Oxidative stress and physical exercise in HIV positive individuals

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ABSTRACT

Human immunodeficiency virus (HIV) infection is characterized by functional and structural changes related to the immunological system. Moreover, increase in oxidative stress (OS) in HIV patients, characterized by a reduction in the glutathione (GSH) levels, increases in glutathione disulfide (GSSG), in the ratio GSSG/GSH and in lipid peroxidation, as well as a reduction in antioxidant enzymes – catalase, superoxid dismutase (SOD) and gluthatione peroxidase (GPx) – is a consequence of the evolution in HIV-infected patients. Higher levels of antioxidant activity are necessary to maintain the immunological system cells redox balance and preserve their function. In an antioxidant depleted state, there is a reduction in the immunological response and an increase in HIV replication. The use of highly active antiretroviral therapy (HAART) has improved the clinical evolution of these patients. However, some patients remain showing higher OS and other effects of HAART, such as changes in lipidic and muscle metabolism. Exercise training has been used as a non pharmacological treatment in HIV-infected patients to promote improvements in anthropometrics, aerobic, muscle and psychological outcomes; however, there are insufficient data about the effects of exercise training in OS. This review analyzes the topics related to the oxidative stress in HIV-infected patients and the possible benefits of the physical exercise in the antioxidant capacity. Physical training is a complementary procedure for the patients, with or without use of the HAART, since it improves the cardiorespiratory, muscle, anthropometrics and psychological performance without inducing immunodepression. In relation to oxidative stress, it is inferred, from the data obtained in non-HIV individuals, that the physical training could promote adaptations that minimize the deleterious effect induced by OS through improvements in the activity of the enzymatic and non-enzymatic antioxidant defenses.

Keywords: HIV. Immunological system. Oxidative stress.

INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) is the final stage of the virus infection of the human immune deficiency (HIV). The main characteristic of this infection is a progressive immune suppression which leads the individual to opportunist diseases which, if not treated, lead him inevitably to death.

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The HIV is basically transmitted by the sexual, parental and vertical ways[1-4]. Since its discovery in the beginning of the 80' until the year 2005, 40.3 million cases have been registered worldwide[4]. In Brazil, there are approximately 362 thousand cases and, currently, AIDS is under a stabilization process, at high parameters, though. The 2003 data registered in men the incidence of 23 cases/100 thousand and, in women, 14 cases/100 thousand[3].

Some individuals present early physiological alterations as the clinical condition derived from AIDS infection progresses; for instance, the viral replication is associated with an increase in the OS which can accentuate the immunological dysfunction and lead to an increase in the viral replication[1]. Moreover, the OS may favor the apoptose of the T cells and be involved in the induction mechanism of the tumoral necrosis factor (TNF)-α[5].

The use of the combined Anti-Retroviral Therapy (ARVT) has dramatically altered the evolution of the disease, with important decrease in mortality and improvement in quality of life of infected individuals. Although[6-7] its adverse effects potential, the ARVT in Brazil increased from 5 to 58 months the over life of individuals with AIDS and decreased in 50% the number of deaths[8].

Strategies complementary to the ARVT have been reached with the aim to improve even more the quality of life of these individuals and physical exercise has demonstrated to be efficient in the anthropometric, cardiorespiratory, muscular and psychological parameters[9-12]. Concerning OS, physical training in HIV-negative individuals, provide adaptations capable of mitigating the deletereal effects caused by OS[13]; however, its use is not elucidated yet in individuals infected by the HIV. From the identification of this gap, an analysis on the interaction among oxidative stress, physical exercise and the HIV infection has come up.

OXIDATIVE STRESS

Oxidative stress is the terminology usually used to decribe the damage caused by the oxygen reactive species (ORS) in the molecules or even in the body as a whole. The level of OS is determined by the balance between pro-oxidative and anti-oxidative activities. Therefore, OS is the imbalance between pro-oxidative and anti-oxidative activities which result in increase of free radicals formation and induces to increase of oxidative injuries[1,14].

