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Physical Training Monitoring Strategies: A Review of Modulation of Training Loads by Oxidative Stress Biomarkers and Creatine Kinase Levels

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Abstract:
Background*: Sports training monitoring parameters serve to determine whether the physical effort load is compatible with the established recovery period. Exercise induces an increase in oxygen consumption and energy demand. The increase in oxygen consumption leads to increased production of reactive oxygen species (ROS). Depending on your concentration, ROS react with cellular structures such as membranes, components and elements of the mitochondrial DNA, which can lead to death of DNA (apoptosis). This condition is also seen as an etiological process of several metabolic, chronic and genetic diseases. The increased athletic performance in recent years is directly related to research that modulate the antioxidant capacity of athletes, reducing the potential oxidative cell.*
Procedure Methodology*: The study was conceived by compiling research conducted and with the participation of Antunes Neto (n = 31), containing papers derived from master's and doctoral studies; theoretical essays on the molecular events of adaptation to physical training; experimental studies reporting the triggering of oxidative stress and the relationship with physical exercise; and experimental studies that collaborate with the validation of procedures for analyzing oxidative stress levels in animal protocols. Experiments with high-performance athletes in tennis, volleyball, soccer, bodybuilding, triathlete and also with obese subjects were illustrated. There are data from animal research simulating the overtraining situation for a better understanding of the installation of oxidative stress.*
Results*: The results showed that molecular responses precede physiological changes in the onset of oxidative stress, which may give clues about the effect of training on the athlete's body. Regardless of the sport modality, what determines the installation of oxidative stress is the increase in training overload and the athlete's inability to recover. The CK analysis is an important parameter of cellular alteration, modulating with the increase of oxidative stress.*
Conclusion: *The increase in plasma CK concentration can indicate the extent of oxidative stress levels in muscle cells, as well as define a safety threshold to determine the modulation of training loads.*
Key Word*: Oxidative stress; Physical training; Biobiobiomarkers; High-performance sport.*

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I. Introduction

The improvement of biomarkers of adaptation to physical training is a constant routine in Sports Sciences. Obtaining specific references for the most distinct modalities becomes a great challenge, because factors such as training volume, specificity of stimulus application, motor requirements, number of competitions in a season, recovery time between one training session and another, among others, establish a complex derivation of information that needs to be considered in an integrated way. It is known that the lack of synchronism of all the factors described and of an adequate methodology for the development of athletic conditioning can generate an overload of the biological systems, causing metabolic and functional overactivity and even disintegration of the body's defense systems[1].

The adaptive responses to physical training are the result of convergences between factors intrinsic to the exercises performed and the endogenous/exogenous conditions interfering in the subject's quality of life. The human organism is controlled from the perspective of homeostasis, with a series of factors that manifest themselves to allow an optimal adaptation to the conditions of the environment [2,4]. Physical training is structured by methodological strategies based on scientific knowledge, whose purpose is the application of a set of stimuli that unbalance the homeostasis of the morpho functional system of the organism, providing a stimulus for

adaptation. The imbalance in homeostasis will require the organism to reorganize its functional mechanism for the reestablishment of an ideal homeostatic state: the positive adaptation will be the result of a correctly programmed alternation between stress induction and regeneration. Thus, the organism adapts to the stressor agent in such a way that, if the same stimulus is imposed again after the adaptation occurs, the homeostatic mechanisms will not be disrupted to the same extent [5,6,7,8].

The monitoring of oxidative stress biomarkers is one of the possibilities of studies focused on sports training to avoid the installation of overtraining. Reactive oxygen species (ROS), also known as free radicals, are formed by the incomplete reduction of oxygen in energy generation processes. These are independent chemical species that have one or more unpaired electrons. This implies a great deal of instability and often high reactivity. As they need to complete their electron pairs in order to stabilize, they behave either as receptors (oxidants) or as donors (reducers) of electrons. The high reactivity of ROS determines the attack on cellular structures, such as membrane proteins and lipids, and even the composition of deoxyribonucleic acid, initially inducing microlesions in muscle fibers and alteration of their homeostatic condition [1,2,3,4,9,10].

In aerobic organisms, oxygen (O_2) is used in the mitochondria as the final acceptor of electrons in the respiratory chain, and water (H_2O) is reduced in the complex IV or cytochrome aa3. By virtue of the spin restriction, O_2 can only be reduced unielectronically. The four reduction steps occur within mitochondrial complex IV, releasing H_2O as the only end product of the reaction. However, it is well documented in the literature that about 5% of the O_2 consumed is reduced to superoxide anion radical (O_2^-), a very common form of free radical formation in biological environments [5,6]. Physical exercise increases around twenty-five times the volume of total O_2 consumed (VO_2) and a hundred times in active muscle fibers, allowing O_2^- to be formed in various ways, such as in the electron transport chain (electron leakage); by the enzyme xanthine oxidase (during the ischemia/reperfusion process); by neutrophils in inflammatory responses (by the univalent reduction of O_2 in the presence of NADPH, catalyzed by the enzyme NADPH oxidase, leading to respiratory burst); in skeletal muscle (producing nitric oxide, which reacts with O_2^-) [1,2,3,4,9,10].

Oxidative stress, therefore, occurs in circumstances in which there is an imbalance between the prooxidant and antioxidant systems, so that the former are predominant. Within a strategy of maintaining the redox state against oxidative conditions, the blood plays a fundamental role, transporting and redistributing antioxidants throughout the body; therefore, the measurement of antioxidant capacity in the blood can give us estimates of oxidative stress levels, allowing a less invasive way of measuring it than by other routes, such as biopsy [1,2,3,4,9,10].

