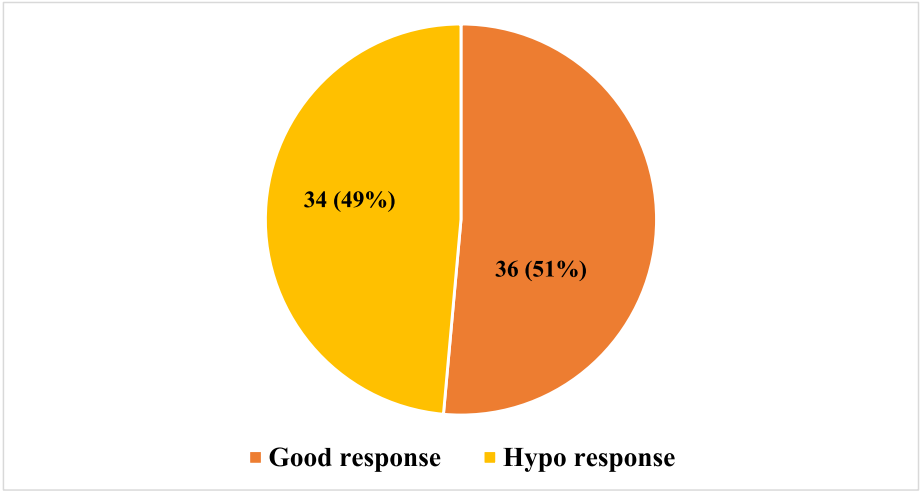

Fig. 3. Prevalence of response to ME-β therapy in patients.

3.4. Dose-response relationship between hemoglobin and ME-β dose per kg per month

There was a negative relationship between ME-β dose and hemoglobin in CKD patients. This relationship increases with time (as evidenced by a higher correlation coefficient at six-month intervals than three months), as illustrated in (Table 2 and Fig. 2).

3.5. Response to ME-β therapy

About half of the patients adequately responded to ME-β therapy (i.e., increased and maintained a stable hemoglobin concentration throughout the study). In contrast, the remaining patients inadequately responded to treatment, as illustrated in (Fig. 3).

Table 3
Association between EP response and ACE gene polymorphism.

Gene	Alleles		Good response	Hypo-response	P-value
ACE	ID	No.	15	11	0.093
		%	41.7%	32.4%	
	II	No.	7	2	
		%	19.4%	5.9%	
	DD	No.	14	21	
		%	38.9%	61.8%	
Chi-square analysis					

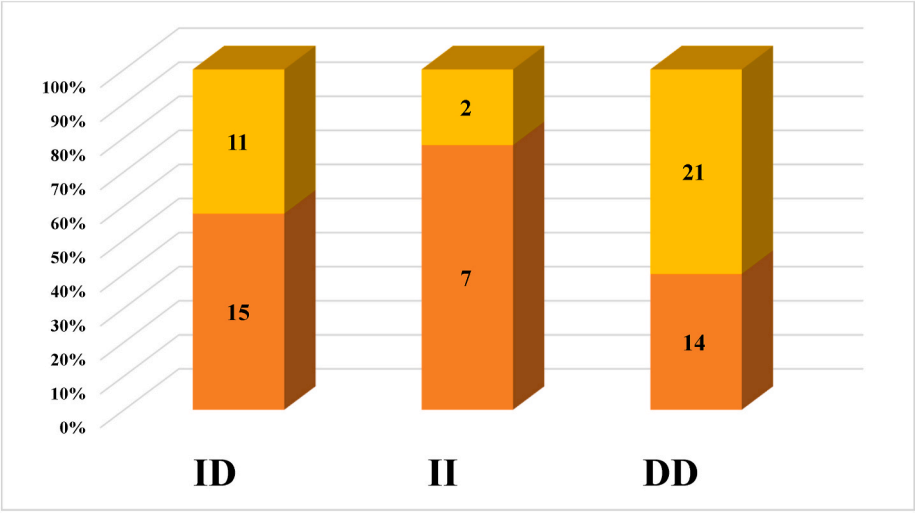

Fig. 4. Histogram of ME-β therapy response according to ACE alleles.

Table 4
ERI of patients divided by the response to EP therapy.

Good response patients		Hypo-response patients		P-value
Median	IQR	Median	IQR	
0.03	0.02275–0.04725	0.0605	0.041–0.077	<0.001
Mann Whitney *U* test				

3.6. ACE gene polymorphism effect on response to ME-β therapy

Comparing ACE polymorphism between good and hypo-response groups showed no significant effect ($p > 0.05$) on ME-β therapy, despite the II allele showing the highest response to ME-β treatment among ACE alleles, as shown in (Table 3 and Fig. 4).

