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REVIEW

# The effects of rosuvastatin on lipid-lowering, inflammatory, antioxidant and fibrinolytics blood biomarkers are influenced by Val16Ala superoxide dismutase manganese-dependent gene polymorphism

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Rosuvastatin is a cholesterol-lowering drug that also attenuates the inflammatory process and oxidative stress via the reduction of superoxide anion production. Superoxide anions are metabolized by manganese-dependent superoxide dismutase (MnSOD or SOD2) in the mitochondria. In humans, there is a gene polymorphism where a change of alanine (Ala) to valine (Val) occurs at the 16th amino acid (Ala16Val-SOD2). The VV genotype has been associated with the risk of developing several metabolic diseases, such as hypercholesterolemia. Thus, to further explore this phenomenon, this study investigated the influence of the Val16Ala-SOD2 polymorphism on the lipid profile and inflammatory and fibrinolytic biomarkers of 122 hypercholesterolemic patients undergoing the first pharmacological cholesterol-lowering therapy who were treated with 20 mg rosuvastatin for 120 days. The findings indicate that the VV patients who present a low-efficiency SOD2 enzyme exhibit an attenuated response to rosuvastatin compared with the A-allele patients. The effect of rosuvastatin on inflammatory and fibrinolytic biomarkers was also less intense in the VV patients. These results suggest some pharmacogenetic effects of Val16Ala-SOD2 in hypercholesterolemia treatment.

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## INTRODUCTION

Statins such as rosuvastatin were originally developed for their low-density lipoprotein (LDL) cholesterol-lowering effects but are now thought to improve cardiovascular morbidity and mortality through pleiotropic effects arising from their antioxidant, anti-inflammatory and antiplatelet properties.[1,2] Rosuvastatin has been studied in clinical trials involving 46 000 patients, and the results have shown its efficacy and safety in patients with a broad range of demographic and clinical characteristics, including younger and elderly patients, men and women, and those exposed to other risk factors or suffering from concomitant diseases.[3]

Prior investigations have shown that reactive oxygen species that generate oxidative stress and inflammation processes are potent target sites for rosuvastatin. This drug attenuates oxidative stress, mediating several antioxidant effects by reduction of NADPH oxidase levels, thus decreasing superoxide anion production.[4] Rosuvastatin also upregulates antioxidant enzymes, decreasing the genotoxic effects caused by high hydrogen peroxide ($H_2O_2$) levels.[5,6] Therefore, the effects of rosuvastatin are important in the maintenance of the redox state of the cells of the vascular wall and in decreasing the atherogenic process.

However, the potential pharmacogenetic effect of rosuvastatin with respect to its ability to alter the basal oxidative metabolism of individuals remains to be explored. Presently, the effect is believed to be due to the presence of a functional genetic polymorphism in molecules participating in the enzymatic antioxidant system. Humans present a polymorphism in the manganese-dependent superoxide dismutase (MnSOD or SOD2) gene located in nuclear DNA.

The SOD2 enzyme is considered a vital enzyme because it dismutases superoxide anion to $H_2O_2$ in mitochondria. Furthermore, its intermediary molecule is catalyzed into $H_2O_2$ and $O_2$ by the glutathione peroxidase enzyme. Increased superoxide anion production is a feature of vascular disease states, including atherosclerosis, hypertension and diabetes.[7] In addition, nitric oxide scavenging by superoxide reduces the bioactivity of nitric oxide and produces peroxynitrite—a strong oxidant molecule that nitrosylates cellular proteins and lipids.[8]

The functional single-nucleotide polymorphism (SNP) occurs via the change of valine (Val) to alanine (Ala) at the 16th amino acid (the 16th amino acid from the beginning of the signal sequence or the 9th amino acid from the first amino acid of the mature protein) of the SOD2 (Val16Ala-SNP) signal sequence. Compared with the Val-SOD2 precursor, the Ala-SOD2 precursor generated 30–40% more of the active processed matrical SOD2 homotetramer.[9]