In order to minimize the effects of ROS, aerobic organisms have developed antioxidant defense mechanisms. Antioxidant is any substance that, when present in concentrations lower than that of the oxidizable substrate, is capable of delaying or significantly inhibiting its oxidation. The result is the prevention of the formation of these reactive species; intercept them as soon as they are formed; repair the oxidative damage caused by them. The antioxidants increase the elimination of damaged molecules and also increase the elimination of those that are not excessively damaged, to minimize the formation of mutations [22,23]. The antioxidant defense system is divided into two types: non-enzymatic system and enzymatic system. Small molecules such as vitamins C and E, flavonoids, selenium, bilirubin, uric acid and carotenoids, mainly derived from food, are part of non-enzymatic system. Molecules containing sulfhydryl (SH) groups are considered to be the largest and most frequent non-antioxidant compounds in plasma. The enzymatic system is mainly made up of three enzymes: superoxide dismutase (SOD); catalase (CAT) and glutathione peroxidase (GPx). These enzymes offer protection to the body by removing O_2^- and H_2O_2, converting them into less reactive species [1,3].

Figure 1. Formation of reactive oxygen species and antioxidant enzymatic action.

$$O_2^{\bullet-} + Fe(III) \leftrightarrow O_2 + Fe(II) \quad (1)$$

$$2O_2^{\bullet-} + 2H^+ \rightarrow O_2 + H_2O_2 \quad (2)$$

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^- + {}^{\bullet}OH \quad (3)$$

Source: adapted from Antunes Neto [1].

Figure 1 indicates that SOD catalyzes the dismutation reaction of the O_2^- into H_2O_2 and O_2 (Reaction 1); while CAT and GPx – the latter, together with glutathione reductase (GR), – are responsible for the reduction of H_2O_2 into H_2O and O_2 (Reactions 2 and 3, respectively). The increase in the activities of these antioxidant enzymes, induced by physical training, is the focus within the strategies of monitoring and reformulation of

training loads, thus avoiding an increase in the indicators of oxidative attack and, consequently, the installation of oxidative stress. In the same way, systematized physical exercise allows the cell to increase its antioxidant capacity, since the progressive and gradual increase in O_2 consumption makes it possible to adapt [1].

Thus, the aim of this study is to present results obtained by the author, which make it possible to verify the levels of oxidative stress in different sports modalities during a competitive period, collaborating for a better understanding of the biochemical mechanisms of detection, analysis and applicability of oxidative and antioxidant parameters in the modulation of physical exertion load.

II. Procedure Methodology

The study was conceived by compiling research conducted and with the participation of Antunes Neto (n = 31), containing papers derived from master's and doctoral studies; theoretical essays on the molecular events of adaptation to physical training; experimental studies reporting the triggering of oxidative stress and the relationship with physical exercise; and experimental studies that collaborate with the validation of procedures for analyzing oxidative stress levels in animal protocols. All studies involving humans and animals were approved by research ethics committees.

From this theoretical-practical construct, it is expected to present a set of information on oxidative stress and applicability in physical training that can contribute to the understanding of such a complex, but no less interesting, theme. The discussion of the results presented in this paper is based on these studies. It was decided to present data obtained from high-performance athletes in the modalities of tennis, volleyball, soccer, bodybuilding and triathlon. To understand the modulation of oxidative stress in a different situation, we have a study with obese, sedentary subjects and beginners of physical activity.

III. Results

Table 1. Blood biomarkers of oxidative stress in youth players tennis during competitive mesocycle (n = 5).

		Tennis		
Antioxidant biomarkers	**Analysis 1**	**Analysis 2**	**Analysis 3**	**Statistical Analysis**
CAT (k/gHb/min)	0,53 ± 0,08	0,56 ± 0,09	0,5 ± 0,07	p > 0.05
TSG (μM)	551 ± 47	553 ± 50	548 ± 44	p > 0.05
Oxidant biomarker				
TARS (nmol/mL)	3,27 ± 0,91	5,3 ± 1,15*	4,6 ± 0,54**	* = p < 0.01 ** = p < 0.05
Cell Damage biomarker				
CK (IU/L)	235 ± 37	476 ± 34*	340 ± 17**	* = p < 0.01 ** = p < 0.05
Correlation Between CK and TARS				c = 0.952

Source: adapted from Antunes Neto et al. [11, 12]. Data are means ± SD (n = 5). Where: CAT = Catalase; TSG = Total Sulfhydryl Group; TARS = Thiobarbituric Acid Reactive Substances; CK = Creatine Kinase.

Table 1 shows that there was no significant increase in CAT levels in the hemolysate (p>0.05) during the competitive phase. However, the values obtained can be considered high in relation to non-athletes [7]. Similarly, there was no significant increase in plasma TSG levels (p>0.05) in the same analysis period. It reinforces the idea that enzymatic (CAT) and non-enzymatic (TSG) parameters act in an integrated manner, since TSG values are also considered high, according to previous analyses.

There was a significant increase in plasma levels of CK and TARS at the time of analysis 2 (p<0.01) and analysis 3 (p<0.05) compared to analysis 1. The correlation index between the parameters of CK and TARS was c=0.952, demonstrating the condition that lipid peroxidation and microlesions induced by exercise can be evaluated in a linear manner.

