THE IMPORTANCE OF POLYMORPHISMS OF REGULATORY AND CATALYTIC ANTIOXIDANT PROTEINS IN CHRONIC KIDNEY DISEASE

ZNAČAJ POLIMORFIZAMA REGULATORNIH I KATALITIČKIH ANTIOKSIDATIVNIH PROTEINA U HRONIČNOJ BUBREŽNOJ SLABOSTI

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Abstract

Both excessive production of reactive oxygen species (ROS) and impaired antioxidant function are found in patients with chronic kidney disease (CKD). Therefore, individual susceptibility towards CKD can be induced by functional variations of genes encoding antioxidant regulatory (nuclear factor erythroid 2 – related factor 2 (Nrf2)) and catalytic (superoxide dismutase (SOD2) and glutathione peroxidase (GPX1)) proteins. Several types of single nucleotide polymorphisms (SNPs) have been found within the genes encoding these proteins, with Nrf2 (-617C/A), SOD2 (Ala16Val) and GPX1 (Pro198Leu) conferring impaired catalytic activity. The most unexplored gene polymorphism in CKD susceptibility, progression and survival, with only two original studies published, is the Nrf2 (-617C/A) polymorphism. The results of these studies showed that there was no individual impact of this polymorphism on the susceptibility towards end stage renal disease (ESRD) development, oxidative phenotype and mortality. However, Nrf2 had a significant role in ESRD risk and survival, when combined with other antioxidant genes. The results regarding the impact of SOD2 (Ala16Val) and GPX1 (Pro198Leu) polymorphisms on either CKD or ESRD are still inconclusive. Namely, some studies showed that patients having variant SOD2 (Val) or GPX1 (Leu) allele were at increased risk of CKD development and progression, while other studies reported only weak or no association between these polymorphisms and CKD. Surprisingly, the only study that reported an association of GPX1 polymorphism with overall/cardiovascular survival in ESRD patients showed a significant impact of low activity GPX1 (Leu/Leu) genotype on better survival. In this review, we comprehensively and critically appraise the literature on these polymorphisms related to oxidative stress in CKD patients, in order to identify gaps and provide recommendations for further clinical research and translation. New developments in the field of antioxidant polymorphisms in CKD patients could lead to better stratification of CKD patients, based on a prognostic antioxidant gene panel, and provide a more personalised medicine approach for the need of antioxidant therapy in these patients.

Keywords:
CKD, Nrf2, SOD2, GPX1, gene polymorphisms

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Introduction

Chronic kidney disease (CKD) is a multifactorial disorder which is comprised of a broad range of adverse outcomes, accompanied with poor quality of life and high medical costs. CKD is a syndrome characterised by structural and/or functional kidney abnormalities, which persist for more than 3 months, or decreased glomerular filtration rate (GFR) below 60 mL/min/1.73 m², irrespective of the underlying cause (1). With regard to GFR, CKD is classified into five stages (G1 - G5). The final stage of CKD is called end stage renal disease (ESRD), which occurs when GFR drops below 15 mL/min per/1.73 m² (stage G5) (1). At this point, kidney function is severely compromised and kidney replacement therapy is required. Therefore, CKD and its final stage, ESRD, are accompanied with excessive morbidity and mortality, mostly due to the cardiovascular complications and cancer (2–4). Oxidative stress has been demonstrated as one of the main contributing factors to CKD pathogenesis, as well as its long term complications (5–9).

Oxidative stress can be described as a disturbance in the balance between the prooxidants and antioxidants, where prooxidant insults predominate (10, 11). Previously, oxidative stress was conceptualized as pertaining to molecular damage (10). However, new findings paved the way towards the understanding of oxidative stress as relevant for redox signalling, as well (11). Both excessive production of reactive oxygen species (ROS) and impaired antioxidant function are frequently reported in CKD patients. Several factors potentiate oxidative burden in CKD. Some of these factors include the following: accumulated uremic toxins, iron therapy, mitochondrial dysfunction, endoplasmic reticulum stress, as well as the increase in oxidative enzymes activity (myeloperoxidase, nicotinamide adenine dinucleotide phosphate-oxidases, xanthine oxidase) and endothelial nitric oxide synthase (eNOS) uncoupling (8, 12–17). Moreover, in ESRD patients, the increased generation of ROS is strongly mediated by haemodialysis treatment itself, mostly due to membrane bio-incompatibility and endotoxin (LPS) release (17, 18). On the other hand, antioxidant systems, including non-enzymatic (thiols, vitamin C, vitamin E), as well as enzymatic systems (superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT)) are both impaired or deficient in patients with CKD (19–22). The antioxidant loss in CKD patients may be a consequence of the therapy with diuretics, illness-specific diet, as well as decreased intestinal absorption (23). Additionally, the haemodialysis in ESRD patients leads to solute loss, including loss of hydrophilic non-enzymatic antioxidants (19, 24, 25). The excessive production of free radicals induces oxidative (OH−), nitrosative (ONOO−) and chlorinative (OCl−) modifications of proteins, lipids and DNA, resulting in cellular and tissue injury (17, 22, 26–29). Indeed, heightened levels of oxidation markers of proteins, lipids and DNA damage have all been consistently reported in studies comparing clinical CKD population with healthy controls (30, 31). Oxidative stress is a mediator of progressive deterioration of kidney function, as well as of cardiovascular, neurological and...
other complications in these patients: it is involved in the pathophysiology of endothelial dysfunction and atherosclerosis, hypertension, reduced erythrocyte half-life, and inflammation (7, 9, 32).

