



Effect of Eight Weeks of Aerobic Exercise and Vitamin D Supplementation on 8-hydroxy-2'-deoxyguanosine and O⁶-methylguanine DNA methyltransferase in Lung of Rats Poisoned with Hydrogen Peroxide

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ABSTRACT

Background and Objectives: Prolonged exercise can reduce physiological capacities and cause DNA damage by inducing oxidative stress and inflammatory responses. Aerobic exercise reduces the risk of cancer by activating DNA repair enzymes and reducing oxidative stress. The aim of the present study was to investigate effects of eight weeks of aerobic exercise with and without vitamin D supplementation on DNA damage.

Methods: Forty-eight adult male rats were randomly divided into six groups: control (C), H₂O₂ (H), H₂O₂ and vitamin D (HD), H₂O₂ and exercise (HE), H₂O₂, vitamin D and exercise (HDE), and dimethyl sulfoxide. Cancer was stimulated through intraperitoneal injection of H₂O₂ (2 mmol/kg). Animals in groups HE and HDE ran on treadmill for eight weeks. Concentration of 8-hydroxy-2'-deoxyguanosine (8-OHdG) and O⁶-methylguanine DNA methyltransferase (MGMT) was measured by enzyme-linked immunosorbent assay. Statistical analysis of data was carried out using SPSS 22 at significance level of 0.05.

Results: Vitamin D supplementation significantly lowered the level of 8-OHdG expression compared to the control group (P=0.0001). The 8-OHdG expression in the exercise group was slightly lower than control group (P=0.063). Combination of exercise and vitamin D supplementation had no significant effect on expression of 8-OHdG (P=0.281). Both exercise and vitamin D supplementation significantly increased MGMT expression compared to the control group (P=0.0001 and P=0.040). However, combination of exercise and vitamin D supplementation had no significant effect on MGMT expression (P=0.326).

Conclusion: The results showed that aerobic exercise and vitamin D supplementation can have protective effects against DNA damage, possibly by increasing antioxidant capacity and DNA repair.

Keywords: DNA, 8-OHdG, 6-Methyl Guanine, Vitamin D, Exercise

INTRODUCTION

Free radicals alter and deactivate enzymatic complexes, cause DNA/RNA damage and increase mutation, which may lead to cancer development (1). Yet, they are essential at physiological concentrations for normal function of cells (2). Reactive oxygen species (ROS) can damage cellular structures and DNA, which may lead to apoptosis (3). The resulting oxidative damage and mitochondrial DNA mutation leads to incomplete translation of subunits of electron transport chain enzymes. This not only disrupts ATP production along this pathway, but also produces more ROS through electron leakage, which may also cause more oxidative damage to mitochondrial biomolecules (4). This phenomenon is more evident in athletes who engage in heavy physical exercise (5). One of the mechanisms through which aerobic exercise lowers the risk of cancer is activation of DNA repair enzymes and reduction of oxidative stress through production of anti-oxidants (6, 7).

Biologically, both nuclear and mitochondrial DNA are targeted by free radicals. DNA repair is a known defense mechanism in humans with significant role in genome integration and resistance against carcinogenicity (8, 9). One of the steps of DNA repair is removal of methyl from O6-methyl guanine atom that is created under influence of alkylating agents. The O6-methyl guanine DNA transferase (MGMT) enzyme is responsible for repairing this anomaly and maintenance of genome structure (10). DNA methylation is regulated by MGMT, and MGMT overexpression is a mutual characteristic of cancers (11) and resistance to chemotherapy (12). DNA methylation is essential for regulation and coordination of key biological processes including cell cycle and differentiation. General lack of methylation causes chromosomal instability and may lead to genetic disorders. In contrast, hypermethylation of tumor suppressor genes down regulates expression of key genes involved in cell cycle, apoptosis and DNA repair (13).

There have been few studies about the role of physical exercise in DNA repair. Chronic exercise reduces oxidative stress in multiple organs and systems through reduction of ROS production, increased anti-oxidant capacity and

improved mitochondrial efficiency. It is expected that exercise would have the ability to reduce nuclear DNA damage and risk of cell mutation related to several illnesses. Nevertheless, physical exercise has an inverse relationship with DNA damage and mitochondrial ROS production, thus exerting positive effects on mitochondrial performance (14).