In all, three analyses were performed during the competitive period, over three consecutive weeks, in the afternoon, prior to the training session. The first analysis took place a week before the main tournament of the season, the second analysis took place 48 hours after the first games of the competition were played; and the third analysis took place one week after the end of the tournament or with the athlete's disqualification [11,12].

Table 2. Blood biomarkers of oxidative stress and cell damage in volleyball players during a competitive macrocycle (n = 9).

		Volleyball		
Antioxidant biomarkers	**Analysis 1**	**Analysis 2**	**Analysis 3**	**Statistical Analysis**
CAT (k/gHb/min)	0,36±0,02	0,32±0,04*	0,38±0,04*	p > 0.05
GR (IU.gHb^{-1} .min^{-1})	12,7±0,5**	11,9±0,3**	13,2±0,3***	** p < 0.05 *** p < 0.01
TSG (μM)	510±40	520±40	505±35	p > 0.05
Oxidant biomarkers				
TARS (nmol/mL)	1,15±0,09	1,25±0,15	1,27± 0,17	p > 0.05
RCD (mol.L^{-1})	122±17	160 ±40*	80±22**	* p < 0.05 ** p < 0.001
Cell Damage biomarker				
CK (IU/L)	200±50*	260±70*	220±80*	* = p < 0.001

Source: Antunes Neto et al. [13]. Data are means ± SD (n = 9). Where: CAT = Catalase; TSG = plasma Total Sulfhydryl Groups; TARS = Thiobarbituric Acid Reactive Substances; RCD = plasma Reactive Carbonyl Derivatives; CK = Creatine Kinase.

This study evaluated the biomarkers of oxidative stress in volleyball players over three distinct phases of a championship to determine if they were able to reflect the different levels of stress: Phase 1, low-intensity exercises; Phase 2, increase in training load and start of the championship; Phase 3, reduction of training sessions and load and final phase of the championship. Antioxidant status (CAT erythrocyte activity), and plasma concentration of total sulfhydryl-TSG groups was measured; oxidizing status (concentrations of plasma RCD and TARS biomarkers); and the levels of muscle damage through plasma CK activity in blood samples from untrained individuals (n = 9) and volleyball players (n = 9)[13].

Table 2 shows the erythrocyte CAT and GR activities and plasma TSG as markers of the antioxidant status, obtained at the three training phases. In comparison with the control group, GR (8,9±0,7 IU.gHb^{-1}.min^{-1}, data not contained in the table) and CAT (0,37±0,03 k.gHb^{-1}.min^{-1}, data not contained in the table) activities showed a different pattern of response with GR activity significantly higher in all three phases analyzed while CAT activity has not been significantly affected during the different phases. On the other hand, we found significant differences (P<0.05) of CAT and GR activities in phase 3 in comparison with phase 2. No significant differences in TSG (C) concentration during all phases analyzed were observed (control: 499±35 mol.L^{-1}) [13].

Plasma RCD and TARS concentrations at the three moments of analysis were taken as markers of oxidative attack in proteins and lipids, respectively. RCD showed a significant increase at phase 2 in comparison with both the control group (p<0.001) and phase 1 (P<0.05). The increase observed at phase 2 was followed by a significant decrease, near to the control value at phase 3 (p<0.001). No significant differences in plasma TARS concentrations were observed [13].

Table 3. Plasma CK concentration over five months of the 2001 Brazilian Football Championship (n = 6)

Soccer		
Cell damage biomarker (CK (IU/L)	**Analysis 1**	**Analysis 2**
Player 1	5133	354
Player 2	1154	680
Player 3	1090	482
Player 4	983	513
Player 5	729	472
Player 6	720	482

Source: Antunes Neto et al. [3]

The values of Analysis 1 (n=6) were individualized, when it was perceived that they were well above the average of the group, and discussed with the physical preparation committee, in order to promote the recovery strategy; on the other hand, the values in Analysis 2 show that the microcycle of two weeks of recuperative training allowed a significant drop to minimize muscle stress. At this moment of detection of the alteration of the biochemical parameters, the players had the load of effort decreased and recovery time increased by two weeks, being reassessed again at the end of these weeks. After the results of the blood tests, it was possible to individualize

and correct the training loads and recovery time of those athletes detected at the stress threshold, allowing the entire group to achieve a positive adaptation, without the occurrence of more serious muscle injuries [3].

Table 4. Plasma biomarkers of cell damage and biochemical changes in bodybuilding during a macrocycle training (n = 10).

	Bodybuilding	
Cell damage biomarker	**Untrained Group (n = 8) (UG)**	**Trained Group (n = 10) (TG)**
CK (IU/L)	78,0 ± 28,58	336 ± 165,08*
CK Mb (IU/L)	11,3 ± 3,10	17,22 ± 2,68
GPT (IU/L)	14,5 ± 7,72	23,44 ± 6,69
GOT (IU/L)	15,5 ± 4,35	25,22 ± 5,69
Biochemical biomarkers		
Creatinine	0,74 ± 0,13	1,13 ± 0,14*
Urea	25,25 ± 9,14	31,77 ± 4,35
Uric Acid	5,25 ± 0,88	5,74 ± 0,88

Source: Antunes Neto et al. [14]. Data are means ± SD (n = 9). Where: CK = Creatine Kinase * P<0.05; CK Mb = Creatine Kinase Cardiac Isoform; GPT = Glutamic Pyruvic Transaminase; GPT = Glutamic Oxaloacetic Transaminase. Creatinine * P<0.05.