Excessive oxidative stress in patients with CKD could be related to specific genetic patterns (17). Namely, genetic polymorphisms of regulatory (nuclear factor erythroid 2-related factor 2 (Nrf2)) and catalytic antioxidant proteins (SOD2 and GPX1) result in alteration in their proteins activity profile, hence affecting individuals antioxidant capacity (33–36). In this comprehensive review, the focus was on the studies examining significance and roles of single nucleotide polymorphisms (SNPs) of Nrf2, SOD2 and GPX1 genes in CKD susceptibility and prognosis, outlining their importance and potential for clinical application.

### NRF2 Polymorphism and CKD

Nrf2 is a cytoprotective transcription factor which regulates basal activity, as well as the coordination of induction of a broad range of genes encoding antioxidant and detoxifying enzymes (SOD, CAT, GPX, glutathione S-transferase (GST), thyroredoxin, etc.) (30, 37–41). It binds to a Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm (39, 42, 43). Keap1, in turn, promotes the ubiquitination and proteasomal degradation of Nrf2 (38, 42, 44, 45). Several reactive cysteine residues present in Keap1 can be modified by electrophilic and oxidative insults which leads to the dissociation of Nrf2 from Keap1 and its transport to the nucleus, where it binds to the regulatory sequences, called antioxidant response elements (AREs) (17, 38, 41, 42, 44–46). AREs are located in the promoter region of an array of antioxidant and detoxifying genes (38, 41, 47). Therefore, Nrf2 has a critical position in cellular protection, orchestrating the expression of aforementioned genes (46, 48).

Increasing evidence from animal models supports the crucial impact that Nrf2 has on renoprotection and kidney disease pathogenesis (30). Namely, animal models with 5/6 nephrectomy–induced CKD had a marked decline in nuclear Nrf2, in contrary to the expected Nrf2 activation and upregulation (46). This points to the impaired remnant kidney capacity to deal with the oxidative stress and inflammation (17, 46). Experimental data showing the influence of Nrf2 in diabetic nephropathy was also reported by other researchers (30, 49, 50). In a model of streptozotocin-induced diabetes, Jiang et al. found that Nrf2-knockout mice had higher ROS levels and consequently higher DNA oxidative damage in glomeruli that wild-type mice (17, 50). Furthermore, Nrf2 - knockout experimental animals developed a lupus - like autoimmune nephritis (46, 51, 52). In addition, in a model of ischemia - reperfusion injury, Nrf2 - knockout mice had a greater decline in renal function and shorter survival than wild - type mice (30, 53). On the other hand, the administration of Nrf2 activators, including resveratrol, curcumin, sulforaphane and bardoxolone methyl, can be protective against kidney dysfunction in CKD (30, 54). Therefore, studies using animal models with targeted deletion of Nrf2 have provided insights into the role of Nrf2 in kidney disease pathogenesis (30, 55). Subsequent studies investigating the genetic and molecular function of human Nrf2, including the relationship of Nrf2 polymorphisms with the CKD and its final stage - ESRD, have emerged recently (54 – 56).