Previous investigations have associated the V allele and/or VV genotype with several metabolic chronic dysfunctions and diseases,[10] including hypercholesterolemia,[11] obesity[12] and elevated oxidized LDL levels.[13,14] The VV and AV cells presented higher levels of inflammatory cytokines such as interleukin 1 (IL-1),

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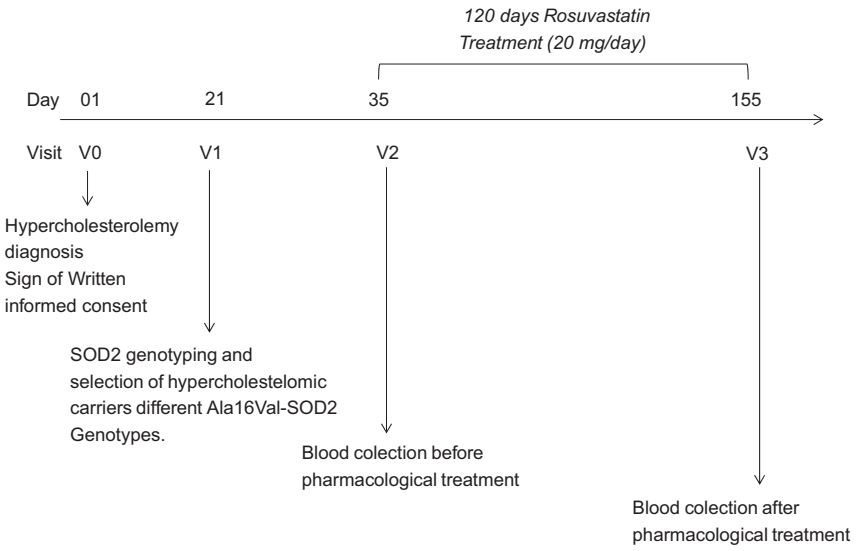


**Figure 1.** General experimental design of the study.

IL-6, tumor necrosis factor alpha (TNFα) and interferon gamma, as well as a reduction in the levels of anti-inflammatory interleukin 10 (IL-10) compared with AA cells.[15] An association between the V allele and the presence of carotid atherosclerosis,[16] as well as with type 2 diabetes development[17] and diabetes complications,[18–22] was also described. In addition, an *in vitro* study yielded findings suggesting that VV genotypes present an impaired anti-inflammatory response to methotrexate, a drug used in the treatment of autoimmune diseases such as psoriasis and rheumatoid arthritis.[14]

To gain a better understanding of these relationships, we investigated whether Ala16Val-SNP was associated with the response to rosuvastatin therapy. This was achieved by evaluating the effect on the lipid profile and the inflammatory and fibrinolytic biomarkers in diagnosed hypercholesterolemic subjects undergoing their first pharmacological cholesterol-lowering therapy. Using multivariate analysis, we also sought to establish whether these results are influenced by the sex, age and body mass index (BMI; kg $m^{-2}$) of patients.

## MATERIALS AND METHODS

### Setting and study sample

This study is a part of a broader research project in which the gene–environmental interaction associated with the aging processes and chronic diseases (Genesis project) was analyzed. The research was developed in free-living populations from southern Brazil[23] and included an investigation conducted by Duarte *et al.*,[11] which described the association between Ala16Val-SNP and hypercholesterolemia. All the study participants provided their written informed consent, and this protocol was approved by the Human Ethics Committee of the Federal University of Santa Maria (number 23081.009087/2008).