The UG was advised not to perform strength exercises for two weeks, keeping their activities of daily living. The TG was in the usual phase of strength training bodybuilding (all practitioners were in mesocycle including strength exercises - had already gone through the phase of strength resistance). The aim was to quantify possible changes to biomarkers studied at the time of peak training, so that an understanding of adaptive events and cellular and metabolic changes [19]. The UG it was composed of 8 (untrained) subjects from the male sex who were not accustomed to perform bodybuilding exercises. The TG was composed by 10 male subjects who had been bodybuilding for two to three years, at least 5 weekly sessions.

Plasma CK has been used as a marker of muscle stress due to physical activity, and can be used as an indicator of a possible future injury, and also to monitor training load. The greater the intensity and duration of this exercise, the greater the amount of muscle micro injuries that allow the extravasation of this enzyme into its extracellular environment. The increase in plasma CK is well related to high-intensity strength exercises or high-volume cyclical activities [24].

Although there was no significant increase in plasma concentrations of CK-MB, TGO and TGP (Table 1), there is a tendency for these parameters to increase. Transaminases are found in the heart, liver, muscles, and kidneys, but in much lower concentrations in striated muscles compared to CK. On the other hand, CK-MB, an isoenzyme of total CK, is found mainly in heart tissue. Complementary dosages of these parameters can help to understand cellular changes, biochemical expression and the etiology of the injurious process. Often, the bodybuilder does not have the full understanding of his health condition.

Table 5. Blood biomarkers of oxidative stress, cell damage and biochemical changes in a triathlete during a competitive macrocycle (n = 1).

Triathlete				
Antioxidant biomarker	**Analysis 1**	**Analysis 2**	**Analysis 3**	**Statistical Analysis**
CAT (k/gHb/min)	0,14	0,46*	0,48**	*p < 0.001 ** p < 0.00.1
Oxidant biomarker				
TARS (nmol/mL)	4,01*	3,7**	2,9	*p < 0.001 **p < 0.01
Cell damage biomarker				
CK (U/L)	123	90*	233**	* = p < 0.01 * = p < 0.001
Biochemical biomarkers				

Creatinine (mg/dL)	0,90*	0,80*	0,70*	*p<0.001
Urea (mg/dL)	52	45	47	P >0.05
Uric Acid	0,88	0,63	0,7	P >0.05

Source: Antunes Neto [5]. Data in absolute values (n = 1). Where: Where: CAT = Catalase (**p< 0.001compared to the control group = 0,30 k/gHb/min.; ** p< 0.001 compared to the control group and analysis 1); TARS = Thiobarbituric Acid Reactive Substances (*p< 0.001 in relation to the control group = 4,01 nmol/mL and analysis 3; **(*p< 0.001 in relation to the control group and analysis 3) CK = Creatine Kinase * P<0.05 (*p< 0.01compared to the control group = 123 U/L and analysis 1; **p< 0.001 compared to the control group = 1,39 U/L , analysis 1 and analysis 2); creatinine (*p<0.001 compared to the control group = 0,79 mg/dL) Urea and Uric Acid (P >0.05 compared to the control group and other analyses).

The level of antioxidant activity of CAT decreased significantly at the time of analysis 1 (p< 0.001), but still with a significant increase in the other analyses (2 and 3), with p< 0.001. It is interesting to note that the highest concentration of TARS was reflected in analysis 1 (p < 0.001) and remained high in analysis 2 p < 0.01). The values returned to a normal level, seen for the control dosage, seen for the control analysis not shown in the table (P >0.05).

Levels of cellular alterations reflected by the plasma analysis of CK concentration show that in analysis 2 there was a significant decrease in relation to the control values and in analyses 1 and 3 (p < 0.001). The highest levels can be seen at the time of analysis 3 (p< 0.001). It is noteworthy that the plasma CK levels for the control group were established according to the dosage standards of the kit manufacturer (Laborlab®).

For the biochemical markers, creatinine, urea and uric acid, no significant increases were obtained established by the manufacturer. It is noteworthy that the creatinine values were at p< 0.001 in relation to the control, which may mean adaptation to the training load and games

Table 6. Anthropometric measurement, blood biomarkers of oxidative stress, cell damage and biochemical changes in subjects S-HBMI; PAG – BMI; PAG – BMI.

Obese and sedentary				
	SN-BMI	**HBMI-S**	**PAP-BMI**	
Anthropometric data				
BMI (kg/m²)	23,10 ± 0,20	33,36 ± 4,60	22,56 ± 2,20	
WHR	0,76 ± 0,02	1,11 ± 0,21	0,75 ± 0,12	
FP (%)	18,20 ± 2,20	34,00 ± 3,60	17,30 ± 2,10	
Antioxidant biomarker				**Statistical Analysis**
CAT (k/gHb/min)	0,30 ± 0,04	0,19 ± 0,10	0,40 ± 0,10	*p < 0.001 ** p < 0.00.1
TSG (μM)	450 ± 111	298,0 ± 67,0	503 ± 121	
Oxidant biomarker				
TARS (nmol/mL)	2,3 ± 1	1,60 ± 0,40	2,80 ± 1,4	p < 0.001 p < 0.01
Cell Damage biomarker				
CK (U/L)	100 ± 25	45,0 ± 25,0	150 ± 45 U/L	* = p < 0.01 * = p < 0.001

Source: Antunes Neto [31]. Data in absolute values (n = 10 subjects in each group). Where: SN-BMI = sedentary group with normal body mass index; S-HBMI = sedentary group with high body mass index; PA – BMI = physical activity group with normal BMI; WHR = Waist-to-hip ratio; FP = Fat percentage; CAT = Catalase; TSG = plasma Total Sulfhydryl Groups; TARS = Thiobarbituric Acid Reactive Substances; CK = Creatine Kinase

Waist-to-hip ratio (WHR) values and percentage of fat (FP) have values increased proportionally to the increase body mass index (BMI). The increase in these two parameters observed in the HBMI-S group is compatible with the state of obesity in which the subjects in this group are higher BMI values are related to higher body mass (body weight) values [31].

