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ASSOCIATION OF SOD2 (ALA16VAL), GPX4 (C718T), AND COL1A1 (C1997A) GENE POLYMORPHISMS WITH GOUTY NEPHROPATHY IN PATIENTS WITH GOUT

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Abstract: Gouty nephropathy is one of the most important renal complications of gout. Oxidative stress, chronic inflammation, and extracellular matrix remodeling play an important role in its development. Therefore, candidate genes involved in antioxidant defense and connective tissue metabolism may influence susceptibility to renal involvement in patients with gout.

To evaluate the association of SOD2 (Ala16Val), GPX4 (C718T), and COL1A1 (C1997A) gene polymorphisms with gouty nephropathy in patients with gout.

A case-control study included 186 individuals. The control group consisted of 96 healthy subjects. Ninety patients with gout were divided into two groups: Group 1 included 45 patients with gout without gouty nephropathy, and Group 2 included 45 patients with gouty nephropathy. Allelic and genotypic frequencies of SOD2 (Ala16Val), GPX4 (C718T), and COL1A1 (C1997A) polymorphisms were compared between the clinical groups and the control group. Statistical analysis included χ^2 test, odds ratio (OR), and p values.

The strongest associations were observed for the SOD2 Ala16Val polymorphism in patients with gouty nephropathy. In Group 2, the Ala allele showed a protective association (χ^2=8.81; p=0.003; OR=0.34), whereas the Val allele was associated with increased risk (χ^2=8.81; p=0.003; OR=2.95). The Ala/Ala genotype also demonstrated a protective effect (χ^2=5.26; p=0.022; OR=0.38), while the Val/Val genotype was associated with a markedly increased risk of nephropathy (χ^2=5.52; p=0.019; OR=9.27). For GPX4 C718T, significant differences in Group 2 were found for the C allele (χ^2=4.00; p=0.045; OR=0.60) and T allele (χ^2=4.00; p=0.045; OR=1.67), while genotype-level associations were not statistically significant. For COL1A1 C1997A, Group 2 showed a lower frequency of the C allele (χ^2=8.81; p=0.003; OR=0.34), a higher frequency of the A allele (χ^2=8.81; p=0.003; OR=2.95), a protective effect of the C/C genotype (χ^2=5.26; p=0.022; OR=0.38), and a significant association of the A/A genotype with nephropathy risk (χ^2=5.52; p=0.019; OR=9.27).

The results indicate that SOD2 (Ala16Val), GPX4 (C718T), and COL1A1 (C1997A) polymorphisms are associated with susceptibility to gouty nephropathy in patients with gout, with the strongest association observed for SOD2 Ala16Val. These findings support the potential role of molecular genetic markers in identifying gout patients at increased risk of renal involvement.

Keywords: gout, gouty nephropathy, SOD2, GPX4, COL1A1, polymorphism, genetic susceptibility, oxidative stress, renal injury

Introduction

Gout is a chronic metabolic disorder characterized by hyperuricemia and deposition of monosodium urate crystals in joints and extra-articular tissues. In addition to articular manifestations, renal involvement is one of the most clinically important complications of this disease. Gouty nephropathy develops as a result of complex metabolic, inflammatory, hemodynamic, and structural mechanisms, ultimately leading to progressive impairment of renal function.

However, not all patients with gout develop kidney damage to the same extent. This suggests that, in addition to classical risk factors, genetic predisposition may contribute to the development of gouty nephropathy. Particular interest is focused on genes associated with antioxidant protection and extracellular matrix remodeling, since oxidative stress and chronic tissue injury play a major role in the pathogenesis of renal damage.

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The SOD2 gene encodes mitochondrial superoxide dismutase, which is one of the key antioxidant enzymes protecting cells from reactive oxygen species. Functional polymorphic variants of this gene may influence the severity of oxidative stress and predispose renal tissue to injury. The GPX4 gene encodes glutathione peroxidase 4, another essential antioxidant enzyme involved in protection against lipid peroxidation. Altered activity of this enzyme may enhance cellular and membrane damage under chronic inflammatory conditions. The COL1A1 gene encodes type I collagen alpha-1 chain and is involved in connective tissue structure and fibrotic remodeling, which are relevant to chronic renal injury and interstitial fibrosis.

Taken together, these genes are biologically plausible candidates for the development of gouty nephropathy. Identification of risk-associated alleles and genotypes may improve early stratification of patients with gout and provide additional insight into the molecular mechanisms underlying renal involvement.

The aim of this study was to assess the association of SOD2 (Ala16Val), GPX4 (C718T), and COL1A1 (C1997A) gene polymorphisms with gouty nephropathy in patients with gout.