The pro-oxidative mechanism includes free radicals, such as the anion superoxide and the radical hydroxyl RO, such as the hydrogen peroxide (H_2O_2) and the singlet oxygen. One of the main cellular injury mechanisms related with OS, is the lipoperoxidation (LPO), which is related with the oxidation of the lipidic layers of the cellular membrane[14]. Besides that, the OS may cause injuries to the DNA, to the proteins and it has also implications in the pathogenesis of many diseases in humans, which include *Alzheimer* disease, diabetes, hypercholesterolemia, hepatorenal syndrome among others, besides being involved in the normal aging process[15]. In the cardiovascular system, OS contributes to the beginning and pro-

gression of diseases such as hypertension, atherosclerosis, cardiac hypertrophy and myocardium infarct[12,16].

Since the pro-oxidative substances are constantly made in small amounts in the normal metabolism, the cells have mechanisms in order to avoid the oxidative imbalance and hence, hamper the damage caused by the agressor mechanisms[14]. It is highlighted that the composition of the antioxidative defenses differs from tissue to tissue, from kind to kind of cell and possibly from cell to cell of the same kind in a given tissue, being divided in two systems: enzymatic and non-enzymatic.

The enzymatic antioxidative system includes the dismutase superoxide enzymes (DSO), catalase (CAT) and glutathione peroxidase (GPx). The non-enzymatic includes composites synthetized by the body such as bilirubin, ceruloplasmin, sexual hormones, melatonin, coenzyme Q and uric acid. In addition to that, other antioxidants are ingested through diet such as ascorbic acid (vitamin C), α-tocoferol (vitamin E) β-carotene and flavonoids[13-14].

Many blood, urine and muscular tissue markers can be used in order to evaluate the OS induced by exercise. The most usual method has been the use of the measurement of products of the lipoperoxidation, such as expired pentane, malondialdehyde (MDA), isoprostanes and conjugated dienes; and the ones from the DNA breakage, such as 8-oxo-7.8-dihydre-2´-deoxyguanosine. Besides these markers, the antioxidant levels, such as glutathione (GSH), reduced glutathione/oxidized glutathione ratio (GSH/GSSG) and the activity of the antioxidative enzymes have also been widely used.

HIV INFECTION AND OXIDATIVE STRESS

The infection of the host cells by the HIV requires the ligation of the virus to two receptors over the host cells: the CD4, a high affinity HIV receptor, and chemokines receptors, known as co-receptors of the HIV (CXCR4 or CCR5). In this initial phase, two glycoproteins from the HIV envelope, gp120 and gp41, which together make the gp160, are crucial for the infectious process by their function in the ligation and the viral content entrance in the host cell[2]. There is another important protein which is the transregulatory protein (Tat), responsible for the viral replication and blockage of the cellular metabolism[17].

The infection by the HIV affects mainly the T lymphocytes which express receptors for the CD4+, and its progression results in progressive depletion of these immune cells, what decreases the body's ability to fight diseases it could usually fight, and for that reason is called opportunist. In healthy adults, the T CD4+ lymphocyte counting is between 800 to 1200 units per mm³ of blood[3]. The T CD4+ lymphocytopenia and the increase of the viral load are parameters which determine the progression by the HIV which reaches its peak at the final stage called AIDS, which is the most advanced phase of the virus infection[3].

Among the mechanisms which contribute to the progression of the HIV virus as well as the development of AIDS we find the OS induced by the ERO production during the leucocytes and macrophages activation. The i*n vitro* experiments have shown that the ERO may activate the NF-κB nuclear transcription factor and induce the expression and replication of the HIV[18]. Lachgar *et al.*[17] have shown that the HIV-1 viral proteins, Tat and gp160, are associated with a fast production of H_2O_2, which possibly is concerned with the subsequent immune suppression induced by the Tat.