Antioxidant biomarkers show that the HBMI-S group had lower CAT values compared to the other groups, suggesting that the activity of this enzyme is decreased proportionally to the increase in BMI. There was a statistically significant difference between the BMI - S and PAP - BMI groups (p<0.05). There was a statistically

significant difference between the BMI-EN and BMI-ES groups ($p<0.01$); between the BMI-NPAF and BMI-ESc groups ($p<0.01$) [31].

The BMI-ES group had lower TARS values in relation to the other groups - BMI-NPAF and BMI NS -, suggesting that this parameter may decrease proportionally to the increase in BMI. There was a statistically significant difference between the BMI-NS and BMI-ES groups ($p<0.05$) [31].

The BMI-SS group had lower CK values in relation to the other groups, suggesting that this indicator responds to the intensity of physical exertion, consistent with the conditions of the other two study groups (low practice of physical activity, with consequent increase in BMI). There was a statistically significant difference between the BMI-NPAF and BMI-ES groups ($p<0.001$) [31].

Table 7. Blood biomarkers of oxidative stress in mice submitted to swimming training (T) and overtraining (OVER) compared to mice with untrained Ascitic Ehrlich tumor (AET) (n = 10 in each group).

Mices				
Antioxidant biomarker	**Training (T)**	***Overtraining* (OVER)**	**AET**	**Statistical Analysis**
CAT (k/gHb/min)	0,55±0,05*	0,35±0,04*	0,14±0,03*	$p < 0.01$
Oxidant biomarker				
TARS (nmol/mL)	5,1±0,05*	7,9±0,13	11,5± 0,35**	$p > 0.05$ $p > 0.001$
Cell damage biomarker				
CK (U/L)	39±03	98±08*	49±04**	* = $p < 0.001$ * = $p < 0.001$

Source: adapted from Antunes Neto et al. [15].

The mice went through a period of adaptation to swimming training, lasting one week (15 minutes of training session). After the adaptation period, the mice started swimming five times a week (Monday to Friday), for a period of four weeks, with the training session time rising from 20 minutes to 60 minutes. After this period, a batch of mice was sacrificed for analysis of this systematized training phase (group T). The surviving animals were submitted to a training cycle, consisting of a weekly progressive increase of one training session, until reaching four training sessions per day, lasting 60 minutes each session (OVER group) [15].

Ehrlich's ascitic tumor is characterized by rapid mitotic activity in the first week after inoculation; The mass generated has continuous growth and promotes invasion of adjacent tissues. It is observed that 90% of the cells of the peritoneum become tumors after 10 days of development. Ehrlich's tumor strain was originally obtained from a strain at the Cancer Hospital, São Paulo. She was kept in the laboratory through successive passages between donor animals. Ehrlich tumor cells grow as ascitic cells in the peritoneal cavity of mice, facilitating their maintenance through consecutive passages. The number and viability of tumor cells (> 95%) were determined in a Neubauer chamber by excluding the blue dye of Tripan. Animals with AET were sacrificed at the same time as the overtraining group. The aim of the experiment was to compare and characterize the induced cytotoxicity between OVER and TAE [15, 16].

IV. Discussion

Measures to predict the athlete's physical condition have always been performed according to the principles of the sport. The most common tests used are those performed in the athlete's own training environment, where the main focus lies on the principle of training specificity. This condition is directly related to the principle of adaptation and systematization of sports training, since the maintenance of planning – or its reorganization – is the guarantee of obtaining adaptive responses. With the development of Sports Sciences and methodologies applied in research laboratories, the principles of the organic adaptations and biological individuality, began to provide an aggregation of important values for a better knowledge of the behavior of the athlete's adaptive pattern, as well as the creation of a profile that locates the subject in relation to a score of the group and its adaptive reserve capacity when thinking about the development of a multi-year plan [1].

However, another fact of great relevance is that the physical condition of the subject interferes with the antioxidant defense capacity, providing an increase in oxidizing biomarkers and, therefore, an increase in oxidative stress. The two conditions, athletes and sedentary subjects, influence the redox state of the cell, but in different ways that can accelerate the state of defense or attack of the organism as a whole [5,11,12,13,14,31]. There is an urgent need to understand how the installation of oxidative stress becomes so harmful to cells in the most different organs. Preliminary research already indicates that the imbalance between oxidants and prooxidants may

be directly and punctually related to the triggering of psychic disorders such as schizophrenia [22, 23]. But that's not the interest for the time of these studies. However, it should not be overlooked that the same stressor can determine the installation or activation of gene regions depending on their potential for aggressiveness. In conclusion, the installation of an oxidative stress condition can trigger several alterations with great potential for disorder at systemic levels.