Human Nrf2 is positioned on the cytogenetic band 2q31.2 of chromosome 2 (55, 57). Numerous SNPs have been found in the Nrf2 gene (33, 42, 55, 58). Of special importance is the functional Nrf2 rs6721961 polymorphism, located in the promotor region of the gene, which is characterised by a C > A substitution (33). It affects ARE-like promoter binding sites, attenuating the efficient binding of this transcription factor to AREs (33, 58). This results in a reduction in the Nrf2 transcription activity, and a consequent decrease in Nrf2-dependent antioxidant and detoxifying gene transcription (33). So far, only two
research studies (table 1) have reported the association of Nrf2 (-617C/A) polymorphism, either with the level of oxidative stress biomarkers in plasma of ESRD patients (54), or the susceptibility towards ESRD development and prognosis (54, 56). In the study conducted on 256 Serbian patients and 374 healthy controls, Nrf2 (-617C/A) polymorphism was not associated with the oxidative phenotype of these patients, nor with the ESRD risk (54). In the same study, Nrf2 C/C genotype had an impact by increasing risk of ESRD, in combination with SOD2 Val/Val genotype, and longer overall survival, after being combined with GPX1 Leu/Leu genotype (54). Nevertheless, no individual association of Nrf2 (-617C/A) polymorphism was observed in relation to the risk, overall and cardiovascular survival among these patients (54). These results are similar to those obtained in a study of Shimoyama et al. using Japanese cohort of 216 ESRD patients and 464 controls (56). In this study, aforementioned Nrf2 polymorphism did not have an impact on the risk of ESRD development or overall/cardiovascular survival. The only significant association was found between other Nrf2 polymorphism, G/A rs35652124 and cardiovascular survival in dialysed patients (56).

Table 1. The association of SOD2, GPX1 and Nrf2 polymorphisms with CKD risk, progression and mortality

| Reference       | Location | Study group | SOD2 rs4880 | GPX1 rs1050450 | Nrf2 rs6721961 |
|-----------------|----------|-------------|-------------|----------------|----------------|
| Crawford et al. 2011. | Australia | 185 CKD patients | Ala/Val and Val/Val genotypes had a significantly greater eGFR decline compared to those with the Ala/Ala genotype | No significant association with the progression of CKD | NR |
| Crawford et al. 2012. | Australia | 230 CKD patients / 224 controls | No significant association with CKD risk | Leu/Leu genotype was associated with increased risk of CKD and lower eGFR | NR |
| Shimoyama et al. 2014. | Japan | 216 ESRD patients / 464 controls | Ala/Ala genotype was associated with increased risk of ESRD | No individual significant association with ESRD risk. GPX1 Leu/Leu genotype was associated with increased risk of ESRD when combined with PPAR - γ G/G genotype. | NR |
| Chao et al. 2016. | China | 671 ESRD patients / 780 controls | Ala/Ala genotype was associated with increased risk of CKD | Val/Val genotype was associated with increased risk of CKD | NR |
| Abbasi et al. 2018. | Iran | 280 CKD patients / 280 T2D controls | Val/Val genotype was associated with increased risk of CKD | No individual significant association with ESRD risk. Nrf2 C/C genotype was associated with increased risk of ESRD when combined with SOD2 Val/Val genotype. Nrf2 (C/C) genotype was associated with longer overall survival when combined with GPX1 (Leu/Leu) genotype. | NR |
| Jerotic et al. 2019. | Serbia | 256 ESRD patients / 374 controls | Val/Val genotype was associated with increased risk of ESRD. No significant association with overall and cardiovascular survival. | No individual significant association with ESRD risk. Nrf2 Leu/Leu genotype was associated with increased risk of ESRD when combined with SOD2 Val/Val genotype. GPX1 (Leu/Leu) genotype was associated with longer cardiovascular survival. | NR |
| Corredor et al. 2020. | Spain | 722 CKD patients / 172 controls | No significant association with CKD risk | No significant association with CKD risk | NR |

Abbreviations: Not reported (NR)

ESRD patients and 374 healthy controls, Nrf2 (-617C/A) polymorphism was not associated with the oxidative phenotype of these patients, nor with the ESRD risk (54). In the same study, Nrf2 C/C genotype had an impact by increasing risk of ESRD, in combination with SOD2 Val/Val genotype, and longer overall survival, after being combined with GPX1 Leu/Leu genotype (54). Nevertheless, no individual association of Nrf2 (-617C/A) polymorphism was observed in relation to the risk, overall and cardiovascular survival among these patients (54). These results are similar to those obtained in a study of Shimoyama et al. using Japanese cohort of 216 ESRD patients and 464 controls (56). In this study, aforementioned Nrf2 polymorphism did not have an impact on the risk of ESRD development or overall/cardiovascular survival. The only significant association was found between other Nrf2 polymorphism, G/A rs35652124 and cardiovascular survival in dialysed patients (56). Even though aforementioned studies contributed to clearer positioning of Nrf2 polymorphisms in the overall picture of complex interactions present in ESRD, there are still numerous unexplored issues in this field. Ongoing, promising developments in therapeutic interventions are underway, with several possible candidates that might be beneficial to patients with diminished Nrf2 expression and function, as present in variant, Nrf2 A carriers. A common feature of these compounds is the potential for inducing Nrf2 pathway. One example of such a compound is bardoxolone methyl, which effects on CKD patients were examined in clinical trial investigations (59). Measurable improvement in clinical parameters of CKD patients determined in those studies included a significant increase in GFR, as well as creatinine clearance (59). These effects could be attributed to bardoxolone methyl's activation of the Nrf2 pathway, and subsequent restoration of redox imbalance (59).