The HIV infection produces OS and secondarily cellular damage of varied severity and its regression is dependent on the redox balance between oxidants and antioxidants[1]. The HIV positive individuals present disturbs in the metabolism of glutathione, seric and tissue antioxidant diminished concentrations, increased LPO products[19-20] and T CD4+ cells characterized by decrease of the GSH levels, increase of GSSG which, consequently generates decrease of the GSH/GSSG ratio, showing OS[5].

OS has a dominant pathogenic action in the HIV infection. Since the GSH and e cysteine levels are significantly reduced in the plasma and leucocytes[1], the HIV positive individuals face increase in the LPO with fluctuations in the high plasma levels of MDA, vitamin C, glutathione peroxidase, selenium and superoxide dismutase[1,19]. These characteristics favor the progression of the infection with increase of viral replication, carcinogenesis, immune dysfunction[1] and increase in the T cells apoptosis[5]. Thus, the clinic significance of the metabolism disturb of glutathione related with the HIV is reflected by the strong association between decrease of survival of these individuals and low levels of tiol in the plasma and CD4+ lymphocytes.

In a recent investigation[20] when analyzing the exposition of endothelial cells of the brain vases of rats (CECR) at 1μg or 2 μg gp120 or 1 μg of Tat, compared with the control group, it was observed that GSH concentrations were decreased and the MDA levels were higher in the exposed group. The catalase, glutathione peroxidase and glutathione redutase activities were diminished in the CECR cells, showing that the HIV proteins may induce OS in the CECR cells.

OXIDATIVE STRESS AND THE COMBINED ANTI-RETROVIRAL THERAPY (ARVT)

The T CD4+ cells of the HIV positive individuals present low anti-oxidative capacity[1,5,20-21]. Before the beginning of the treatment with the ARVT, the individuals present significant decreases in the plasma levels of vitamin C. The ARVT induces to an increase of the markers of this antioxidant vitamin, with the highest levels occurring after treatment; however, the values do not reach normality. Moreover, during treatment with the ARVT, decreases in the MDA levels were found; however, as observed for vitamin C, they did not reach the control level individuals. Besides that, it has also been observed that the maximal alteration in the viral load was negatively correlated with the maximal altration in vitamin C, and the reduced glutathione ratio by the total glutathione ratio in CD4+[5].

Since the immune system cells usually require high concentrations of antioxidants to keep the redox balance as well as to preserve its integrity and function, it is acceptable that the antioxidant depletion causes a decrease of the immune response[1].

These results support the premise that the increase in the OS production contributes to the HIV infection pathogenic and the *in vitro* findings suggest that the therapeutic intervention, which points to the normalization of the oxidative disturbs, may be relevant for individuals who make use of the ARVT. Within this context, the glutathione supplementation may contribute to the recovery of the redox state and may also influence in the immune capacity[5].

Despite the significant improvement in the clinic, viral and immunological parameters of the HIV positive individuals who use the ARVT, some medications which compose it may increase OS[15,22].

Concerning the treatment effect of *efavirenz* medication, Hulgan *et al.*[15] evaluated the formation of F_2 isoprostanes in the HIV+ patients and observed that the use of this medication was associated with the increase of these LPO markers. The authors highlighted that it is possible that the increase of OS is a component of the immune reconstitution process in some subjects. The association between the increase of F_2 isoprostanes and low plasma viremia more consistenly supports this hypothesis.

While analysing the effect of ZDV (*Zidovudina*), García de la Asunción *et al.*[22], in an investigation performed with cardiac mitochondria of rats, found increase in the 8-oxo-7.8-dihydro-2´-deoxyguanosine levels, in the GSSG levels and in the GSSG/GSH ratio, all OS markers. In addition, increases in the formation of MDA were verified, showing lipoperoxidation. In all cases, the results were normalized with the use of supra-nutritional doses of anti-oxidative vitamins (C and E) in the diet of rats.