Despite the effectiveness of exercise for treatment of some respiratory diseases such as asthma, some researchers have emphasized on consumption of supplements as a complementary treatment method. It has been shown that vitamin D (VD) supplementation results into a slightly better lung performance (15). Calcitriol and its analogs have anti-cancer, regulatory, apoptotic and angiogenic activities (16), especially in lung cancer cells which express VD receptors (17). Calcitriol can also regulate some signaling pathways involved in some cancers, including colorectal cancer, prostate cancer and melanoma (18). Moreover, VD causes apoptosis in most cancer cells, stabilizes chromosomal structure and prevent double-stranded DNA break through internal and external factors. It also stimulates DNA synthesis and provides a new mechanism of regulation for epithelial cell duplication, leading to lung development and damage repair (19). Furthermore, VD protects keratinocytes and melanocytes against DNA damage caused by UVB through reduction of ROS formation and elevation of DNA repair capacity (20). The present study aimed to determine effect of eight-week aerobic exercise and VD supplementation on DNA damage and repair in male rats poisoned by H₂O₂.

MATERIALS AND METHODS

The study was carried out on 48 adult male Wistar rats aged 8-10 weeks (weighting 220±20 g). The rats were kept at 22 °C on a 12:12 h light/dark cycle. All experiments on the animals were approved by the ethics committee of the Kerman University of Medical Sciences (ethical approval code: IR.KMU.REC.1396.1562). The rats were randomly and equally divided into six groups: control group (C), poisoned with hydrogen peroxide (H), hydrogen peroxide and VD (HD), hydrogen peroxide and aerobic exercise (HE), hydrogen peroxide, VD and aerobic

exercise (HDE) and dimethyl sulfoxide (DMSO) with saline. Animals were weighed every two weeks and their food consumption was monitored on a daily basis. Rats in the HD, HE, H and HDE groups received intraperitoneal injection of 0.2 mg/Kg H₂O₂ (Merck, Germany) three times a week and 1 hour before exercise (21). Rats in the HD and HDE group received daily intraperitoneal injection of 0.5 µg/Kg body weight VD (300,000 IU, Dithrecol, Caspian Tamin Co., Iran) for eight weeks (22). Normal saline was used to dilute VD and DMSO was used to dissolve VD in saline. Subjects in the HE and HDE group ran on a rat running wheel for eight weeks. Table 1 shows the duration and speed of exercise over the eight-week intervention (23). Rats began running at speed of 15 m/min for 2 minutes. The speed of running wheels was increased by 1.8 m/min every 2 minutes until the rats were no longer able to run. The VO₂max values were calculated at baseline, at the end of the fourth week and at the end of eighth week based on the correlation between speed of running wheel and rats' VO₂max (24).

Twenty four hours after the last training session and following 12 hours of fasting, the rats were sacrificed and lungs were exposed to avoid extra production of internal ROS (25). The lung tissue was removed, immediately washed with 0.1% phosphate buffer and fixed in RNAlater solution (Ambion, L/N: 1206029, USA). The tissue samples were homogenized using a rotor stator homogenizer (Tissue Rupture, 230V, 50-60 Hz, QIAGEN,

Germany) and then kept at -55 °C for 20 minutes. Urinary level of 8-OHdG was measured using a high sensitivity ELISA Kit (catalog NO:CSB-E10526r, Germany). The samples were left to clot for two hours at room temperature or overnight at 4°C. After centrifugation for 15 minutes at 1000 ×g, serum was separated and stored at -80°C until analysis. Data were reported as mean and standard deviation. One-way ANOVA was used to compare the effect of oxygenated water (2 mmol/kg) and solvent with control. The Bonferroni post hoc test was used to evaluate differences. Two-way ANOVA was used to determine the effect of exercise and vitamin D alone and combined. All statistical analyses were performed in SPSS 22 and at significant level of 0.05.

RESULTS

The concentration of 8-OHdG was significantly higher in group H compared to group C and DMSO (P=0.001). Exercise slightly decreased 8-OHdG concentration (P=0.063), but VD supplementation significantly decreased 8-OHdG concentration (P=0.0001). Combination of exercise and VD supplementation had no significant effect on 8-OHdG concentration (P=0.281) (Figure 1).

According to the results, concentration of MGMT was significantly lower in group H compared to group C and DMOS (P=0.0001). Both exercise and VD supplementation significantly increased the concentration of MGMT (P=0.040 and P=0.0001). However, combination of exercise and VD supplementation had no significant effect on 6 MGMT concentration (P=0.326) (Figure 2).