Considering the experiments presented in this study, the quantification of oxidative stress levels allows the monitoring of the athlete's training status, giving margins for the modulation of training loads, as seen in Tables 1 [11,12] and 2 [13]. Results showed that molecular responses precede physiological responses in the onset of oxidative stress, which may give indications of the effect of training on the athlete's body [30].

One of the possibilities of studying oxidative stress responses lies in the monitoring of athletes' training. As these studies still lack many answers, experimental studies with animals can provide relevant information and this was the first step of the experiments designed by the team (Table 7). Both the master's and doctoral studies focused with great discretion to establish relationships between stress and exhaustion in animal experiments, using other biomarkers that proved the installation of a severe oxidative stress condition, such as the study of heat shock proteins (HSP) [2,3,10]. The response of cells to environmental stress involves the synthesis of HSP. The HSP70 family has been the most widely studied and well characterized due to its critical and protective role as a molecular chaperone system, involved in a variety of conditions such as hyperthermia, glucose deprivation, increased intracellular calcium ion concentration, oxidative stress, hypoxia and others [10]. All these data point to the severity of the installation of an oxidative stress condition, which led to a characteristic situation of overtraining when simulating an exhaustive training situation [3].

It was observed that there is an increase in lipid peroxidation (TARS) in all groups studied (T, OVER and TAE) when compared with the CO group (reference values not shown in the Table 7. CO group = 2,5 ± 0,08 nmol/mL) [15]. However, it is also observed that the antioxidant activity, measured through the CAT enzyme, through systematized and properly controlled training, is capable of modulating this parameter to the new redox state of the cells and combating the deleterious effects caused by ROS, with the possibility of reversing a possible situation of oxidative stress installation. On the other hand, poorly structured training, without adequate recovery periods, such as the one developed in the OVER group, can increase the action of ROS, causing the antioxidant defense system to be unable to modulate to this oxidative process, so that an increase in the amount of TARS and, concomitantly, a decrease in the values of CAT activity can be observed, thus characterizing a situation of oxidative stress [16,17,18,19,20]. All this evidence was important for the second phase of experiments, with humans (athletes, sedentary and obese subjects).

The present review sought to understand several factors that can alter the redox state of the cell, so that there is no belief that only subjects involved in high-intensity physical activities can modulate the cellular antioxidant/oxidant relationship. In the case of obese and sedentary subjects (Table 6) [31], significantly lower CAT activity was observed in the BMI-ES group, in relation to the other groups; This condition can be understood as if overweight and obesity interfere with the function of this enzyme – which consequently causes a decrease in efficiency antioxidant and more likely to increase oxidative stress [31]. The data presented suggest that the decreased CAT levels of the BMI-SS group – compared, especially with athletes [24] – are the result of the absence of a stimulus or a potent stressor, such as physical activity. Systematized physical exercise allows the cell to increase its antioxidant capacity, since the progressive and gradual increase in oxygen consumption makes it possible to adapt. Studies that have shown an increase in CAT activity in the obese population can be understood by the fact that this enzyme undergoes modulation – i.e., transient regulatory adjustment – even in unfavorable or pathological circumstances.

The increase in plasma concentrations of TARS and CK observed in the IMC-NPAF group, compared to the BMI-NS and BMI-ES groups (Table 6) [31], is a circumstance of chronic exposure to high levels of ROS. Again, we emphasize that the production of these species increases with oxygen consumption – observed during physical activity – inducing cellular disturbances such as microlesions of the membranes and the consequent intracellular CK extravasation [6]. This fact explains, then, the decrease in the concentration of TARS observed in the BMI-ES group – since the sedentary lifestyle imposes lower oxygen consumption and, therefore, lower ROS production, providing milder oxidative attack compared to active practitioner's physics. Thus, it should be emphasized that, in an abrupt exposure situation to the increase in ROS, whether due to physical activity or even pathology, sedentary/obese subjects may undergo extremely severe intracellular changes. Such observations reinforce the importance of routine and progressive practice of physical activity for the functional increase of the antioxidant system and the greater stabilization of the atomic bonds of membrane components.

The results complement each other as stressful and adaptive stimuli are applied to adapted or non-adapted organisms. It is important to emphasize that the comparative values for the OVER group (Table 7) in animal experiments should be made with the data obtained by the T group, since there is only a situation of overreaching (metabolic stress) in organisms that are in a training method. Thus, the decrease in CAT activity is considered significant for the OVER group compared to the T group. The increase in lipid peroxidation, for the OVER group,

corroborates the idea that the enzymatic levels of CAT (despite the comparative increase with the CO group) are not sufficient to prevent the increase in the concentration of hydroperoxides [15].

However, it is also observed that the antioxidant activity, measured through the CAT enzyme through systematized training and properly controlled, is able to modulate such a parameter to the new redox state of the cells and combat the deleterious effects caused by ROS, having the possibility of reversing a possible stress installation situation oxidative. This is the principle of the biological adaptation of training: to increase the adaptive potentialities of the physical valences so that a new load increment can be inserted into the structure of the previously determined macrocycle. The molecular techniques for detecting the situation of oxidative stress (CAT and TARS), together with the analysis of tissue injury biomarker (CK), are precise tools that can collaborate with the prescription of physical training, but, above all, predict more acute lesions. Another point to be emphasized is that blood levels indicate with high sensitivity the changes that occur in the systems organic diseases as a whole, which can replace more invasive techniques, such as biopsies, which are difficult to allow and access in our country, and that always encounter resistance from athletes and technical committees. Finally, it is strongly evidenced that the lack of control of the training can lead the body to levels of oxidative stress that they are confused with a pathological situation. The search for positive adaptive responses can cross highly challenging thresholds, where the difference may be the training control methodologies. At this very moment, this is what Nanotimize Technology Company has been looking for to solve this need to speed up the responses to the athlete's physical conditions and enable the technical committee to make quick and accurate decisions for the preservation of the athlete's physical condition [36,37].