Figure 1 presents the general experimental design of the study discussed in this work. The sample consisted of 122 hypercholesterolemic individuals (41 AA, 41 VV and 40 AV genotypes) that have not previously undergone pharmacological cholesterol-lowering therapy. All the patients were diagnosed between 1 January 2013 and December 2014 and were prospectively enrolled at LABIMED, located in Santa Maria-RS, Brazil. All the study participants had high cholesterol levels, ranging from $\geqslant 240$ to 529 mg $dl^{-1}$ (6.47–13.70 mmol $l^{-1}$) and LDL cholesterol $\geqslant 160$ mg $dl^{-1}$ (4.15 mmol $l^{-1}$). We used a maximum value of 529 mg $dl^{-1}$ to decrease the possibility of including individuals with familial hypercholesterolemia, who typically present with very high levels of total cholesterol.[24] The exclusion criteria were previous coronary disease, stroke, neoplasias, morbid obesity ($>35$ kg $m^{-2}$), type 2 diabetes and metabolic syndrome. Individuals undergoing hypolipemic treatment or taking anti-inflammatory or other medications that could alter cholesterol levels were also excluded, as were smokers and carriers of other diseases or dysfunctions that could influence the data. Patients' weight (in kilograms) and height (in meters) was obtained using a mechanical scale with a tape measure. Their BMI was calculated by dividing the weight in kilograms by the square of the height in meters (kg $m^{-2}$). The systolic and diastolic blood pressure (SBP and DBP, respectively) were measured using a mercury sphygmomanometer with an adequate cuff for the right arm circumference. Each participant remained at rest (sitting) for at least 5 min before the measurements.[23]

### Outcome

In this study, the outcome of interest was the effect of a 120-day therapy consisting of daily 20 mg doses of rosuvastatin on patients' lipid profile (mainly total and LDL cholesterol) response, as well as on the modulation of other lipid molecules (HDL cholesterol and triglycerides), glucose and several inflammatory and fibrinolytic biomarkers, influenced by Val16Ala-SOD2 SNP. To analyze the pharmacogenetic influence, the reductions in these biochemical variables among subjects grouped by genotype were determined. The reduction was calculated as the difference between the last measurement before starting the statin therapy and the first measurement after its completion. The differences between these two values were presented as a percentage of the basal values of each variable.

### Covariables

Age, sex and BMI were considered as potential confounders or effect modifiers in the association between the Val16Ala-SOD2 polymorphism and the change in lipid and other biochemical biomarkers.

### Val16Ala-SOD2 genotyping

At baseline examination, the Val16Ala-SOD2 genotyping was determined by polymerase chain reaction using a direct total

**Table 1.** Comparison among several biological and biochemical variables of hypercholesterolemic subject's carrier's different Ala16Val-SOD2 genotypes

| *Variables* | *SOD2 genotypes* | | | P |
|---|---|---|---|---|
| | *AA* Mean ± s.d. | *VV* Mean ± s.d. | *AV* Mean ± s.d. | |
| BMI (kg $m^{-2}$) | $22.4 \pm 2.3^a$ | $22.5 \pm 2.7^a$ | $22.5 \pm 4.7^a$ | 0.98 |
| SPB (mmHg) | $118.5 \pm 4.7^a$ | $122.2 \pm 7.2^b$ | $120.2 \pm 5.3^a$ | 0.02 |
| DBP (mmHg) | $78.5 \pm 4.7^a$ | $101.4 \pm 6.4^a$ | $80.2 \pm 5.3^a$ | 0.29 |
| Cholesterol (mg $dl^{-1}$) | $281.6 \pm 20.8^a$ | $320.3 \pm 53.1^b$ | $300.6 \pm 63.0^a$ | 0.02 |
| HDL cholesterol (mg $dl^{-1}$) | $46.2 \pm 10.8^a$ | $36.95 \pm 14.0^b$ | $42.23 \pm 11.4^{ab}$ | 0.03 |
| LDL cholesterol (mg $dl^{-1}$) | $200.4 \pm 24.4^a$ | $242.2 \pm 57.6^b$ | $213.1 \pm 71.4^a$ | 0.03 |
| Triglycerides (mg $dl^{-1}$) | $174.1 \pm 45.1^a$ | $205.9 \pm 82.1^a$ | $226.3 \pm 87.3^a$ | 0.14 |
| Glucose (mg $dl^{-1}$) | $82.7 \pm 9.0^a$ | $81.7 \pm 9.0^a$ | $81.8 \pm 7.8^a$ | 0.85 |
| PCR | $1.6 \pm 1.5^a$ | $2.30 \pm 1.8^a$ | $1.77 \pm 1.4^a$ | 0.17 |
| Interleukin 1 | $175.9 \pm 66.8^a$ | $269.3 \pm 54.7^b$ | $175.73 \pm 45.0^a$ | 0.0001 |
| Interleukin 6 | $192.1 \pm 67.0^a$ | $315.6 \pm 47.4^b$ | $186.53 \pm 48.2^a$ | 0.0001 |
| TNFα | $206.6 \pm 76.3^a$ | $335.3 \pm 61.8^b$ | $224.13 \pm 46.9^a$ | 0.0001 |
| Interferon gamma | $229.5 \pm 80.2^a$ | $398.6 \pm 59.1^b$ | $305.90 \pm 43.9^c$ | 0.0001 |
| Interleukin 10 | $65.1 \pm 20.3^a$ | $37.6 \pm 10.0^b$ | $71.3 \pm 13.3^a$ | 0.0001 |
| Alpha | $110.8 \pm 33.7^a$ | $161.7 \pm 25.9^b$ | $119.33 \pm 8.0^a$ | 0.0001 |
| Fibrinogen | $318.9 \pm 94.7^a$ | $334.0 \pm 87.8^b$ | $322.1 \pm 41.1^b$ | 0.657 |
| d-dimer | $474.0 \pm 141.7^a$ | $622.7 \pm 200.8^b$ | $500.3 \pm 75.7^a$ | 0.0001 |