3.7. Correlation between erythropoietin resistance index (ERI) and response to ME-β

ERI is lowered significantly ($p < 0.001$) in good responders to ME-β therapy compared to the hypo-response group, as shown in (Table 4 and Fig. 5).

3.8. Relationship between ERI of patients and response to ME-β therapy and ACE gene polymorphism

Comparing the ERI of the patient, the good response group to the hypo-response group showed no significant association ($p > 0.05$) with ACE gene polymorphism in response to ME-β therapy. In addition, subjects who carried DD and ID alleles in the good response group had median values below the optimal cut-off value (≤0.0365), as illustrated in (Table 5 and Fig. 6), while subjects who carried the II allele had a high median value. However, because this group contains only two patients, this may lead to weak accurate prediction, and more samples are needed.

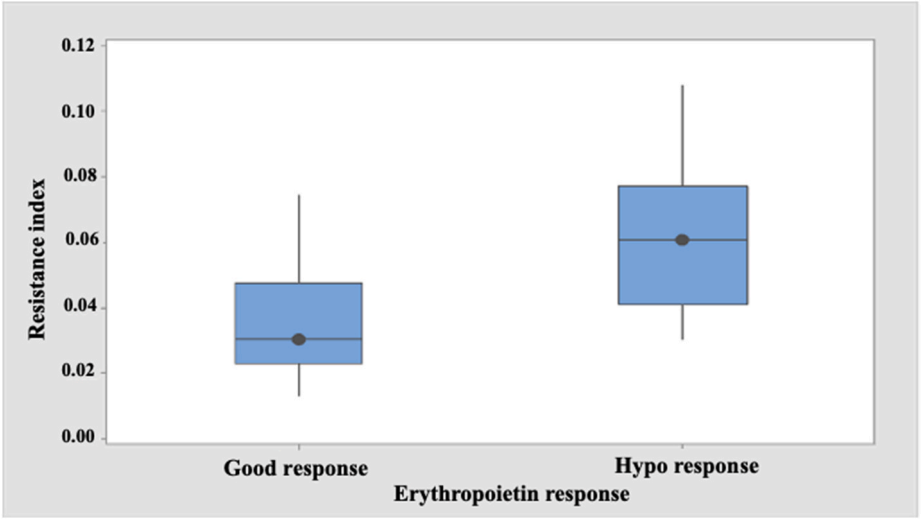

Fig. 5. Box plot of ERI in patients according to ME-β therapy response.

Table 5
ERI of patients divided by the response to ME-β therapy and ACE gene polymorphism.

Parameters	Good response patients			Hypo-response patients		
	DD	II	ID	DD	II	ID
(n)	11	2	21	15	7	14
Median (IQR)	0.026 (0.21–0.036)	0.64 (0.06–0.064)	0.031 (0.0225–0.0545)	0.066 (0.044–0.076)	0.041 (0.039–0.075)	0.062 (0.0405–0.086)
P-value Kruskal Wallis test	0.078			0.675		

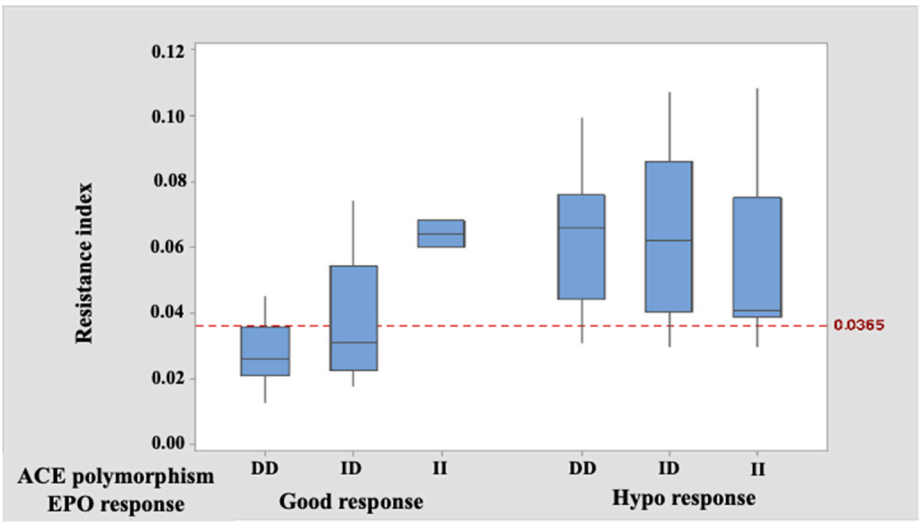

Fig. 6. ERI for ACE gene alleles according to ME-β response.