Table 1. Duration and speed of exercise over the eight-week intervention period

Week	Speed (m/min)	Duration (min)
1	8	30
2	12	30
3	16	45
4	20	45
5	20	60
6	20	60
7	20	60
8	20	60

Figure 1. Concentration of 8-OHdG protein in the study groups

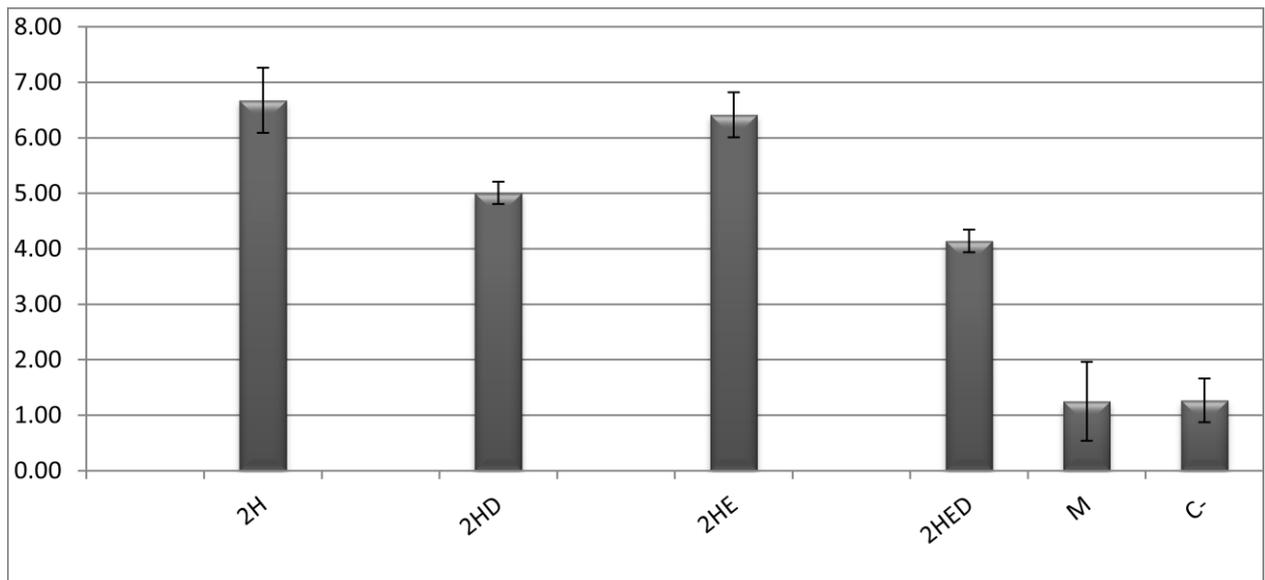
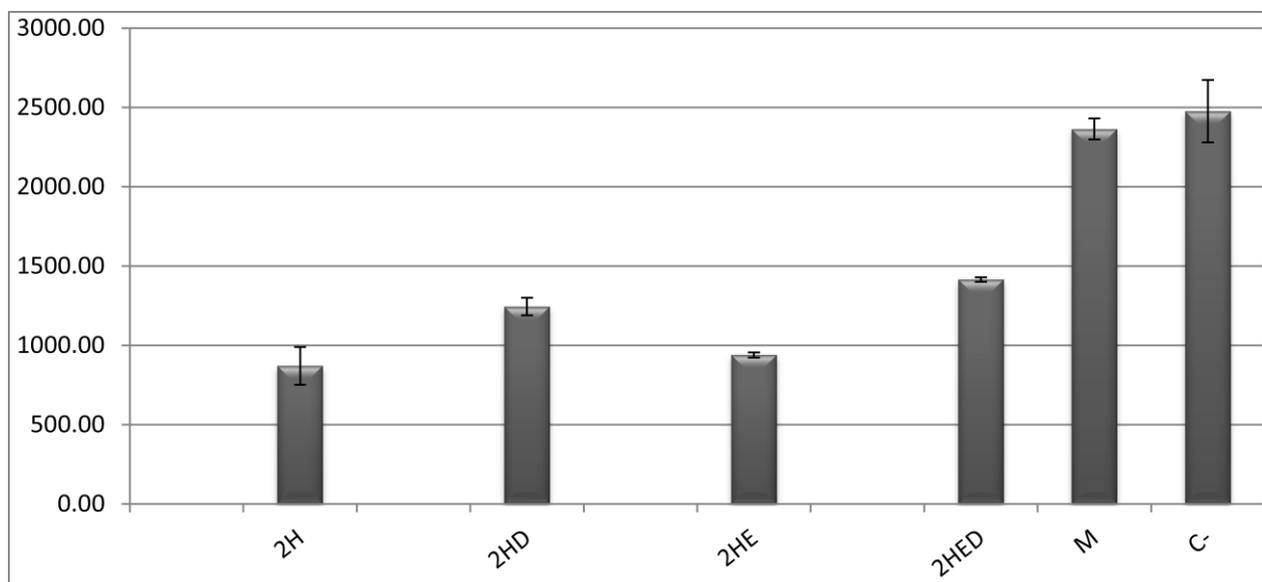


