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Aris Verdecia Peña
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APRESENTAÇÃO

A Editora Pantanal em seu 3º Volume do E-book "Tópicos nas ciências da saúde", com seis capítulos traz novos temas no atuar da medicina. A obra, vem a materializar o anseio da Editora Pantanal na divulgação de resultados, que contribuem de modo direto no desenvolvimento e saúde humana.

No primeiro capitulo o trabalho nos apresenta uma patologia que, embora muitos pensem que não é comum, tem grande impacto em nossa população mundial. A frequência desta patologia na década de 80 - 90 foi de 2 - 4 x 10.000 habitantes, porém com estudos atuais e levando em consideração não apenas o transtorno autista, mas todos os transtornos generalizados do desenvolvimento ou TEA (sigla em inglês), nesse novo cenário as estimativas aumentam de 21 para 35 x 10.000 habitantes. Com uma intervenção comportamental intensiva precoce, terapia cognitivo-confuctual e treinamento em habilidades sociais, obteve-se que em alguns casos leves os sintomas desaparecem, razão pela qual o diagnóstico precoce e o apoio incondicional da família são necessários; tudo isso refletido em nosso primeiro tópico.

Em seguida, nosso pequeno volume faz uma incursão no campo das vitaminas que, como muitos estudiosos sabem, há um total de 13 vitaminas classificadas em dois grupos, solúveis em água (8 do complexo B e vitamina C) e quatro solúveis em gordura; A; D; E e K, que desempenham um papel fundamental no nosso organismo porque participam nos processos e reações que nele ocorrem e é importante não só tomá-los na forma de comprimidos, mas também incorporá-los através de uma alimentação equilibrada, saudável e saudável, para mim sobretudo a fonte da juventude porque atrasa o envelhecimento devido à sua ação antioxidante, aqui mostramos vários deles nas suas diferentes funções.

Por fim, encerramos nosso livro com a apresentação de um caso onde mostramos que não é importante apenas tratar o somático, mas fazer um diagnóstico psicossocial do indivíduo se quisermos obter bons resultados em nossa prática profissional.

Agradecemos aos autores pela dedicação e os encorajamos a continuar colaborando em nosso projeto. Aos autores dos capítulos, pela dedicação e esforços sem limites, que viabilizaram esta obra que retrata os recentes avanços científicos e tecnológicos na área de Ciências da Saúde, os agradecimentos da Organizadora e da Pantanal Editora. Por fim, esperamos que este e-book possa colaborar e instigar mais estudantes e pesquisadores na constante busca de novas tecnologias e avanços para a medicina. Assim, garantir uma difusão de conhecimento fácil, rápido para a sociedade.

Aris Verdecia Peña

SUMÁRIO

Chapter II

Changes in oxidative stress and modulation of Val16Ala-SOD2 polymorphism in sickle cell trait patients

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INTRODUCTION

Sickle cell anemia (SCA) is the most frequent structural change in the hemoglobin molecule and was the first disease to receive molecular characterization (Pauling et al., 1949). This pathology results from the substitution of glutamic acid by the amino acid valine at position 6 on the β-globin chain and generates mutated hemoglobin, known as hemoglobin S (HbS). The SCA gene can manifest itself in two ways: by homozygosis and heterozygosis. Sickle cell disease is characterized by homozygosis of HbS (SS) and has sickle-shaped red blood cells in its bloodstream, which causes one of the main symptoms related to the disease: vaso-occlusive crises (Chakravorty et al., 2015; Mathew et al., 2016; Farias et al., 1995). The heterozygote (HbAS), is the carrier of the S gene, being able to produce both HbA and HbS (approximately 40% of HbS). According to the Ministry of Health, in Brazil, approximately 200,000 people with sickle cell trait (SCT) are born per year, and it is estimated that 7.2 million people carry the trait (Felix et al., 2010). However, heterozygotes are individuals, largely asymptomatic, and without significant hematological alterations (Behera et al., 2012). Over the years, however, numerous questions about the veracity of the "asymptomatic" concept for these people began to emerge. This uncertainty raises doubts since this condition is frequently found in association with other disorders and because, in these individuals, there is still the production, even to a lesser extent, of HbS (Kotiola, 2016). Studies that are more recent suggest that SCT should be reevaluated and point

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out the increase in oxidative stress in these individuals, especially under stressful conditions such as low oxygenation and physical exercise, contribute to greater tissue oxidative damage (Chirico et al., 2012).

