Review Article

Genetic Variants *(HIF1α , ACE I/D, STIM1, ORAI1 and TMPRSS6)* on Erythropoietin Resistance in Dialysis Patients with Chronic Kidney Disease: Scoping Review

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ABSTRACT

Background

Anemia is one of the most important chronic kidney disease (CKD) complications that usually managed with Erythropoietin Stimulating Agent (ESA). Some factors are responsible for ESA response included genetic predisposition. This review aimed to summarize variant genetics of HIF1α, ACE I/D, STIM1, ORAI1, and TMPRSS6 that are associated with EPO resistance in hemodialysis patients

Materials and Methods

Seven databases were searched through Scopus, PubMed, Cochrane Library, Proquest, Science Direct, Wiley, and EBSCOhost to identify potential articles. The year of publication ranges from 2012 to 2022. The study included dialysis patients who defined measures for the erythropoietin resistance index (ERI), body weight, and hemoglobin (Hb). Synthesis is done by grouping according to thematic analysis for elaborative results.

Results and Discussion

There are 2,712 articles in the initial registration, 7 articles met the eligible criteria. There were four studies about polymorphism of the ACE I/D gene, one study about minor alleles of STIMI and ORAI 1, one study about TMPRSS6, and one article study about HIF1α. ACE I/D polymorphisme showed some different effect, but patient with I/D allele tend to have lower Hb. STIM1 was associated with a lower risk of EPO resistance and ORAI1 was also associated with a higher risk of EPO resistance. The TMPRSS6 736V variant is associated with higher hepcidin levels in chronic hemodialysis patients.

Conclusion

These study showed many genetic variants affect the success of EPO therapy with different mechanisms. Genetic variants recognized earlier than therapy may help predict the effectiveness and efficiency of EPO therapy.

Keywords

Genetic Variants; EPO Therapy; Chronic kidney disease.

INTRODUCTION

Anemia is one of the most important chronic kidney disease (CKD) complications, which develops early and worsens during the long-term progression of the disease[1]. Anemia is frequently observed in Patients living with advanced CKD and is associated with adverse outcomes[2]. The leading main causes of anemia in maintenance hemodialysis patients are erythropoietin and iron deficiency [3].

Anemia of CKD is currently managed with oral or intravenous (IV) iron and erythropoiesis-stimulating agents (ESAs) to promote erythropoiesis. Erythropoiesis-stimulating agents (ESAs) used to increasing red blood

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Table 1. Characteristics of source evidence

No	Study Title	Author (Year of publication)	Study site	Study design	Sample size
1	Haematological Indicators of Response to Erythropoietin Therapy in Chronic Renal Failure Patients on Haemodialysis: Impact of Angiotensin-Converting Enzyme rs4343 Gene Polymorphism	Hamdan Almaeen, A., & Mostafa-Hedeab, G. (2021)	Egypt	Observational study	265 patients and 160 control
2	ACE gene polymorphism and its association with serum erythropoietin and hemoglobin in Iraqi hemodialysis patients	Al-Radeef, M. Y., Fawzi, H. A., & Allawi, A. A. (2019)	Iraq	Observational study	70 patients and 20 control
3	Association of I/D angiotensin-converting enzyme genotype with erythropoietin stimulation in kidney failure	Savin, M., Hadzibulic, E., Damnjanović, T., Šantric, V., & Stankovic, S. (2017).	Serbia	Observational study	53 patients (26 oral iron and 27 intravenous iron)
4	Effect of angiotensin-converting enzyme gene insertion/deletion polymorphism and angiotensin-converting enzyme inhibition on erythropoiesis in patients on haemodialysis	Kiss, Z., Ambrus, C., Kulcsár, I., Szegedi, J., Kiss, I., & ACEGENE-BB_HU workgroup. (2015)	Hungary	Observational study	660 patients
5	The effects of hypoxia-inducible factors-1α and -2α and erythroferrone on hepcidin in patients with chronic kidney disease stages 3–5 and renal anemia	Hong, J., Lai, J., Chen, X., Yan, Y., Hong, Y., Ke, H., & Zheng, J. (2022).	China	Observational study	90 patients (30 stage 3 CKD, 30 stage 4 CKD, 30 stage 5 CKD) and 30 control
6	The role of genetic polymorphisms in STIM1 and ORAI1 for erythropoietin resistance in patients with renal failure	Kao, C. C., Wong, H. S. C., Wang, Y. J., Chou, W. H., Perwitasari, D. A., Wu, M. S., & Chang, W. C. (2021).	Taiwan	Observational study	194 patients
7	The A736V TMPRSS6 polymorphism influences hepcidin and iron metabolism in chronic hemodialysis patients: TMPRSS6 and hepcidin in hemodialysis	Pelusi, S., Girelli, D., Rametta, R., Campostrini, N., Alfieri, C., Traglia, M., ... & Valenti, L. (2013).	Italy	Observational study	199 patients and 188 control

The study used subjects of chronic kidney disease or ESRD patients on hemodialysis in several populations. We found four article studies about polymorphism of the ACE I/D gene, one article study about minor alleles of STIMI and ORA 1, one article study about TMPRSS, and one article study about HIF1α. [7–12]

cell production rates worsen the supply and demand balance the production rate of red blood cells worse the balance of supply and demand. The iron supplementary is mandated to overcome this condition. However, both the ESA's use and the therapeutic dose of iron supplementation varied between individuals, with some patients developing tolerance and resistance to such intervention.