Abbreviations: Ala, alanine; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCR, protein C-reactive; SBP, systolic blood pressure; SOD2, manganese-dependent superoxide dismutase; TNFα, tumor necrosis factor alpha; Val, valine. *P*-value is determined by analysis of variance followed by Bonferroni *post hoc* test. Different letters (a, b) indicate significant differences among genotypes to each variable investigated.

blood cell sample and the Tetra-Primer ARMS-PCR assay, as described by Barbisan *et al.*[25] with slight modifications.[26] This procedure resulted in three bands in heterozygotes (514, 366 and 189 bp) and two bands in homozygotes (Val/Val resulting in bands of 514 and 189 bp and Ala/Ala resulting in bands of 514 and 366 bp).

### Laboratory analyses

Blood samples from volunteers obtained before and after rosuvastatin treatment were collected by venous puncture into gray and red top Vacutainers (BD Diagnostics, Plymouth, UK) tubes after 12 h overnight fasting. Plasma was used to measure the levels of fasting glucose and serum total cholesterol, and triglyceride concentrations were measured by applying standard enzymatic methods using Ortho-Clinical Diagnostics reagents on a fully automated analyzer (Vitros 950 dry chemistry system; Johnson and Johnson, Rochester, NY, USA). High-density lipoprotein cholesterol was measured in the supernatant plasma after the precipitation of apolipoprotein-B containing lipoproteins with dextran sulfate and magnesium chloride, as previously described.[27] LDL cholesterol was estimated using the Friedewald equation.[28] Plasma-citrate was collected for the subsequent analysis of coagulation parameters. The D-dimer and fibrinogen levels were measured by immunoturbidimetric method on a Cobas INTEGRA 400 (Roche Diagnostics, Basel, Switzerland).

The following inflammatory metabolism biomarkers were measured: high-sensitivity C-reactive protein, determined by nephelometry (Dade Behring, Newark, DE, USA), the inflammatory cytokines IL-10, IL-6, TNFα, interferon gamma and anti-inflammatory cytokine IL-10, quantified using the Quantikine Human (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

### Statistical analysis

The statistical analysis was performed using SPSS (Version 19.0, São Paulo, SP, Brazil). Initially, the lipid, inflammatory and fibrinolytic variables were compared among hypercholesterolemic carriers of different Val16Ala-SOD2 genotypes (AA, VV and AV) using analysis of variance, followed by the Bonferroni *post hoc* test. A second analysis was performed to evaluate whether rosuvastatin response was influenced by the polymorphism investigated here using two-way analysis of variance, followed by the Bonferroni *post hoc* test or repeated-measures analysis of variance. A multivariate analysis using logistic regression (Backward Wald Model) was also performed to observe the potential influence of sex, age and BMI, as the independent variables. $P < 0.05$ was considered significant.