The data above show that HIV positive individuals are character-

ized by a decrease in reduced glutathione and in vitamins C and E, the two most important hydrophilic anti-oxidants. Thus, the reduced glutathione is one of the most important regenerating agents of the oxidized kind ascorbic acid and, in return, the vitamin C deficiency leads to an increase in the use of reduced glutathione, a condition which would promote the depletion of both antioxidants (in individuals with or without SRVT), contributing to the increase of OS production.

Increased OS may increase the TNF-α production in many cells and the depletion of reduced glutathione may increase the inflammatory response for these cytokines[5]. Therefore, the disturb in the redox state of the glutathione and the increase in the TNF-α activation may represent a pathogenic cycle, leading to increase in inflammation and OS, and this mechanism may also be acting during the ARVT. This inflammatory interaction can not only harm the T cells function, but also can promote the HIV replication and the apoptosis of the T cells, contributing for the depletion of the CD4+ lymphocytes.

Thus, since the glutathione redox state remains altered and the levels of the antioxidants are reduced, there is a permanent contribution to the immune deficiency of these patients, improving the TARV toxicity. According to what has been confirmed, if on one hand the pre-oxidant state hampers the HIV patient, on the other hand, the anti-oxidant state inhibits the viral replication, increases the latency period and improves the overall state of the HIV positive individual.

PHYSICAL EXERCISE AND OXIDATIVE STRESS

Physical exercise, due to higher oxygen uptake, may promote an increase in production of oxygen reactive species and can therefore modify the redox state of the cell[13,23]. Moreover, there is an increase in the catecholamine release and their self-oxidation may produce free radicals. There is also the possibility of muscular damage subsequent to physical exercise cause inflammation and release superoxide by the oxidation of the NADPH of the neutrophyls. Another important way in the formation of oxygen reactive species present in physical exercise is the production of superoxide by the mitochondria, by the flavine reaction or ubisemiquinone with oxygen[23].

However, there is not always increase of OS induced by physical exercise. When comparing the effect of three physical exercise intensities (low, moderate and high) between triathletes and non-trained individuals, Schneider *et al.*[24] found an increase in the total antioxidant capacity in the two groups after physical exercise and the triathletes presented increased GPx activity compared with the non-trained group. The authors suggest that the increase of the total antioxidant capacity, joined with the higher concentration of plasma uric acid, vitamins and other antioxidants, have avoided oxidative damage induced by physical exercise. The increase of the antioxidant capacity after physical exercise has been found by other authors[25], as well as higher concentrations in the non-enzymatic antioxidants, such as uric acid, ascorbic acid and α-tocopherol[26].

According to what was seen above, the adaptations derived from physical training are able to attenuate the deletereal effects caused by the OS[13], being them concerned with the enzymatic and the non-enzymatic systems. Moreover, these adaptations despite the controversies concerning the involved mechanisms, promote greater tissue resistance to oxidative challenges, such as those provided by physical exercise of high intensity and long duration.

Within this perspective, Linke *et al.*[27] have evaluated the effect of aerobic training in 23 patients with chronic cardiac insufficiency and observed, after six months, improvement in CAT and GPx enzymes activity, as well as decrease of mRNA for TNF-α and for IL1-β, 46% and 35%, respectively. The authors suggest that the increase of the inflammatory cytokines is associated with the harmed activity of the SOD, GPx and CAT enzymes, which results in increase of local OS and cellular damage verified by the increment of the apoptosis. A decrease of the inflammatory cytokines as well as an implement in the GPx and CAT activities was verified with the physical training, resulting in decrease of OS and apoptosis. The authors justify that the TNF-α uses GSH. Since physical training induced in a reduction in TNF-α, such fact improved the GSH levels, providing increase in the GPx activity. Similar results were found in the work by Miyazaki *et al.*[28] who evaluated the effect of 12 weeks of aerobic training of moderate intensity: one hour of running at 80% of maximal HR, 5 times per week, and found increases of SOD and GPx after training, when the individuals were at rest. In this same investigation, the authors compared the response of an exhausting exercise session, pre and post-traning, verifying that the production of superoxide of the neutrophyls as well as the lipoperoxidation were increased in both sessions; however, attenuated in the post-training session. Such evidence suggests that even with increase of antioxidant enzymes after training, the extenuating physical exercise caused a slight increase in exercise-induced OS.