Erythropoietin Stimulating Agent (ESA) hyporesponsiveness is defined as means having no increase in hemoglobin concentration from the baseline after the first month of treatment on appropriate weight-based dosing. Moreover, the crucial important factors associated with ESA hyporesponsiveness include absolute or functional iron deficiency, inflammation, and uremia [4].

Genetic predispositions were also responsible for the EPO response. Several lines of evidence suggest an association between genetic polymorphisms (variant genetics) and EPO resistance [5,6]. Variant genetics were associated with EPO resistance in hemodialysis patients are HIF1α, ACE I/D, STIM1, ORAI1, and TMPRSS6 [7–12].

Objective: to analyze the published data on the genetic variants (HIF1α, ACE I/D, STIM1, ORAI1, TMPRSS6) on erythropoietin resistance in dialysis patients with chronic kidney disease.

RESEARCH METHODS

This scoping review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. We searched Scopus, PubMed, Cochrane Library, Proquest, Science Direct, Wiley, and EbscoHost databases for publications including the following keywords: erythropoietin

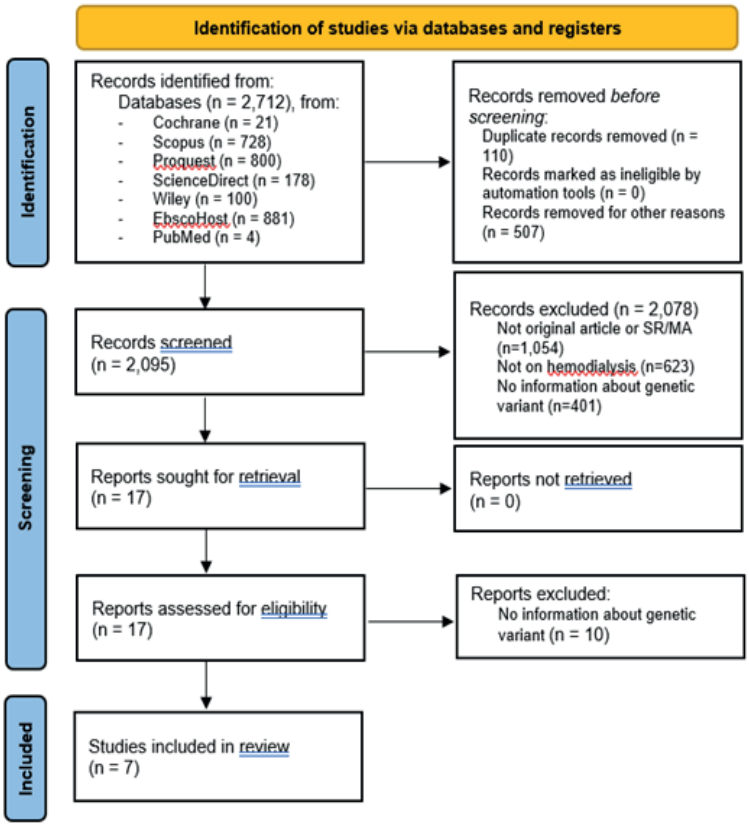

Figure 1. Article Synthesis Flow

AND chronic kidney failure AND (““orai1”” OR ““stim1”” OR ““angiotensin-converting enzyme”” OR ““tmprss6”” OR ““hif1a””). The year of publication ranges from 2012 to 2022. English is the language used. Observational studies (case-control, cohort, cross-sectional) are examples of study designs; a total of seven papers were retrieved and analyzed.

RESULT

There are 2,712 articles of search results using keywords in seven databases consisting of Cochrane (n=21), Scopus (n=728), Proquest (n=800), Science Direct (n=178), Wiley (n=100), EBSCOhost (n=881), and PubMed (n=4). There are 110 duplicate articles and 507 records removed for other reason, such as unreadable title, or only one word title, no author description reasons, such as unreadable titles, only one-word titles, no author descriptions, etc. The next following process is the screening of screening titles and abstracts, from 2,095 articles, 17 articles are filtered. There were 2,078 articles excluded because they were not original articles or systematic reviews/ meta-analysis, not patients with chronic kidney disease on hemodialysis, and no information about genetic variants. Then, 17 full-text articles were tested for eligibility, and 1010 articles were excluded due to no information about genetic variants. At the final end, seven articles were included in the review (Figure 1).