4. Discussion

Erythropoietin production is significantly reduced in CKD patients, resulting in renal anemia. EP use led to a substantial rise in Hb concentration and improved quality of life for the predominance of CKD people. However, about 5–10% of CKD individuals on EP appeared to resist the therapy [12]. Individual responses to EP may vary depending on genetic variants [16]. The relationship between the IL-1B gene, ACE gene polymorphisms, and ERI in hemodialysis patients was examined [17]. The IL-1B–511C/C and ACE D/D

genotypes were linked to decreased ERI, suggesting that these polymorphisms could be valuable genetic markers in determining the necessary EP dosage in people undergoing hemodialysis [17]. The ACE I/D polymorphism influences ACE activity levels in the blood and tissues, and the highest levels of this enzyme are found in people with the ACE DD genotype [18]. The current study found that the resistance to ME-β in Iraqi patients was unrelated to ACE genetic polymorphisms. These findings are supported by recent research by Hyeong et al. [19] who showed no marked influence of the ACE I/D polymorphism on EP necessity in hemodialysis individuals. On the other hand, our findings contradict two recent studies that included continuous ambulatory peritoneal dialysis people and found that the ACE II/ID genotypes are linked to inadequate EP response [20,21]. These findings' variances are attributed to the ethnic differences between people. Additionally, this study revealed an increase in the negative relationship between the dose of ME-β and the level of Hb with time. Hence, patients on hemodialysis require dose adjustments every three months. These results agree with the investigation performed by Regidor et al. [22], which demonstrated that patients' hemoglobin on maintenance hemodialysis is lower in those who injected the highest doses of ESA. Furthermore, patients given ESA, especially those who required higher doses, had a lower survival rate and died from cardiovascular reasons at a higher rate [22]. Long-acting ESA is associated with more mortality due to cardiovascular diseases, infections, and malignancies, so strict dose adjustment is needed [23]. About 50% of patients respond well to the ME-β; these results agree with Saglimbene et al. [24], who stated the effectiveness of long-acting ESA in increasing Hb and the survival of patients. Although ERI was lower in the good response group, no relation was determined between it and gene polymorphism in Iraqi patients. These results are controversial to Means et al., which found that patients with the ACE D/D or I/I genotype responded to ESA better than those with the I/D genotype [24]. Other factors contributing to Iraqi patients' resistance include inflammation, significant independent predictors of EP treatment resistance, and pro-inflammatory cytokines that were proven to impair erythropoiesis [25]. IL-1, for example, decreased EP synthesis and lowered bone marrow erythroid progenitor colony formation [26]. Furthermore, pro-inflammatory cytokines may have a deleterious impact on iron use, interfering with Hb production [27]. These findings further imply that the pro-inflammatory cytokine IL-1, which is genetically controlled, may be linked to EP resistance. A recent study has linked the IL-1B–511C/T polymorphism to various inflammatory disorders [18]. The modest sample size and single-center emphasis of this investigation hampered its findings. Korean genotype frequencies were reasonably uniform and similar despite being centered compared to those of more varied populations, making it applicable to extrapolate the findings of a single-centric study to the larger population [17]. Family-based related research or a longitudinal study with adequately customized clinical factors might be beneficial in determining the precise effect of IL-1B and ACE gene polymorphisms on EP resistance in hemodialysis people. There are a few more potential drawbacks to this research. We didn't assess angiotensin II levels, and it was unclear whether angiotensin II is involved in the link between ACE genotype and erythropoietin response based on our findings.

Additionally, we did not assess EP levels, which could be another reason for discrepancies in the resistance of EP. In summary, we discovered that the ACE genotype is unrelated to ERI values in hemodialysis patients. Moreover, when evaluating EP responsiveness, the ACE polymorphism has an unanticipated value.

5. Conclusion

There was no relation between gene polymorphism of ACE and resistance to the ME-β administration in CKD Iraqi patients.

Declarations

Author contribution statement

Waleed K Abdulsahib: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper. Sattar J. Abood; Mohanad Y. Al-Radeef: Performed the experiments; Contributed reagents, materials, analysis tools, or data.

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Data availability statement

Data included in article/supplementary material/referenced in article.

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