SOD2 Polymorphism and CKD

SOD and GPX are antioxidant enzymes that work in a mutually supportive fashion in scavenging superoxide...
radicals and decreasing oxidative stress, abundantly produced in CKD. SOD converts superoxide (O$_2^-$) to hydrogen peroxide (H$_2$O$_2$) with three isoforms being described in the literature (17, 60, 61). Two SOD isoforms contain copper (Cu) and zinc (Zn) within the active site: intracellular SOD1 - present in red blood cells, and extracellular SOD3 - present in interstitium and extracellular fluids (17, 62, 63). On the other hand, SOD2 contains an manganese within the active site (MnSOD) and is positioned within mitochondria, where it scavenges superoxide radicals (22, 63). In humans, the polymorphisms have been identified in all these three SOD isoforms (64). Nevertheless, the most highly active SOD isoform in the human kidney is SOD2 isoform and its rs4880 functional polymorphism has the highest implication in human diseases investigated so far. Therefore, the main focus of this review will be the association of SOD2 rs4880 polymorphism and CKD risk and progression.

MnSOD gene is positioned on chromosome 6q25 (34). The SOD2 rs4880 SNP, located in exon 2, is characterised by a C > T nucleotide substitution resulting in the amino acid alanine (Ala) > valine (Val) substitution at position 16 (SOD2 Ala16Val genotype) (64, 65). Importantly, the Val variant of this SNP compromises the ability of SOD2 to neutralize superoxide radicals within the mitochondria by altering SOD2 expression, as well as mitochondrial transport (34, 64). In this line, there are indications that the Ala allele, accompanied with higher SOD2 mitochondrial activity, may provide better protection against the progression of oxidative stress associated diseases such as CKD (54, 61).

To the best of our knowledge, six original investigations have so far tested an association between SOD2 rs4880 SNP and either CKD or ESRD, with contradictory results (table 1). In the Crawford et al. study, among 185 CKD patients included, those carrying low activity SOD2, Val allele had a marked drop in GFR, in comparison with patients carrying the Ala/Ala genotype (61, 66). In addition to the influence that Val allele has in terms of faster progression of CKD measured through the GFR deterioration, it has been shown that it might influence the risk of the CKD and ESRD development, as well. Namely, in a study of Jerotic et al., SOD2 Val/Val genotype resulted in a greater susceptibility towards ESRD (54). Similarly, in an Iranian cohort of 280 type 2 diabetic (T2D) patients with CKD and 280 T2D controls, patients with the Val/Val genotype exhibited higher CKD risk than those having the Ala/Ala or Ala/Val genotypes (67). Additionally, several studies consistently confirmed that the Val allele increases the risk and the progression of diabetic nephropathy with a faster decline in GFR (68–71). On the other hand, in a cohort of 671 ESRD patients and 780 healthy controls from China, the Val allele appeared to be protective, given that the Ala/Ala genotype correlated with increased risk of ESRD (72). This could be due to differences in the genotype distribution between Asian and Caucasian population. Namely, the frequency of the Ala/Ala genotype in Caucasians was 32%, whereas in the Asian population it was only 2% (54, 66, 72). On the contrary to the aforementioned reports, two studies conducted in Australia (230 CKD patients and 224 healthy controls) and Spain (722 CKD patients and 172 controls), reported no association between SOD2 rs4880 polymorphism and CKD risk (61, 73).

As discussed above, increased production of ROS is accompanied by impaired antioxidant defense in CKD. However, the functional significance of antioxidant enzyme polymorphisms in terms of the level of oxidative stress byproducts in these patients still remains elusive. Jerotic et al. have also shown that polymorphisms of enzymes front-line protection against free radicals, such as SOD2, can raise byproducts of oxidative damage in ESRD patients (54). In addition to having higher susceptibility to ESRD development, dialysis patients with the SOD2 Val/Val genotype also had higher plasma levels of byproducts of protein oxidative damage (thiol and carbonyl groups, advanced oxidation byproducts (AOPP, nytrotyrosine), as well as lipid oxidative damage (MDA and MDA adducts) (54). The substantial role of SOD2 polymorphisms on
oxidative stress in patients with impaired kidney function was also confirmed in a large study conducted on patients with diabetes mellitus induced nephropathy (70).