The characteristics of the evidence source consist of the study title, studier name, year of publication, study site, study design, and sample size presented in tabular form (Table 1).

DISCUSSION

In this scoping review, we summarized the effect of gene polymorphism on erythropoiesis response. One prospective study, revealed that patients with the I/D genotype had a more significant elevation in serum EPO levels with time, followed by the D/D genotype. In contrast, the I, whereas I/I genotype had a nonsignificant increase. There were no significant differences in hemoglobin levels between patients with CKD and control groups. The EPO and Hb serum positively correlated A significant positive correlation was observed between serum EPO and Hb in normal healthy subjects with different ACE genotypes. The results is indicated that Hb levels will increased when EPO serum increased. A nonsignificant and negative correlation was observed between serum EPO and Hb in CKD patients with different ACE genotypes throughout the study. The negative correlation means is indicates that that Hb levels will decrease decreased despite increasing EPO serum even though serum EPO increased [9].

The angiotensin-converting enzyme (ACE) insertion/ deletion (I/D) gene polymorphism, correlating with circulating and cellular ACE concentrations. Hemodialysis patients with the ACE G2350A (rs4343) D/D and I/I genotypes respond better to rHuEpo therapy than those with the I/D genotype, as evidenced by the higher Hb level among the former group. This higher Hb level among D/D and I/I genotypes were not related to iron level. The study showed that patients with the I/D allele had higher iron than patients with each of the D/D and I/I genotypes, despite the lower Hb level of the I/D allele holders [10,11].

Another prospective study displayed an affiliation between the D/D genotype and an early increase in blood hemoglobin concentration, erythrocyte count, and hematocrit. There was a significant decrease of

Table 2. Study Summary of Genetic Variants

No.	Source	Types of Genetic Variants	Information	Conclusion
1.	Hamdan Almaeen, A., & Mostafa-Hedeab, G. (2021)	ACE G2350A (rs4343)	rs4343 I/D most prevalence genotype. D allele is the most prevalence allell. Influence on rHuEpo, anemia biomarkers, ACE content, inflammatory biomarkers, serum EPO, and soluble Epo EPO receptor (sEpoR)	Screening In HD patients, screening for ACE G2350A (rs4343)gene polymorphisms before rHuEpo administration may help predict patient response in HD patients.
2.	Al-Radeef, M. Y., Fawzi, H. A., & Allawi, A. A. (2019)	ACE I/D Polymorphism	Evaluation of the frequency of angiotensin-converting enzyme gene polymorphisms in hemodialysis patients in Iraqi and knowing the relationship between ACE gene polymorphisms on serum erythropoietin and hemoglobin levels.	Chronic kidney disease did not significantly alter angiotensin-converting enzyme genotypes, and angiotensin-converting enzyme gene polymorphism greatly affected had a significant effect on serum erythropoietin levels and had a nonsignificant effect on hemoglobin levels.
3.	Savin, M., Hadzibulic, E., Damnjanović, T., Šantric, V., & Stankovic, S. (2017).	ACE I/D Polymorphism	Comparing the efficiency of intravenous and oral iron supplementation in CKD patients during hemodialysis and ACE I/D genotype factors	An important impact of ACE-I/D genotype on hematological regulation was observed in patients on hemodialysis. The genetic ACE typing can provide valuable information regarding the optimal dosage of rHuEpo and iron supplementation via oral or intravenous administration.
4.	Kiss, Z., Ambrus, C., Kulcsár, I., Szegedi, J., Kiss, I., & ACEGENE-BB_HU workgroup. (2015)	ACE I/D Polyphorphism	To determine the effect of the combination of ACE I/D polymorphism and ACE-inhibitor therapy on the erythropoiesis of hemodialysis patients.	The ACE gene I/D polymorphism (I/I, I/D, D/D) and age were not associated with haemoglobin levels. ACE I therapy may increase erythropoietin resistance and worsen erythropoiesis in hemodyalisis patients with the D allele.
5.	Hong, J., Lai, J., Chen, X., Yan, Y., Hong, Y., Ke, H., & Zheng, J. (2022).	Hypoxia-inducible factors-1α and -2α and erythroferrone	To determine the effect of HIF 1a, HIF-2a, and erythroferrone (ERFE) on the hepcidin of patients with CKD stages 3-–5 and renal anemia	HIF-1α, HIF-2α, and SF are factors which have an effect on influence hepcidin in patients with CKD stages 3–5 and renal anemia. The increase of HIF-1α, HIF-2α, and ERFE does not seem to inhibit the increase of hepcidin.
6.	Kao, C. C., Wong, H. S. C., Wang, Y. J., Chou, W. H., Perwitasari, D. A., Wu, M. S., & Chang, W. C. (2021).	STIM1 dan ORAI1	To determine the relationship between genetic polymorphisms in the SOC signaling pathway and erythropoietin resistance in patients with renal failure	The minor allele of rs1561876 in STIM1 was associated with a lower risk of EPO resistance. The minor allele of rs6486795 in ORAI1 was also associated with a higher risk of EPO resistance. Functional annotations of the polymorphisms suggested that the underlying mechanism of calcium-dependent pathways, addressing further investigations into the roles of SOC polymorphisms in regulating the regulation of inflammation and EPO signaling.
7.	Pelusi, S., Girelli, D., Rametta, R., Campostrini, N., Alfieri, C., Traglia, M., ... & Valenti, L. (2013).	A736V TMPRSS6 polymorphism	Evaluation of the A736V TMPRSS6 polymorphism, as a major genetic determinant of iron metabolism in healthy patients, affects on serum hepcidin levels of hepcidin. This hormone, a hormone that regulates iron metabolism and erythropoiesis in chronic hemodialysis.	The A736V TMPRSS6 genotype influences hepcidin levels, erythropoiesis, and anemia management in CHD patients. Evaluation of the effect of the TMPRSS6 genotype on clinical outcomes in prospective studies of in CHD may help predict be useful to predict the results outcomes of hepcidin manipulation, and to guide treatment personalization by optimizing anemia management.