Another purpose of this paper was to understand how athletes, from different modalities (Tennis, Volleyball, Triathlon, Bodybuilding and Soccer), corresponded to variations in the levels of oxidative stress and cell damage, data of extreme importance for the evaluations of the redox state of the muscle cell. All studies that involved athletes were possible since there was great interest on the part of the technical and physical preparation teams in integrating themselves on the methods presented and knowing the theoretical and literary supports. The monitoring of certain patterns, especially those that provide information about the state of adaptation or impairment of the muscle cell, are extremely relevant in the training period of a high-performance athlete. The stressful stimulus should lead the organism submitted to sports training to a new homeostatic stage, respecting the recuperative events; In this way, improvements in athletic performance are expected. In the case of athletes in training, the possibility of injurious conditions is increased, as they are still in the improvement of the specific techniques of the modality, as well as in an accentuated phase of the processes of maturation of the organism [1,6].

The literature produced so far and corroborated by the authors shows evidence that exercise-induced oxidative stress is a source of relevant collaboration with the harmful mechanisms in muscle cells, sarcoplasmic reticulum, membrane structures and, mainly, DNA. Secondary events, such as infiltration of inflammatory and phagocytic cells in the cell interior, act aggressively on the disorganization of Z Lines, A Bands and the inability to couple the cross bridges, which further contributes to the destabilization of the sarcomere and the sarcoplasmic reticulum. The increase in the concentration of calcium activates classes of phospholipases – especially phospholipase A2 – and proteases sensitive to such concentrations, triggering cascade events of degradation of other cellular structures, until finally, in an extreme state, leading to the installation of apoptosis (cell death). Extravasation of the enzyme creatine kinase (CK) is one of the most well-known events in these degenerative conditions [1 2].

It is extremely important to highlight the etiology of the oxidative stress process. CAT is an enzyme that acts in the detoxification of ROS, more specifically in the control of intracellular H_2O_2 levels. Although H_2O_2 is not a radical species, nor does it have a high oxidizing potential, it can react with transition metals, especially iron, bound or not to heme groups located within cells, giving rise to the hydroxyl radical ($OH^{\bullet}$), a powerful oxidant. Therefore, the maintenance of low levels of this substance is of fundamental importance so that no cellular structure suffers intense oxidative attack and maintains its proper functions [22,23]. H_2O_2 is enzymatically dehydrated to H_2O and O_2 by CAT. For all modalities (Tables 1, 2, 3, 5) and even animal experimentation (table 7), it is shown that CAT activity levels remain high, even during the intense situation between training and competition, when compared to sedentary control subjects. First, it is necessary to consider the previous training cycles, which allowed the athletes to arrive at the competition period in adequate conditions to withstand the stressful demands. The consensus is that aerobic training increases the capacity of antioxidant enzymes in the erythrocyte. However, the measurement of CAT still lacks more agile experimental conditions made available by clinical laboratories, which makes it impossible to use this biomarker as a determinant of oxidative stress levels [2,3].

It is speculated that H_2O_2 itself could have a stimulatory effect on another antioxidant enzyme, SOD, also seen in erythrocytes, while the O_2^{-} radical would act on CAT. Another hypothesis for the increase in CAT activity would be the reduction from Fe_3^{+} to Fe_2^{+} present in the heme group of its molecule, which would make it more active when reduced [4]. One possibility would be the velocity constant (Km) of the CAT for the peroxides, which would thus justify its high activity value in this intense phase of competition, a period in which the

production of ROS would be higher (see the results of lipid peroxidation, Tables 1 and 2, analysis 2, in the competitive period) and the capacity for saturated (but not decreased) intracellular detoxification [11,12,13].

Another interesting biomarker of antioxidant defense is plasma TSG levels (Tables 1 and 2) [11,12,13]. Most plasma proteins have cysteine residues, with free sulfhydryl (-SH) groups, which can be oxidized by the action of ROS. The quantification of the plasma concentration of TSG provides an idea of oxidative attack on proteins and, consequently, of the level of antioxidant defense. Regarding the increased concentration of TSG in plasma, there seems to be a relationship with the maintenance of high CAT activity, indicating that oxidative damage was not relevant for significant oxidation of free SH groups in plasma. The increase in oxidation of plasma SH groups due to oxidative stress can also be induced by physical training itself. However, the increase in CAT activity together with the TSG indices observed seems to outweigh the levels of oxidative stress achieved during the competitive period [1,2,3].

Table 1 also shows an important correlation between TARS and CK [11,12]. The plasma measurement experiment of TARS is a recognized lipid peroxidation index, which indirectly measures the concentration of malondialdehyde (MDA), providing parameters for the evaluation of ROS-induced data in sites with abundant presence of phospholipids, such as biological membranes. The high plasma concentration of MDA is also related to the training status [3]. The athletes in the present study form a homogeneous group, with years of general and basic preparation to reach the specific stage of inducing overload in the modality. This fact suggests that molecular changes induced by the ROS themselves are triggered to promote capacitance of long-lasting adaptations and allow an adaptive "window" for athletic performance enhancement [6].