Cases of death associated with exercise in patients with SCT may be directly related to the structural abnormality of the falciform erythrocyte, which may increase in number during physical exercise in these individuals (Eichner, 2010). Another contributing factor seems to be the increase in oxidative stress in these carriers during exercise (Das et al., 1993), and both the resultant reactive oxygen species (ROS) induced endothelial dysfunction and adhesion to the capillary endothelium (Chirico et al., 2012; Voskou et al., 2015).

To combat or neutralize the intense production of reactive species, organisms have developed a complex defense system: enzymatic and non-enzymatic antioxidants (Jeong et al., 2012; Narendhirakannan et al., 2013). An important antioxidant enzyme in mitochondria is SOD that converts free radicals to oxygen and hydrogen peroxide. It has three isoforms, with the manganese-dependent SOD (SOD2) being the focus of this study (Church et al., 1992). This enzyme is encoded by a gene that contains five exons and is located at position 25 on the long arm of chromosome 6 (6q25) (Wispé et al., 1989). One of the common polymorphisms of SOD2 (Ala16Val polymorphism) results in a mutation that replaces a cytosine with a thymine in the peptide sequence at the start of this enzyme, causing the original codon GTT (valine) to be converted to GCT (alanine). This variation decreases the transport efficiency of this enzyme into the mitochondria, where it has an active function (Rosenbum et al., 1996). Therefore, individuals carrying the Val (V) allele have a lower enzymatic efficiency than those with the Ala (A) allele and, consequently, their antioxidant capacity is reduced, resulting in a possible increase in their oxidative stress (Duarte et al., 2010; Shimoda et al., 1996). Recent studies compared the presence of the Ala16Val-SOD2 polymorphism in people with asthma (Despotovic et al., 2015), where the V allele was significantly higher and showed that it might be directly linked to carcinogenic processes (Atilgan et al., 2014).

A clinical study demonstrated that the SCT carrier has a higher formation of the reactive species (Eichner, 2010). However, there is still no study linking this factor to the Ala16Val-SOD2 polymorphism, which generates a decrease in the antioxidant potential to correlate with the increase in oxidative stress in these carriers. Therefore, the aim of this study was to analyze the presence of the Val16Ala-SOD2 polymorphism in SCT individuals and to verify its association with oxidative stress biomarkers.

MATERIAL AND METHODS

STUDY POPULATION

Participants for the study were recruited together with the register in the Blood Bank of the Santa Casa de Caridade Hospital of Uruguaiana (State of Rio Grande do Sul/Brazil). A total of 119 individuals were enrolled, 67 in the control group and 52 in SCT group. All individuals were residents in the municipality of Uruguaiana and had a similar lifestyle. The detection of HbS on the Blood Bank screening is performed by hemoglobin electrophoresis. Participants were matched by age and without distinction of gender and ethnicity. Pregnant women were excluded from the study, as were participants taking iron and antioxidant therapy. After providing written informed consent, participants answered a questionnaire to obtain demographic and socioeconomic data and permitted collection of venous blood. Deficient of glucose-6-phosphate dehydrogenase (G6PD) in red cells were not detected in both groups.

The research project was approved by the Research Ethics Committee of UNIPAMPA and CONEP under the number 977827.

LABORATORY ANALYSES

Whole blood samples (10 mL) were collected by venipuncture and then stored in two EDTA tubes (Vacutainer-Becton, Dickinson and Company-New Jersey-USA). One of the tubes was prepared for polymorphism analysis, and the other was used to determine hematological parameters and biomarkers of oxidative stress. Whole blood and plasma were fractionated into Eppendorf tubes for further analysis and stored at −70 °C.

HEMATOLOGIC PARAMETERS

Blood samples were analyzed immediately after collection. The complete blood count and platelet count were performed using a Sysmex® KX 21N automatic counter. Separation of hemoglobin fractions (HbA, HbF, HbS, and HbC) was performed using Bio-Rad® D10 High-Performance Liquid Chromatography (HPLC) equipment.

OXIDATIVE STRESS PARAMETERS

ENZYMATIC AND NON-ENZYMATIC DEFENSES

Catalase (CAT) activities in erythrocytes were determined according to the Aebi method (1984). Packed erythrocytes were hemolyzed by adding 100 volumes of distilled water, then, 20 µL of this hemolyzed sample was added to a cuvette and the reaction was started by the addition of 100 µL of freshly prepared 300 mM H_2O_2 in phosphate buffer (50 mM, pH 7.0) to 32 give a final volume of 1

mL. The rate of H_2O_2 decomposition was measured spectrophotometer at 240 nm during 120 s. The CAT activity was expressed as UI/mg protein.