in rHuEpo dosage in patients with the D/D genotype within the second month of the study. The patients with either I/D or I/I genotype were not as responsive to changes in rHuEpo measurement, and their hemoglobin levels remained much more steadier at the same time [14].

One study evaluated the effect of the combination of ACE I/D polymorphism and ACE-inhibitor therapy on the erythropoiesis of hemodialysis patients. Haemoglobin levels were lower in patients on ACE-I therapy in the entire cohort and patients with I/D and D/D genotypes. In patient pairs treated with ACE-I therapy, subjects with the D/D genotype had lower haemoglobin levels and higher erythropoietin resistance index (ERI) than individuals with the I/I genotype. These results indicate that ACE-I therapy may increase erythropoietin resistance and worsen erythropoiesis in haemodialysis patients with the D allele [15].

The screening in dialysis patients for ACE G2350A (rs4343) gene polymorphisms before rHuEpo administration may help predict patient response. This Predicting patient response is integral important to to determining the next therapeutic step in receiving blood transfusions or not. Evaluation of the frequency of angiotensin-converting enzyme (ACE) gene polymorphisms in hemodialysis chronic kidney disease did not significantly alter angiotensin-converting enzyme genotypes, and angiotensin-converting enzyme gene polymorphism had a significant effect on serum erythropoietin levels and a nonsignificant effect on hemoglobin levels. The impact of the ACE-I/D genotype on hematological regulation was observed in patients on hemodialysis. The genetic ACE typing can provide valuable information regarding the optimal dosage of rHuEpo and iron supplementation via oral or intravenous [16.]

For patients with CKD and renal anemia, due to a progressive increase in hepcidin, a decrease in serum iron, and a decrease in EPO production, the degree of anemia is more severe, resulting in hypoxia, and the progressive increase of HIF and ERFE expressions inhibits grow than increase in hepcidin. Although HIF cannot directly regulate ERFE, HIF can indirectly alter ERFE by regulating EPO [17].

One article explain that the minor allele of rs1561876 in STIM1 was associated with a lower risk of EPO resistance, and the minor allele of rs6486795 in ORAI1 was also associated with a higher risk of EPO resistance in a dominant model. Anemia is a common complication in patients with renal failure. While erythropoietin is commonly used to treats anemia, some patients exhibit a poor response to erythropoietin. Since store-operated calcium channel (SOC) signaling is one of the erythropoietin-activated pathways [18].

Another study found that the TMPRSS6 gene was not associated with mortality and cardiovascular disease in ESRD patients. The TMPRSS6 736V variant is associated with higher hepcidin levels in chronic hemodialysis patients. Serum transferrin was affected by the combined effect of sex and polymorphism TMPRSS6 A736V in ESRD patients [7,19].

CONCLUSSION

These study related to EPO therapy has been discussed, and many genetic variants affect the success of EPO therapy, with different mechanisms. However, all studies explain that EPO therapy is given after seeing the success of Fe therapy at the previous stage. Meanwhile, the genetic variants discussed in the study are related to iron deficiency mechanisms, hypoxia, inflammatory factors (Hepcidine), and calcium pumps. Genetic variants recognized earlier than therapy may help the effectiveness and efficiency of EPO therapy.

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