## RESULTS

The mean age of the study sample was 45.7 ± 11.2 years old (minimum = 23; maximum = 70). Moreover, 50.8% ($n = 62$) of the patients were male, and 49.2% ($n = 60$) were female. The sex and age were similar among patients with different Val16Ala-SOD2 genotypes. Comparisons of biochemical variables among hypercholesterolemic subjects were performed, and the results are presented in Table 1. Hypercholesterolemic carriers of the VV genotype presented higher levels of SBP, total cholesterol, LDL cholesterol, IL-1, IL-6, TNFα, α-acid glycoprotein and d-dimer compared with carriers of the A-allele (AA and AV) carriers. However, VV patients also presented lower HDL cholesterol and IL-10 levels compared with the AA and AV carriers.

Rosuvastatin lowered the lipid levels after 120 days of treatment. However, the intensity of the response was significantly influenced by the Val16Ala-SOD2 polymorphism (Table 2). More specifically, in AA carriers, a high response to rosuvastatin on total cholesterol, as well as HDL and LDL cholesterol, was noted. However, the VV group showed a less pronounced response to statin treatment. The response found in the heterozygous subjects was lower than that in AA carriers, indicating a dose–allele response effect of the Val16Ala-SOD2 polymorphism. Glucose levels did not change in all the participants, independent of the Val16Ala-SOD2 genotype.

Rosuvastatin exhibited a lowering effect on the inflammatory biomarkers analyzed here. However, the intensity of the effect was

**Table 2.** Impact of Ala16Val-SOD2 polymorphism on rosuvastatin response of lipid, glicemic, inflammatory and fibrinolytic biomarkers

| *Variables* | *AA* | | *VV* | | *AV* | |
|---|---|---|---|---|---|---|
| | *Mean ± s.d.* | *% Of basal value* | *Mean ± s.d.* | *% Of basal value* | *Mean ± s.d.* | *% Of basal value* |
| Cholesterol total (mg $dl^{-1}$) | 175 ± 31 | 62 | 292 ± 40 | 91 | 254 ± 39 | 84 |
| LDL cholesterol (mg $dl^{-1}$) | 105 ± 43 | 52 | 215 ± 47 | 88 | 176 ± 40 | 82 |
| HDL cholesterol (mg $dl^{-1}$) | 57 ± 9 | 124 | 42 ± 8 | 116 | 45 ± 8 | 107 |
| Triglycerides (mg $dl^{-1}$) | 94 ± 40 | 54 | 169 ± 71 | 82 | 162 ± 68 | 71 |
| Glucose (mg $dl^{-1}$) | 79 ± 8 | 95 | 80 ± 6 | 97 | 80 ± 5 | 97 |
| Protein C-reactive | 1 ± 0.9 | 59 | 1.5 ± 1 | 63 | 1.2 ± 0.8 | 70 |
| Interleukin 1 | 120 ± 30 | 68 | 260 ± 55 | 96 | 160 ± 34 | 91 |
| Interleukin 6 | 147 ± 38 | 76 | 303 ± 43 | 43 | 170 ± 36 | 92 |
| TNFα | 163 ± 32 | 79 | 331 ± 61 | 61 | 196 ± 34 | 87 |
| Interferon gamma | 204 ± 36 | 89 | 382 ± 65 | 65 | 263 ± 38 | 86 |
| Interleukin 10 | 112 ± 19 | 173 | 41 ± 9 | 109 | 90 ± 10 | 127 |
| Alpha | 61 ± 30 | 64 | 157 ± 25 | 97 | 85 ± 11 | 72 |
| d-dimer | 315 ± 103 | 67 | 329 ± 86 | 99 | 284 ± 25 | 88 |
| Fibrinogen | 218 ± 71 | 68 | 621 ± 183 | 99 | 406 ± 55 | 81 |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TNFα, tumor necrosis factor alpha. Percentage (%) of basal value was calculated based in the value observed after 120 days rosuvastatin treatment in relation to value observed before start the treatment.