Methods

Study design and participants. This case-control study included a total of 186 individuals. The control group comprised 96 apparently healthy subjects. The patient cohort included 90 individuals with gout, who were divided into two clinical groups:

Group 1: 45 patients with gout without gouty nephropathy Group 2: 45 patients with gouty nephropathy

The grouping was based on the presence or absence of clinical and laboratory signs of renal involvement.

Genetic analysis. The study investigated the following candidate polymorphisms: SOD2 (Ala16Val), GPX4 (C718T), COL1A1 (C1997A)

Allelic and genotypic frequencies were assessed and compared between the control group and each clinical subgroup.

Statistical analysis. Statistical analysis was performed using the χ^2 test to compare frequencies between groups. The strength of association was expressed as odds ratio (OR). A p value of less than 0.05 was considered statistically significant.

Results

SOD2 (Ala16Val) polymorphism. Comparative analysis of the SOD2 Ala16Val polymorphism showed no statistically significant differences between the control group and patients with gout without nephropathy (Group 1). The Ala allele demonstrated χ^2=0.34, p=0.142, OR=0.55, whereas the Val allele showed χ^2=2.95, p=0.142, OR=1.82. Similarly, no significant differences were observed for the Ala/Ala genotype (χ^2=0.38, p=0.153, OR=0.53), Ala/Val genotype (χ^2=1.38, p=0.193, OR=1.82), or Val/Val genotype (χ^2=9.27, p=0.581, OR=2.16).

In contrast, statistically significant differences were identified in patients with gouty nephropathy (Group 2). The Ala allele was less frequent and demonstrated a protective association (χ^2=8.81, p=0.003, OR=0.34), whereas the Val allele was more frequent and associated with increased risk (χ^2=8.81, p=0.003, OR=2.95). At the genotype level, the Ala/Ala genotype was associated with a protective effect (χ^2=5.26, p=0.022, OR=0.38), while the Val/Val genotype showed a strong association with gouty nephropathy (χ^2=5.52, p=0.019, OR=9.27). The Ala/Val genotype was not significantly associated with renal involvement (χ^2=1.69, p=0.193, OR=1.38).

Indicators	1-group			2-group		
	χ^2	p	OR	χ^2	p	OR
Ala	0,34	0,142	0,55	8,81	0,003	0,34
Val	2,95	0,142	1,82	8,81	0,003	2,95

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Ala/Ala	**0,38**	**0,153**	**0,53**	**5,26**	**0,022**	**0,38**
Ala/Val	**1,38**	**0,193**	**1,82**	**1,69**	**0,193**	**1,38**
Val/Val	**9,27**	**0,581**	**2,16**	**5,52**	**0,019**	**9,27**

Table 1. Association of SOD2 (Ala16Val) alleles and genotypes with gout without nephropathy (Group 1) and gouty nephropathy (Group 2).

GPX4 (C718T) polymorphism. Analysis of the GPX4 C718T polymorphism revealed no significant differences between the control group and Group 1. The C allele showed χ^2=0.01, p=0.938, OR=0.98, while the T allele showed χ^2=0.01, p=0.938, OR=1.02. Likewise, the C/C genotype (χ^2=0.01, p=0.917, OR=0.96), C/T genotype (χ^2=0.01, p=0.926, OR=1.03), and T/T genotype (χ^2=0.01, p=0.992, OR=1.00) were not significantly associated with disease in Group 1.

In Group 2, however, a statistically significant allelic association was observed. The C allele was less frequent in patients with gouty nephropathy and demonstrated a protective association (χ^2=4.00, p=0.045, OR=0.60), whereas the T allele was associated with increased risk (χ^2=4.00, p=0.045, OR=1.67). At the genotype level, the C/C genotype tended to be less frequent (χ^2=2.86, p=0.091, OR=0.50), and the T/T genotype tended to be more frequent (χ^2=2.29, p=0.130, OR=1.89), although these findings did not reach statistical significance. The C/T genotype was not significantly associated with nephropathy (χ^2=0.11, p=0.735, OR=1.13).

Кўрсткиичлар	1-гуруҳ			2-гуруҳ		
	χ^2	p	OR	χ^2	p	OR
C	0.01	0.938	0.98	4.00	0.045	0.60
T	0.01	0.938	1.02	4.00	0.045	1.67
C/C	0.01	0.917	0.96	2.86	0.091	0.5
C/T	0.01	0.926	1.03	0.11	0.735	1.13
T/T	0.01	0.992	1.00	2.29	0.130	1.89

Table 2. Association of GPX4 (C718T) alleles and genotypes with gout without nephropathy (Group 1) and gouty nephropathy (Group 2).