Elevation in plasma CK levels indicates alteration of the musculoskeletal cell membrane, possibly due to hypoxia/reperfusion reactions or ischemia resulting from exhaustive exercise [1,2,3,6]. Both tennis players (Table 1) [11,12], volleyball players (Table 2) [13], soccer players (Table 3) [3], bodybuilders (Table 4) [14] and triathlete (Table 5) [5] are involved in activities, especially in the competitive period, where there is strenuous application of intermittent loads, with limited periods of active recovery. All these conditions allow the installation of ischemia/reperfusion conditions, promoting more accentuated extravasation of CK in the plasma. Exhaustive eccentric exercise, common in braking, lateral displacements and changes of direction during such modalities, could destabilize sarcomere structures and increase the intracellular concentration of calcium levels, activating calcium-dependent proteases in biological membranes [1].

Considering Figures 1 and 2 (analysis 2), where the main competitive period of the season begins, CK levels are higher, but there is support from the antioxidant system (CAT and TSG analyses at the same times) to support these cell damages. It is evidenced that the adequate, individualized and planned periodization according to the competitive season makes it possible to induce an increase in antioxidant levels to attenuate a possible increase in oxidizing biomarkers and cell damage [28].

Antunes Neto et al. [24] considered that the increase in the concentration of plasma CK could be an early event for the installation of adaptive responses positive. This study observed that the CK levels remain elevated in subjects adapted to strength training, but not suffering significant changes, even when the training loads are high during a second shock microcycle. It can be suggested that there is a threshold of acceptable cellular alterations for the occurrence of positive adaptive events. If a higher than acceptable stress threshold is installed, synthesis events can be disintegrated and the unsuitable structure of strength raining induce injuries rather than stimulative micro lesions, just like in bodybuilders who are in demand for muscle strength all the time

It is interesting to note that, even though there was no significant increase in plasma concentrations of CK-MB, GPT and GOT (Table 4) [14], there is a tendency to elevation of these parameters for bodybuilding [14]. Transaminases are found in the heart, liver, muscles, and kidneys, but in much lower concentrations in the striated muscles compared to CK. On the other hand, CK Mb, an isoenzyme of total CK, is found mainly in heart tissue. Complementary dosages of these parameters can help to understand cellular changes, biochemical expression and the etiology of the injurious process. Often, the bodybuilder does not have the full understanding of your health condition [14].

The values for creatinine levels were significant statistically in TG (Table 4) [14]. Creatinine testing is done to determine the end product of catabolism muscle, while urea allows stablish the end product of purine metabolism. Significant increases in creatinine and urea for bodybuilding may indicate that the stressful stimulus of weight training increases the degradation of purine bases and protein catabolism, respectively. The creatinine data may reflect an increase in protein turnover (increased relationship between protein synthesis and degradation), since there is an increase in mass lean and continuous micro injurious process, evidenced by plasma CK values. Planned analyses of creatinine, urea and uric acid throughout the training period allow us to understand whether the events established recovery systems for training are having the desired effect [14].

A result of great relevance is shown in Table 3 [3], indicating that it is possible to individualize the training and analyze those (n = 6) who had very high CK parameters in relation to the group close to the most important competitive phase 3. At this moment of detection of the alteration of the CK parameters, the players had the effort load decreased and the recovery time increased by two weeks, being reevaluated again at the end of these weeks.

With this, after the results of the blood tests, it was possible to individualize and correct the training loads and recovery time of those athletes detected at the stress threshold, allowing the entire group to achieve a positive adaptation, without the occurrence of more serious muscle injuries. This intervention strongly suggested that the biomarker CK, in the phase of greatest muscle stress, which is the competitive period, makes it possible to identify athletes with greater injury potential and who may suffer more severe damage if they remain in a strenuous training condition [3, 25, 26, 27].

Results of an important study proved the possibility of using plasma CK concentration analysis as a biomarker for the initiation of fatigue or muscle overload detection activity in soccer players [29]. By determining an upper limit for plasma CK levels (a value determined for 975 U/L), the measurement of players in relation to this value can contribute not only to protect them physically, but also to optimize their training schedule. Players with CK values below the upper limit are likely to have sport-specific adaptive muscle responses, which may allow them to participate in training and games without major risks of suffering significant muscle injuries [29].

V. Conclusion

Studies indicate a high possibility of correlation between the modulation profile of plasma concentrations of CK and TARS. The high levels of these parameters of cellular alterations suggest the installation of oxidative stress. On the other hand, by means of an integrative analysis, the action of the antioxidant biomarkers, CAT and TSG, on the three dosages performed in the different modalities, predicts an adaptive situation favorable to intense conditions between overload and recovery period during the competitive mesocycle. The understanding of the dynamics of variations of the analyzed biomarkers brings the possibility of outlining more solid guidelines on the structuring of multiannual periodization cycles. It is important to emphasize that the finding of oxidative stress precedes the onset of muscle injury, which makes the use of these biomarkers a formidable strategy for monitoring sports training. In the case of soccer, with the early detection of increased plasma CK levels, it was possible to individualize training loads over a two-week period and recover players for the most important phases of the season. There is a need to make the use of the set of these biomarkers presented accessible, not being restricted only to laboratory research studies in the scientific sphere. Thus, the task arises to leverage an important stage of development and progress of physical assessment in Sports Sciences.

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