**Table 3.** Multivariate analysis of association between VV subjects and low response to rosuvastatin treatment when compared with A-allele subjects

| *Variables* | *Wald* | P-*value* |
|---|---|---|
| Cholesterol total | 11.899 | 0.001 |
| HDL cholesterol | 4.980 | 0.026 |
| LDL cholesterol | 0.161 | 0.698 |
| Triglycerides | 6.454 | 0.011 |
| Age | 0.524 | 0.469 |
| Gender | 0.002 | 0.964 |
| BMI | 0.172 | 0.679 |
| SBP | 0.166 | 0.684 |
| DBP | 0.001 | 0.971 |

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure. Analysis included sex, age and body mass index (BMI) as potential intervenient variables in the differential response of VV genotype to rosuvastatin treatment. The multivariate analysis was performed using the percent of lipid values after 90 days treatment in relation to basal values (0 day).

influenced by the Val16Ala-SOD2 polymorphism. Hs-protein C-reactive levels decreased by approximately 30–40% when compared with the basal levels in all patients treated with rosuvastatin during the first 90 days ($P = 0.001$). The lowering effect on IL-1 cytokine levels was more intense in the AA-allele group than in the V-allele group ($P = 0.001$). However, lower IL-6 cytokine, TNFα and interferon gamma concentrations were observed in VV relative to the A-allele group ($P = 0.001$). All the patients presented an increase in IL-10 levels after completing the rosuvastatin treatment. However, this effect was higher in the AA-allele group than in the V-allele group ($P = 0.001$). The concentration of fibrinolytic biomarkers did not change in the VV individuals treated with rosuvastatin, whereas in the A-allele group, the concentration of α-acid glycoprotein, d-dimer and fibrinogen decreased relative to the basal levels ($P = 0.001$).

A multivariate analysis was performed to establish whether the low responsiveness to rosuvastatin associated with the VV genotype was independent of gender, age and BMI. As seen in Table 3, the association between the VV group's low response to rosuvastatin was independent of confounders such as total cholesterol, HDL cholesterol and triglyceride levels. However, the lowering effect of rosuvastatin on the LDL cholesterol level was effective and exhibited similar intensity among subjects with different Val16Ala-SOD2 genotypes.

## DISCUSSION

Rosuvastatin is considered to provide benefits in reducing the risk factors for many diseases by its potent lowering effect, mainly on LDL cholesterol and triglyceride levels. Its effects involve maintenance of the balance between oxidant production and oxidant scavenging molecules.[1] For this reason, this study aimed to ascertain whether a basal oxidative imbalance related to a human SNP mutation in the MTS target sequence of the SOD2 gene could affect the rosuvastatin response. To test this hypothesis, we selected hypercholesterolemic patients who were carriers of different Val16Ala-SOD2 genotypes as study participants. These individuals were treated with rosuvastatin for 120 days. Our results showed that despite the general lowering effect of rosuvastatin observed in the patients, the intensity of this effect was directly influenced by Val16Ala-SOD2. More specifically, VV genotype carriers presented a less effective response in terms of lipid levels compared with the A-allele carriers (AA and AV groups). These results are mostly in agreement with those obtained in previous investigations that described the association between the VV genotype and high levels of lipid and oxidant biomarkers in hypercholesterolemic[12] and obese individuals.[13] Recently, Becer and Çırakoğlu[29] also described association of high levels in the total cholesterol of obese and non-obese VV carriers.