Figure 2. Concentration of MGMT in different groups



DISCUSSION

Structural changes of DNA due to ROS exposure has been extensively investigated by researchers since these changes have a significant role in incidence of aging as well as in etiology of several illnesses, including cancer, diabetes, atherosclerosis and Alzheimer's disease (26). This research was conducted to study effect of eight weeks of aerobic exercise and vitamin D supplementation on DNA damage and repair. Based on the results, the eight-week aerobic training and vitamin D supplementation reduced DNA damage by lowering the level of OHdG. This effect could be related to two mechanisms: reduction of ROS production and increased level of anti-oxidant defense, both of which are considered as important modulators of DNA damage. Some of these mechanisms might help lower the level of oxidant production, regulate amounts of anti-oxidant or even increase DNA repair activity (14). There is a direct relationship between higher daily physical activity and higher aerobic fitness with reduced DNA breaks. At the same time, exercise provides a certain compatibility that protects DNA integrity (27). Diaz-Castro et al. reported that 50 km run would elevate OHdG-8 level and oxidative stress induction (28). Also, McMillan et al. reported that six weeks of moderate-intensity resistance training (at 60% VO_{2max}) resulted into DNA fragmentation in soleus muscle of exercised rats (29). Similarly, two weeks of aerobic training in 15 triathlon elites increased OHdG-8 levels, which can be related to increased level of DNA repair enzymes (30). Acute exercise elevates OHdG-8 urinary excretion (31). However, some studies reported no change in OHdG-8 levels following exercise (32). Polsen et al. claimed that acute or moderate chronic exercise does not lead to DNA oxidative damage and may even reduce oxidative DNA damage in tissues (33). In another study, Nakaya et al. showed that moderate aerobic exercise does not alter OHdG-8 level nor mRNA expression in leukocytes, which can indicate neuronal-hormonal changes in the entire body (35). Other studies reported no significant change

in OHdG-8 level after 30 minutes of aerobic exercise at 70% VO_{2max} (34) and no DNA damage in well-trained endurance athletes (35). Mild exercise as well as moderate chronic exercise can reduce DNA damage (36) that can be related to increase of DNA repair enzymes (30). However, an increase of oxidative DNA was observed after long-term exercise (33). Some researches even provided evidence of decrease in OHdG-8 level after exercise. Nojima et al. showed that 12 months of moderate aerobic exercise (50% VO_{2max}) decreased OHdG-8 urinary level in type 2 diabetic patients (37). Similarly, 12 weeks of endurance exercise reduced OHdG-8 level in all subjects (38). Radak et al. showed that eight weeks of regular treadmill running at a speed of 6-8 m/min and 5% slope for 10 minutes/day could significantly decrease the age-related increase in 8-OHdG content of rat gastrocnemius muscle (39). Disparity in findings of the mentioned studies may be related to differences in the duration or intensity of exercises (40).

Chronic inflammation induces DNA damage and mutation through oxidative stress (41).

Yet, other mechanisms might be responsible for association of exercise-related DNA modifications, inflammatory responses and reactive oxygen and nitrogen species. Signal transmission pathways sensitive to redox including NF- κ B nuclear factor or P53 cascade in inflammation as well as cellular stress management are involved in response to DNA damage (42). New results and evidences emphasize on responses of gene expression to exercise and unknown molecular mechanisms in exercise immunology (43).

We found no significant change in MGMT enzyme level in the exercise group. This enzyme plays an essential role in DNA damage and inhibition of tumorigenesis in humans. DNA repair pathway is a known defense mechanism responsible for genome integrity and resistance against carcinogenicity in humans (8).

Aerobic exercise reduces risk of cancer through activation of DNA repair enzymes and reduction of oxidative stress (7). It has been suggested that exercise may also have positive effects on all malignant tumors through unknown mechanisms (44). Epigenetic mutation in cancerous cells causes

uncontrollable growth, which can be reversed by exercise via overexpression of tumor suppressor genes and downregulation of oncogenes (45). Epigenetic signals have an important role in balancing gene expression through mechanisms such as DNA methylation and histone modifications. In humans, physical activity also influences DNA methylation (46). In our study, VD supplementation increased MGMT level. It has been shown that VD can exert anti-cancer effects through inhibition of cell proliferation and protection against DNA damage (47, 48).

CONCLUSION

Our findings indicate that eight weeks of

regular aerobic exercise can reduce DNA damage through elevation of anti-oxidant capacity as well as increased DNA repair. In addition, VD can have protective effects against DNA damage by increasing DNA methylation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article.

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