Superoxide dismutase (SOD) activity was measured in erythrocytes using the Kit RANSOD® (Randox Laboratories, UK). This method employs xanthine and xanthine oxidase to produce superoxide radicals which react with 2-(4-iodophenyl)-3-(4-nitrophenyl)-5- feniltetrazol chloride (INT) to form compound formazan red. The superoxide dismutase activity was measured by the degree of inhibition of this reaction at 505 nm. The SOD activity was expressed as UI/mg protein.

Measurement of glutathione peroxidase (GPx) activity in erythrocytes was determined using the Ransel® Kit (Randox Laboratories, UK). GPx catalyzes the oxidation of glutathione (GSH) by cumene hydroperoxide. In the presence of glutathione reductase (GR) and NADPH the oxidized glutathione (GSSG) is immediately converted to the reduced form with a concomitant oxidation of NADPH to NADP+.

The quantification of the total glutathione (GSH) levels was taken at 412 nm, observing the appearance of a yellow color oxidation The standard containing 1 mM GSSG and white were measured separately (Akerboom & Sies, 1981). All assays were performed in triplicate product of 5,5'-bisditio-2-nitrobenzoic acid (DTNB).

OXIDATIVE DAMAGE TO BIOMOLECULES

Thiobarbituric acid reactive substances (TBARS) were determined in plasma by the method of Ohkawa and collaborators (1979). In brief, samples were incubated at 100 °C for 60 min in acid medium containing 0.45% sodium dodecyl sulfate and 0.6% thiobarbituric acid. After centrifugation, the reaction product was determined at 532 nm using 1,1,3,3- tetramethoxypropane as standard and the results were expressed as nmol MDA/mL.

Content protein carbonyl was determined as described by Levine and collaborators (1990). The carbonyl protein presence is indicative of oxidation. Plasma samples were added 0.2 mL of trichloroacetic acid, 10% and placed on ice for 5 min. After centrifugation (5 min, 8000), was added 1 mL of 2,4-dinitrophenylhydrazine (DNPH) in 2 M HCl to 10 mM and samples 1 mL of 2MHCl in white tubes and incubated for 90 min at 37° C. The proteins were dissolved in 6Mguanidine and interference was removed after washing with ethanol-ethyl acetate 1:1 (v/v). The extent of the damage will be done by reading absorbance at 370 nm. The results were expressed as nmolcarbonyl/mg protein.

The frequency of micronuclei was evaluated in leukocytes. Global blood was collected and a sample was placed on the surface of the blade and made a smear, the blood was spread over the surface of the blade. After 24 h, the slides were fixed in 96% ethanol for 30 min. The slides were stained with anoptic dye and washed in water and put to dry. After drying the cells analyzed were considered as

micronuclei the particles in relation to the main core: not exceed 1/3 of their size, are clearly separated with discernible edges and with the same color and refringence core (Schmid, 1975).

SOD2 POLYMORPHISM ANALYSIS (RS4880)

Genomic DNA was extracted from peripheral blood leukocytes using a QIAmp DNA Mini Kit (QIAGEN®). SOD2 polymorphism analysis (rs4880) was performed by real time PCR using the Step OneTM System (Thermo Fisher Scientific) and Taqman Genotyping Assays (ID: C___8709053_10).

STATISTICAL ANALYSIS

Results were expressed as the mean ± standard deviation (SD). Data were plotted in an Excel spreadsheet and then transferred and analyzed by the Graph Pad Prism 5 statistical program. The Hardy-Weinberg equilibrium test was performed using ARLEQUIN software (Geneva, Switzerland). Quantitative variables were analyzed using the ANOVA test with post hoc de Tukey and the chi-square test was used for genotypic comparisons. Statistical analyses were performed where all values of p were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

In this study, the association between the Val16Ala-SOD2 polymorphism and oxidative stress parameters was analyzed. The studied population was in Hardy-Weinberg Equilibrium (x2 = 3.237; p = 0.534) and presented the following genotypic frequencies: TT 29 (24.4%), TC 69 (58%) and CC 21 (17.6%).

The hematological profile of study participants are shown in Table 1. The control group consisted of 67 individuals, 34 (50.7%) men and 33 (49.3%) women and the mean age of this group was 37.4±11.6 years. The SCT group was composed of 52 participants, of whom 27 (51.9%) were men and 25 (48.1%) were women, with an average age of 35.5±12.3 years. There were no differences between genders and groups (p = 0.899). Regarding hematological parameters, there was no significant difference between the groups studied.