Schneider and Oliveira[13] highlight that physical exercise induced-oxidative stress is influenced by the intensity and by the level of exhaustion of the practitioner. Therefore, the use of different protocols, as well as distinct intensities and times of exposition, joined with the use of varied techniques for OS detection justify the differences in the results.

PHYSICAL EXERCISE AND HIV

Concerning physical exercise in HIV positive individuals, many authors[9-11,29], agree that many times these individuals respond to training similarly to the negative ones. Moreover, regular physical training, in healthy individuals, has shown benefits, such as lower blood pressure, less risk to diabetes, coronary arterial disease and obesity[11].

The keyword for physical training is specificity[9-10]: aerobic training improves cardiovascular fitness and strength training increases strength and muscular mass. In recent essays[12,29] interesting results concerning aerobic fitness have been verified, showing that aerobic unfitness reported in HIV positive individuals can be reverted with aerobic training. Concerning strength training, significant increases in strength, circumferences, free fat mass and functional state have been found when compared with the control group. Concerning the alterations presented in the lipid profile, the results are still controversial; however, significant results have been found when the total body fat was evaluated, with more important reductions in the chest region[11]. Terry *et al.*[12] have analyzed the lipid profile in HIV positive patients under treatment with protease inhibitors in response to 36 aerobic training sessions (walks or runs between 70% and 85% of the heart rate obtained in maximal test) and recommendations in diet. Increase in oxygen uptake peak at the end of the training was found; however, significant alterations have not been observed in the lipid profile of these patients when they were compared with the control group which was only following diet orientations and flexibility work. The authors suggest that the treatment with protease inhibitors is a powerful stimulus for dyslipidemia which cannot be reverted with aerobic training and diet recommendations. Concerning the physical exercise response, Roubenoff *et al.*[30], evaluated an exercise session and verified that there was not increase of mRNA in any moment (2, 6, 24 and 168 hours) after a physical exercise session. Based on these results, the authors affirm that physical training may be safely performed by individuals infected by the HIV.

Remarkably, is the fact that studies have shown a mixed aerobic training (aerobic and strength), as an alternative to improve the parameters affected by the infection[9-11]. Unfortunately, despite this indication, there is a lack of studies with mixed training.

Specific recommendations include aerobic training program, 3-5 weekly sessions at 50-85% of maximal heart rate, or 45-85% of $\dot{V}O_{2max}$, being strength training performed for large muscle groups, at moderate intensity with 8-12 repetitions per exercise[9-10].

CONCLUSION

The OS mechanisms and its relationship with the HIV and the possible benefits from physical exercise to the antioxidant capacity have been analyzed in this review. The evidence points to an early oxidative imbalance in HIV positive individuals, which can be related with the immune dysfunction and the viral replication presented by them. The ARVT, widely applied in this population, seems to have distinct effects depending on the used medication, decreasing or not the OS parameters. Finally, physical training is an auxiliary strategy for patients, with or without the use of the RAVT, since it can bring advantages in the cardiorespiratory, muscular, anthropometric and psychological aspects with no induction of immunosuppression.Concerning the OS, it is inferred from the data in HIV negative individuals, that physical training may cause adaptations which minimize the deletereal effects caused by the OS through improvement in the GSH levels, antioxidant enzymes activity, such as CAT, SOD and GPx joined with improvement of the non-enzymatic mechanism, such as plasma uric acid, vitamins and other antioxidants. These hypothesis should verified in studies which contemplate differentiated protocols which use more sensitive techniques in order to evaluate its efficiency in the improvement of quality of life of HIV positive individuals.

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