The most widely studied impact of SOD2 rs4880 polymorphism, in terms of kidney pathology, was the one associated with the onset and progression of diabetic nephropathy (66, 68–71). These studies consistently showed that the low activity, Val allele affects the higher susceptibility to diabetic nephropathy and its progression. However, association of SOD2 polymorphism with an antioxidant status, levels of oxidative stress biomarkers and their implications to CKD triggered by either diabetes or other factors, still need to be clarified in future studies.

**GPX1 Polymorphism and CKD**

Dismutation of O2- to H2O2 by SOD is followed by H2O2 reduction to water, which is a process primarily mediated by another antioxidant enzyme, glutathione peroxidase (17). GPX is a selenoprotein containing the rare amino acid selenocysteine at its active site (17, 74). Noteworthy, the activity of GPX enzyme is significantly altered in all stages of CKD (22). Multiple studies consistently reported marked decrease in GPX activity from the CKD onset through the progression of uremia, with the lowest activity found in ESRD patients (21, 22, 75, 76). Several isozymes of glutathione peroxidase family that vary in cellular location and substrate specificity have been identified so far (17, 77). GPX1 is the most abundant isozyme in the glutathione peroxidases family (17, 35, 77). This enzyme is cytosolic and produced in all tissues (17, 64, 77). Nevertheless, the main sources of GPX1 are erythrocytes, liver and kidneys (17, 64, 77).

The GPX1 gene is positioned on the 3p21.3 chromosome and has two exons (78). Of a particular importance is the functional GPX1 rs1050450 polymorphism, which induces C > T substitution changing the amino acid proline (Pro) with leucine (Leu) at position 198 (GPX1 Pro198Leu genotype) (64). The Leu allele of GPX1 gene confers with significantly impaired enzyme activity, which was found in vitro and also confirmed in humans (35, 79). Moreover, Leu allele makes this enzyme less responsive to oxidative stress byproducts (AOPP and isoprostanes) and oxidative stress in plasma of these patients (54). However, another study demonstrated correlation of other GPX1 gene polymorphisms (rs3448, rs9819758, rs8179164 and rs1987628) and oxidative stress byproducts (AOPP and isoprostanes) (54, 81). In this study, T allele of GPX1 rs3448 gene had an impact on higher susceptibility to ESRD among diabetic patients, as well as, higher levels of AOPP and isoprostanes, while other examined GPX1 polymorphisms did not show any significant association (54). The aforementioned study of Jerotic et al. is also the only one examining the potential predictive influence of GPX1 rs1050450 polymorphism on ESRD patients survival (54). Unexpectedly, low activity, GPX1 Leu/Leu genotype contributed to longer overall, as well as cardiovascular survival in ESRD patients (54). Even though there are a few studies suggesting the adverse influence of GPX1 Leu allele on CVDs, such as coronary
heart disease, calcification of coronary arteries and increased intima-media thickness (74), there are also several studies conversely reporting that this allele may be protective (54, 74, 82, 83). Namely, it has been shown that Leu allele may reduce the risk of thoracic aortic aneurysm in patients with hypertension (74, 83). Moreover, Soerensen et al. showed that GPX1 Leu allele influenced longer survival in the oldest population (82). Overall, there is a subtle balance between the beneficial and deleterious effects of ROS, with complex signalling mechanisms that need to be explored further, in order to provide better understanding and enable clinical translation.

Conclusion

Already recognized causes of CKD converge at the final common pathway – oxidative stress mediated loss of renal function. Therefore, individual susceptibility to CKD seems closely linked to functional variations of genes, encoding antioxidant regulatory and catalytic proteins. The results reported so far in the literature suggest that these three different polymorphisms could be important targets for better patient outcomes. Identifying important polymorphism in CKD patients could lead to better stratification and more personalised treatment of CKD patients. Given that CKD is a multifactorial disease, a number of different biomarkers based on the presence of polymorphisms and biomarkers of oxidative stress should be included as part of the risk stratification strategies. The multimarker panel could be explored for prediction of CKD patients’ survival, or as an indicator of the need for antioxidant therapy on individual patient basis. New promising therapeutic possibilities are underway that might be beneficial to CKD patients with diminished Nrf2, SOD2 or GPX1 expression and function.

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