Table 1. Hematological profile of the control and SCT groups. Source: the authors.

		Control (n=67)	SCT (n=52)
Hematological profile	Red Blood Cells (10^6/mm³)	4.45 ± 0.43	4.31 ± 0.63
	Hemoglobin (g/dL)	13.21 ± 1.14	13.12 ± 1.25
	Haematocrit (%)	37.14 ± 3.72	36.83 ± 4.11
	MCV (fL)	87.31 ± 3.62	86.11 ± 5.19
	MCH (pg)	29.34 ± 3.25	30.70 ± 3.04
	MCHC (g/dL)	34.4 ± 1.32	35.71 ± 1.74
	White Blood Cells (10^3/mm³)	6.56 ± 1.65	6.32 ± 1.72
	Platelets (10^3/mm³)	249 ± 65.73	237 ± 72.81
	HbS (%)	-	42.49 ± 1.30
	Free iron (mg/dL)	69.54 ± 16.52	73.83 ± 20.80

Data expressed as mean ± standard deviation and analyzed using the Student's t-test for independent samples.

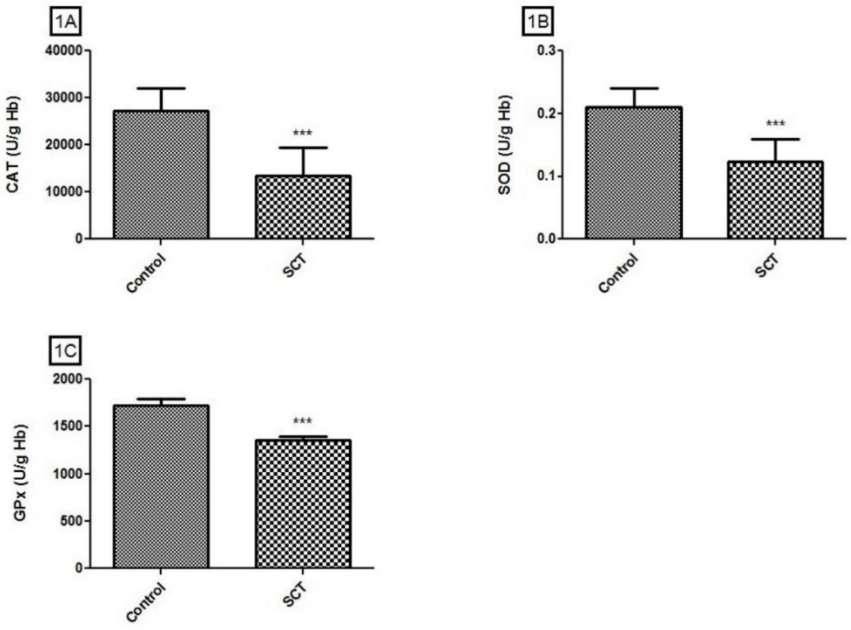

Figure 1. Enzymatic defenses of controls and the sickle cell trait (SCT). Activity of CAT (1A), SOD (1B), and GPx (1C) *** $p < 0.0001$ in relation to the control group. Student's t-test for independent samples. Source: the authors.

The activity of the enzymes catalase (CAT) (Figure 1A), superoxide dismutase (SOD) (Figure 1B) and glutathione peroxidase (GPx) (Figure 1C) between the groups are shown in Figure 1 and is significantly reduced ($p < 0.0001$) in the SCT group.

Figure 2 shows the non-enzymatic antioxidant defenses of the groups studied. It can be observed that the levels of total glutathione (GSH) (Figure 2A) and Total Antioxidant Status (TAS) (Figure 2B) were significantly reduced ($p < 0.0001$) in the group SCT compared with the control group.