In contrast, AA patients' lipid profiles presented an intense response to rosuvastatin. The authors of several extant studies have estimated that statins could decrease LDL cholesterol by 37–57% in patients with primary hypercholesterolemia.[28,30–32] In the present case, when AA patients were treated with 20 mg rosuvastatin, their LDL cholesterol levels decreased by 52% compared with the basal level observed on day zero. The differential response to rosuvastatin treatment is in line with the view shared by Simon *et al.*, who noted that the magnitude of LDL cholesterol response is related to genotypic, phenotypic, demographic and as-yet unexplained characteristics.[33]

In genetic terms, evidence suggests that ~ 50% of the variability in the LDL cholesterol plasma is associated with some type of genetic inheritance.[34] However, thus far, pharmacogenetic studies have primarily focused on lowering LDL cholesterol through statin therapy. Thus, a large number of studies have been conducted

analyzing the influence of genes involved in cholesterol synthesis, lipoprotein lipid transport and some other genes associated with lipid metabolism, such as apolipoprotein E, on statin response.[35] The results presented here suggest that a genetically caused oxidative imbalance affects the pharmacological response to rosuvastatin treatment.

Rosuvastatin has anti-atherogenic properties owing to its hypolipidemic, anti-inflammatory and antioxidant effects.[36] However, notably, its different effects on two Val16Ala-SOD2 homozygous genotypes (VV and AA) exhibit imbalance in the levels of superoxide anion and hydrogen peroxide. The AA genotype produces an excess of hydrogen peroxide owing to the high efficiency of the SOD2 enzyme. However, because the VV genotype has low SOD2 enzyme efficiency, this may cause a potential increase in superoxide anion levels.[11]

The greater impact of superoxide anion accumulation in the VV genotype is due to the high affinity of this free radical with nitric oxide molecules generating peroxynitrite, a reactive nitrogen species. This molecule causes an extensive lipoperoxidation of cellular membranes, thus decreasing endothelial function, which is recognized as an important indicator of the risk of developing cardiovascular diseases.[11]

Our results also showed that inflammatory and fibrinolytic biomarkers were affected by rosuvastatin in a Val16Ala-SOD2 genotype-dependent way. Consistent evidence showed that rosuvastatin has anti-inflammatory effects, including reduction of inflammatory cytokines such as TNFα.[37] However, VV individuals presented lower anti-inflammatory and anti-fibrinolytic responses when treated with rosuvastatin compared with those of AA patients. These results corroborate those of an investigation that described high levels of inflammatory cytokines in VV carriers compared with A-allele carriers.[16] A recent *in vitro* study also described a differential response of peripheral blood mononuclear cells to exposure to methotrexate—a drug used to treat autoimmune diseases with a high inflammatory grade, such as psoriasis and rheumatoid arthritis.[25]

However, whether the effect of the Val16Ala-SOD2 polymorphism on the response to rosuvastatin also involves pharmacokinetic alteration of the drug remains an open question. Previous evidence showed that the pharmacological response to rosuvastatin can involve genes related with other important metabolic pathways that interfere in the pharmacokinetics. A study performed in white male volunteers showed the occurrence of the rosuvastatin peak concentration in plasma 5 h after dosing, and complete excretion had occurred by 10 days after dosing.[38] However, recent investigations suggested a large inter-individual variability in rosuvastatin pharmacokinetics mainly associated with uptake and efflux transporter metabolism. Birmingham *et al.*[39] conducted an investigation that evaluated the potential pharmacokinetic differences among Asian and Caucasian subjects residing in California after the intake of a single 20 mg dose. The results showed higher rosuvastatin concentrations and metabolism in Asian subjects than in Caucasian subjects. These pharmacokinetics differences have been attributed to genetic polymorphisms. This is the case of organic anion-transporting polypeptide, which is a drug transporter, and breast cancer resistance protein (BCRP; ABCG2), which decreases intestinal absorption and mediates biliary excretion of some drugs and metabolites.[40]

When our results are considered as a whole, noting some methodological constraints such as the relatively small number of participants, we have provided evidence to suggest that the VV genotype of the Val16Ala-SOD2 polymorphism is associated with some level of resistance to lipid-lowering rosuvastatin therapy.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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