COL1A1 (C1997A) polymorphism. Evaluation of the COL1A1 C1997A polymorphism did not reveal statistically significant differences between the control group and Group 1. The C allele showed χ^2=2.16, p=0.142, OR=0.55, while the A allele showed χ^2=2.16, p=0.142, OR=1.82. Similarly, the C/C genotype (χ^2=2.04, p=0.153, OR=0.53), C/A genotype (χ^2=1.38, p=0.193, OR=1.82), and A/A genotype (χ^2=0.31, p=0.581, OR=2.16) were not significantly associated with disease in Group 1.

In contrast, in Group 2, significant differences were found. The C allele was less frequent and demonstrated a protective association (χ^2=8.81, p=0.003, OR=0.34), while the A allele was more frequent and associated with increased risk (χ^2=8.81, p=0.003, OR=2.95). The C/C genotype also showed a protective association (χ^2=5.26, p=0.022, OR=0.38). The A/A genotype was significantly associated with gouty nephropathy (χ^2=5.52, p=0.019, OR=9.27), whereas the C/A genotype did not show a statistically significant relationship (χ^2=1.69, p=0.193, OR=1.82).

Indicators	1-group			2-group		
	χ^2	p	OR	χ^2	p	OR

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C	2,16	0,142	0,55	8,81	0,003	0,34
A	2,16	0,142	1,82	8,81	0,003	2,95
C/C	2,04	0,153	0,53	5,26	0,022	0,38
C/A	1,38	0,193	1,82	1,69	0,193	1,82
A/A	0.31	0,581	2,16	5,52	0,019	9,27

Table 3. Association of COL1A1 (C1997A) alleles and genotypes with gout without nephropathy (Group 1) and gouty nephropathy (Group 2).

Discussion.

The present study demonstrated that the investigated gene polymorphisms were more strongly associated with gouty nephropathy than with gout without renal involvement. This finding supports the concept that molecular genetic factors may contribute specifically to renal susceptibility in patients with gout.

Among the studied markers, SOD2 (Ala16Val) showed the strongest and most consistent association with gouty nephropathy. The protective effect of the Ala allele and Ala/Ala genotype, together with the increased risk associated with the Val allele and especially the Val/Val genotype, suggests that impaired mitochondrial antioxidant defense may play an important role in renal injury in gout. Since SOD2 is a major antioxidant enzyme in mitochondria, reduced efficiency of reactive oxygen species neutralization may increase oxidative damage in renal tubular and interstitial structures.

The GPX4 (C718T) polymorphism demonstrated a weaker association. Significant findings were limited mainly to the allelic level in Group 2, where the C allele appeared protective and the T allele was associated with greater risk. Although genotype-level associations did not reach statistical significance, these data still suggest a possible contribution of impaired antioxidant membrane protection to the development of nephropathy.

The results obtained for COL1A1 (C1997A) are of particular interest because they point not only to genetic susceptibility but also to possible structural mechanisms of renal damage. The protective role of the C allele and C/C genotype, together with the strong association of the A allele and A/A genotype with gouty nephropathy, may reflect the role of connective tissue remodeling and fibrotic processes in disease progression.

An important observation is that in all three genes, statistically significant associations were much more evident in the nephropathy group than in the group without renal involvement. This indicates that these polymorphisms are likely related not simply to gout itself, but more specifically to the risk of renal complication development.

From a clinical point of view, these findings support the potential utility of molecular genetic markers in identifying patients with gout who are at increased risk of nephropathy. Such patients may benefit from closer follow-up, earlier detection of renal injury, and more individualized preventive and therapeutic strategies.

This study has several limitations. The sample size was moderate, and only three candidate polymorphisms were evaluated. In addition, gene-gene and gene-environment interactions were not analyzed. Therefore, the results should be interpreted as evidence of association rather than causality. Further studies in larger populations are necessary to validate these findings and to determine their predictive value in clinical practice.

Conclusion.

The present study showed that SOD2 (Ala16Val), GPX4 (C718T), and COL1A1 (C1997A) gene polymorphisms are associated with gouty nephropathy in patients with gout.

The most pronounced association was observed for SOD2 (Ala16Val), where the Ala allele and Ala/Ala genotype were protective, while the Val allele and Val/Val genotype were associated with increased risk of nephropathy. For GPX4 (C718T), significant associations were observed mainly at the allelic level in patients with gouty nephropathy. For COL1A1 (C1997A),

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the C allele and C/C genotype were protective, whereas the A allele and A/A genotype were associated with increased renal risk.

These findings indicate that molecular genetic markers involved in antioxidant defense and connective tissue remodeling may contribute to susceptibility to gouty nephropathy and may be useful in the early identification of high-risk patients with gout.

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