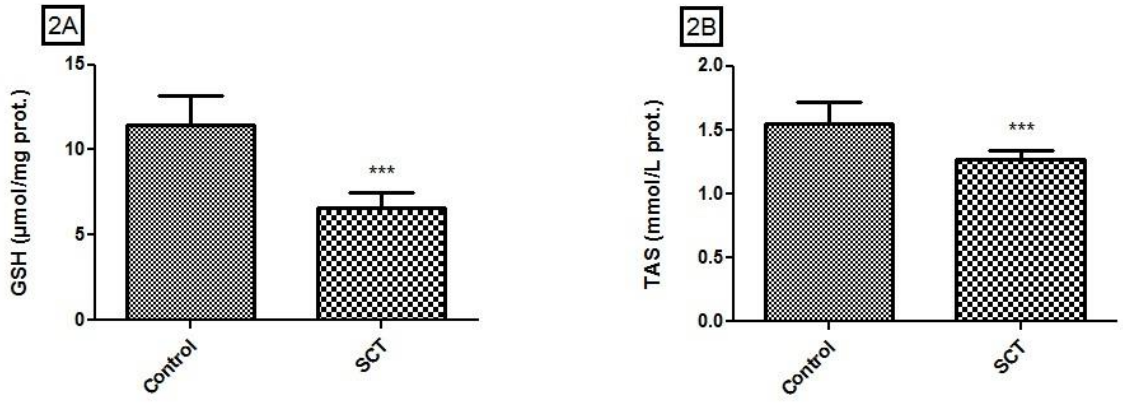

Figure 2. Non-enzymatic defenses of controls and the sickle cell trait (SCT). GSH (2A), and TAS (2B) *** $p < 0.0001$ relative to the control group. Student's t-test for independent samples. Source: the authors.

Figure 3 shows the results obtained for the evaluation of oxidative damage to biomolecules. The content of carbonylated proteins (Figure 3A), TBARS levels (Figure 3B), and micronucleus frequency (Figure 3C) were statistically increased ($p < 0.0001$) in the SCT group when compared to the control group.

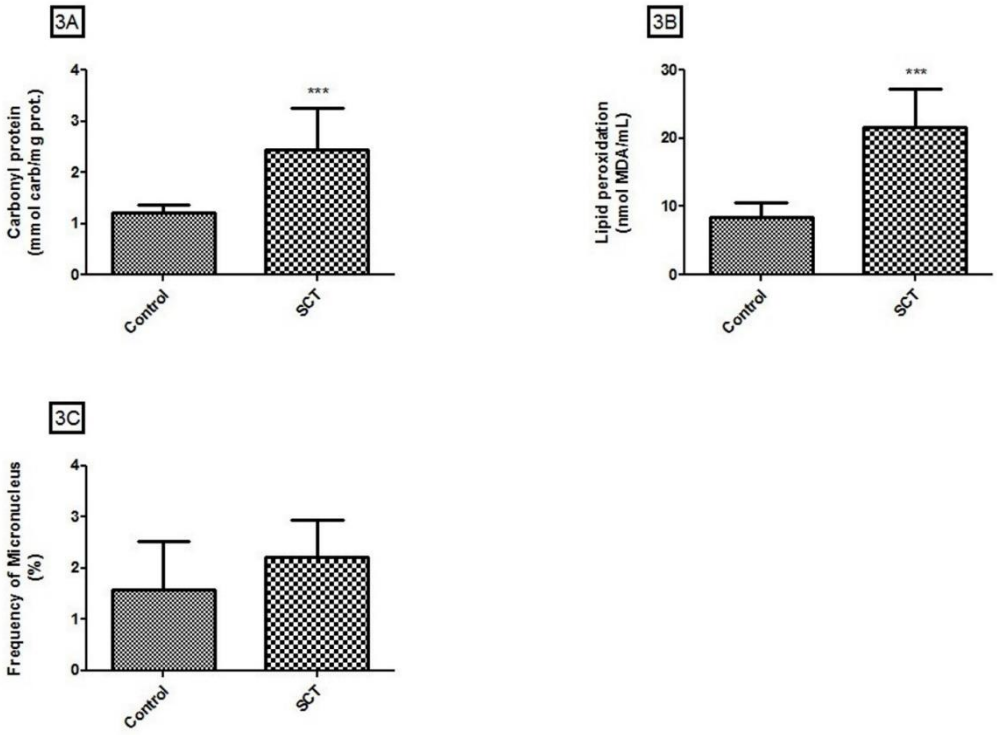

Figure 3. Oxidative damage of controls and sickle cell trait (SCT**).** Carbonyl (3A), TBARS (2B) *** $p < 0.0001$ relative to the control group; Micronucleus (3C) ** $p < 0.0006$ in relation to the control group. Student's t-test for independent samples. Source: the authors.

The Val16Ala-SOD2 polymorphism genotypes were obtained in the control and SCT groups, and the results are shown in Table 2.

Table 2. Frequencies Genotypes of the Val16Ala-SOD2 polymorphism between the control and SCT groups. Source: the authors.

SOD2	Control (n=67)	SCT (n=52)	p*
TT	14 (20.9)	7 (13.5)	
TC	34 (50.7)	35 (67.2)	
CC	19 (28.4)	10 (19.2)	0.303
TC+CC	53 (79.1)	45 (86.5)	0.291

*Pearson Chi-Square Test.

The comparison between the levels of oxidative stress parameters and the genotypes of the Val16Ala-SOD2 polymorphism was performed between the control and SCT groups and is shown in Table 3, where it is observed that there was a statistically significant difference in the SCT group between the concentrations of catalase ($p = 0.026$) which were higher in the CC genotype when compared to the other genotypes and in GPx which was significantly lower in CC than in TT.

This is a pioneering study that demonstrated that in a group of patients with sickle cell trait it presented higher levels of protein carbonylation and lipid peroxidation, as well as, lower levels of antioxidant defenses when compared to a control group. And that the SOD2 Val16Ala polymorphism affected the antioxidant defenses in sickle cell traits, indicating a possible genetic modulation involved in this process.

The SCT is a heterozygous carrier for the HbS gene and, despite producing a significant amount of mutated hemoglobin (approximately 40%), it does not present important hematological changes, as evidenced in this study and corroborated by other investigations (Naik; Haywood, 2015; Serjeant, 1997). However, studies with patients with SCT have already shown associations with other diseases (Biedrzycki et al., 2006; Saxena et al., 2015) that can affect their quality of life and the condition.

Individuals with SCT have low levels of antioxidant defenses, which further contributes to oxidative stress. In the present study, antioxidant defense indicators were significantly lower in the SCT group. When compared to the control group, the activity of the CAT enzyme in the SCT group was reduced, as well as the GPx activity. These results corroborate with previously published studies, linking SCT patients to physical effort and oxidative stress (Chirico et al., 2012; Eichner, 2010).

Table 3. Genotypes of the Val16Ala-SOD2 polymorphism and levels of oxidative stress parameters of controls and SCT groups. Source: the authors.

Oxidative Stress Biomarkers	Control (n=67)			SCT (n=52)		
	TT (n=14)	TC (n=34)	CC (n=19)	TT (n=7)	TC (n=35)	CC (n=10)
Catalase (CAT) (U/mg Hb)	5750.0 ± 1416.2	5055.9 ± 1061.2	5477.8 ± 1644.4	9729.0 ± 3013.3	9346.7 ± 4037.1	9865.0 ± 4189.7
Superoxide Dismutase (SOD) (U/g Hb)	0.19 ± 0.05	0.19 ± 0.04	0.19 ± 0.03	0.11 ± 0.03	0.11 ± 0.03	0.14 ± 0.04
Glutathione peroxidase (GPx) (U/g Hb)	1802.4 ± 122.5	1746.7 ± 141.2	1784.0 ± 113.7	1384.6 ± 6.6	1358.5 ± 39.2	1332.2 ± 44.8**
Total glutathione (GSH) (µmol/mg prot)	10.1 ± 0.4	11.6 ± 1.7	11.8 ± 1.3	7.1 ± 1.1	6.6 ± 0.9	6.5 ± 0.5
Total Antioxidant Status (TAS) (mmol/L prot)	1.43 ± 0.07	1.54 ± 0.16	1.37 ± 0.07	1.26 ± 0.08	1.27 ± 0.07	1.19 ± 0.03
Carbonil (mmol carb/mg prot)	5.7 ± 2.7	5.9 ± 2.0	6.4 ± 2.8	2.6 ± 1.9	2.7 ± 1.3	3.2 ± 1.2
TBARS (nmol MDA/mL)	22.3 ± 9.2	22.3 ± 11.2	23.2 ± 8.3	20.3 ±13.4	23.8 ± 10.9	17.9 ± 6.8
Micronucleus frequency (%)	2.5 ± 0.7	1.61 ± 0.9	2.1 ± 0.6	2.4 ± 0.8	1.9 ± 1.0	2.1 ±1.2

Data expressed as mean ± standard deviation and analyzed using the ANOVA test with post hoc de Tukey. ** p= 0.021 between CC and TT genotypes in the SCT group.

The SOD enzyme is the first line of defense, as it neutralizes endogenous free radicals, which helps cells to keep the amounts of superoxide anion and hydrogen peroxide low. Similar to catalase, our study demonstrated a significant decrease in SOD activity in the SCT group. SOD activity has already been studied in patients with sickle cell (Schacter et al., 1988), and the results of this study agree with those found in sickle cell and β-thalassemia anemias (Voskou et al., 2015; Taufer et al., 2005).

The denaturation of the hemoglobin molecule, a process that occurs due to the falcization of red blood cells, generates the release of iron and this, in turn, increases the amount of free radicals by acting as a catalyst for biochemical reactions. Oxidative stress impairs the erythrocyte membrane and the production of reactive species is significantly higher in hemoglobinopathies compared with healthy individuals (Bhagat et al., 2012; Finkel; Holbrook, 2000). In the SCT group of this study, it was possible to verify that there was no increase in plasma free iron, by comparing them with the control group. Thus, it is suggested that iron does not participate directly in the oxidative stress pathways in sickle cell carriers in this case.

As the main endogenous intracellular antioxidant, GSH helps prevent cell damage caused during oxidative stress. Levels of GSH analyzed in this study also showed a significant decrease in the SCT group when compared with the control group. These data agree with the findings of other studies involving sickle cell syndromes (Gizi et al., 2011; Hierso et al., 2014).

Total antioxidant status (TAS) evaluates a pool of plasma antioxidants and is a good parameter to evaluate the antioxidant status of each individual. The plasma reduction of TAS has been implicated in several pathologies such as cancer and heart disease (Qasim et al., 2016; Wu et al., 2017). In this study, the SCT group presented significantly reduced levels of TAS compared with the control group. Similar results were also found in another study investigating TAS in sickle cell patients at steady state (Fasola et al., 2007). In this case, patients who had TAS < 1.00 mmol/L had more than three vaso-occlusive crises in one year. The mean TAS of those patients presenting more than three cases of occlusive seizures was significantly lower than those with SCT who had fewer seizures during the same year.

In the present study, the parameters used to evaluate oxidative damage to biomolecules caused by oxidative stress were higher in the group of patients with SCT, such as TBARS and frequency of micronucleus. These results are within the expected range, since they have been reported by other studies in sickle cell patients (Castilhos et al., 2017; Naga et al., 2016) and are associated with numerous diseases described in the literature, such as hypercholesterolemia, cardiovascular diseases, and cancer, for example (Duarte et al., 2010; Sundararajan et al., 2017; Walter et al., 2004).

Proteins are immediate targets of reactive species. When the side chains of proteins are oxidized, carbonyl groups are produced, which serve as the most common markers of oxidative damage to proteins (Levine et al., 1990). In the SCT group of this study, there was an increase in the amount of carbonyl groups, when compared with the control group. This factor also corroborates the findings of other studies in patients with sickle cell anemia (Manfredini et al., 2008; Bhagat et al., 2012).

The transport of manganese-dependent SOD to mitochondria occurs through specific encoding in the nucleotide sequence. The polymorphism studied here replaces a thymine (T) with a cytosine (C) in that sequence, causing the original GTT codon (valine) to be converted into GCT (alanine). This variation leads to reduced transport efficiency of the MnSOD valine variant to the mitochondria compared to the alanine variant (Rosenblum et al., 1996; Shimoda et al., 1996). Despite the higher efficiency of the T allele, studies have described an association between cancer and this variant (Mikhak et al., 2008; Bica et al., 2009). It is believed that this phenomenon occurs due to the greater efficiency of SOD2, which, if not accompanied by an increase in the levels of CAT and GPX, or of non-enzymatic antioxidant compounds stored in the cell, results in the excessive generation of H_2O_2. Hydrogen

peroxide can react with transition metals via the Fenton reaction, resulting in the radical OH •, which is a strongly mutagenic radical and against which the organism has no defense mechanisms.

However, GPx was significantly lower in the CC genotype than in the TT genotype among patients with sickle cell trait. This data suggests that the CC genotype that does not have a functioning SOD2, has less GPx activity (Figure 1C) and a lower level of GSH Figure 2A), a substrate for enzymatic action. And the low enzymatic activity of both CAT, SOD and GPx leads to oxidative damage in biomolecules such as protein and lipids (Figures 3A and 3B) as noted.

Studies have suggested that the Val16Ala-SOD2 polymorphism is associated with certain types of diseases that are induced by oxidative damage suggested a 1.5 times greater chance of patients with the VV genotype being obese than in CC and CT subjects. Complementing the above, Duarte et al.(2010), in a study with hypercholesterolemic patients, demonstrated that VV allele carriers are more predisposed to increased oxidative stress. Other authors (Despotovic et al., 2015; Fujimoto et al., 2010; Souiden et al., 2016) associated the MnSOD polymorphism and its T allele as risk factors for certain health conditions, such as cardiovascular diseases and asthma.

A recent study of Farias et al. (2018) investigated the association of the SOD2 polymorphism and SOD activity with the vaso-occlusive crisis and acute splenic sequestration in children with sickle cell anemia. The CT and CC genotypes were associated with lower SOD activity compared with the TT genotype. Other data shows that CT and CC were more frequent in patients with vaso-oclusive crisis or acute splenic sequestration. These results suggest that the SOD2 polymorphism associated with low SOD activity could be a susceptibility factor for these events.

Analysis of the polymorphism showed 96% of the CT genotype and 4% of the CC genotype in the control group, 21% of the CC genotype, and 79% of the CT genotype in the SCT group. However, none of the patients with the SCT belonged to the TT genotype, which does not allow the analysis of this probable association.

Another issue that may be involved with the low gene frequency of the T allele in this study is the low penetrance of this gene in the population. However, this question remains largely unanswered by current studies. Penetrance of a gene is the percentage of individuals in a population with a given allele (both dominant and recessive) that exhibit the phenotype associated with it. In the existing literature, there are differences among results, depending on the study population. In the study by Mao et al.(2010) associating Val16Ala-SOD2 and risk factors for prostate cancer, it was suggested that the allele Alanine has a low penetrance, especially in Caucasians. In contrast, the Cox et al. (2006) study in breast cancer patients associated the presence of two polymorphisms (including the MnSOD polymorphism) and pointed to the T allele as a low penetrance allele. Thus, evidence may suggest the low penetrance of the T allele in certain situations and populations as an underlying cause responsible

for its low allelic frequency in the MnSOD polymorphism. Therefore, it is emphasized that there is still much to be studied and investigated regarding the Val16Ala-SOD2 polymorphism and its associations.

Concluedes SCT have increased oxidative stress evidenced by the reduction of antioxidant defenses and increased oxidative damage to biomolecules. Val16Ala-SOD2 polymorphism seems to be associated with GPx activity analyzed in this pioneering study.

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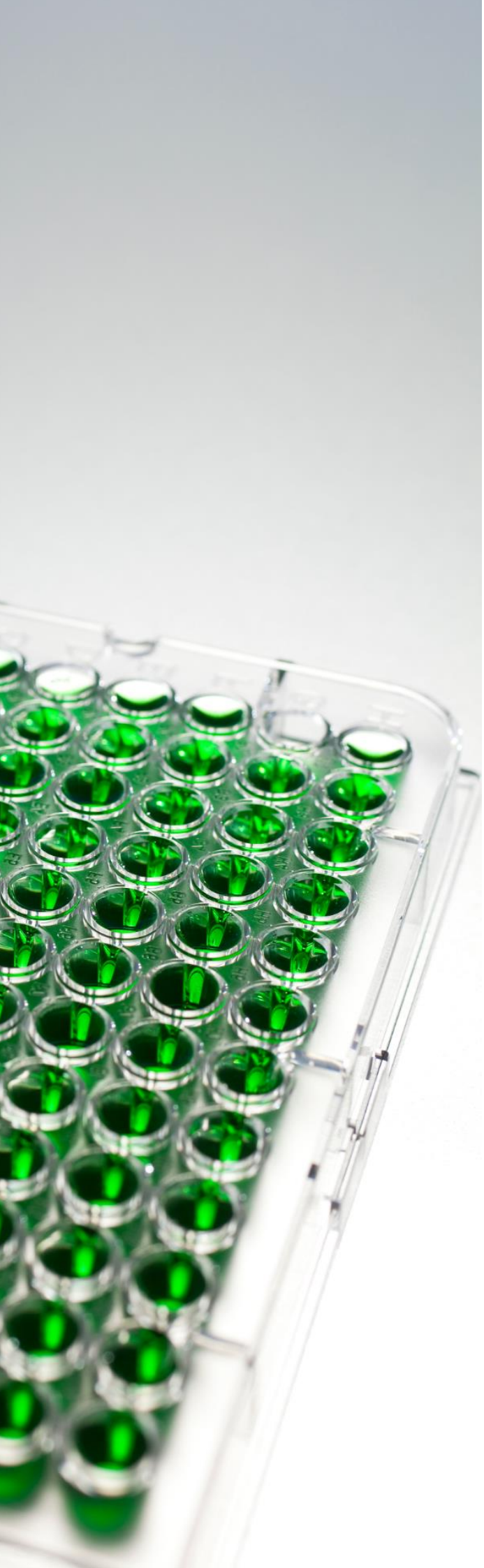
ÍNDICE REMISSIVO



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