Sport Sciences for Health (2019) 15:183–190
https://doi.org/10.1007/s11332-018-0508-4

ORIGINAL ARTICLE

The beneficial effect of α-tocopherol succinate supplementation on DNA oxidation induced by intensive exercise training

Hossein TaheriChadorneshin[1] · Seyed-Hosein Abtahi-Eivary[2] · Meysam Alipour-Raz[1] · Zainab Nezamdoost[3]

Received: 2 September 2018 / Accepted: 8 October 2018 / Published online: 22 October 2018

Abstract

Production of reactive oxygen species (ROS) induced by exercise training yields serious oxidative damage to cellular structures. Antioxidant supplements are widely used to reduce the deleterious effects of such endogenous ROS. This study aimed to investigate the effect of two types of intensive exercise training along with α-tocopherol succinate supplementation on serum levels of 8-oxoguanine DNA glycosylase (OGG1), 8-hydroxy-2′-deoxyguanosine (8-OHdG), creatine kinase (CK), and lactate dehydrogenase (LDH). Forty-two male albino Wistar rats were randomly assigned into sedentary control (SC), sedentary vehicle (SV), sedentary supplementation (SS), continuous exercise (CE), continuous exercise + supplementation (CES), intermittent exercise (IE), and intermittent exercise + supplementation (IES), with six rats in each group. Intensive continuous and intermittent running on treadmill, combined with α-tocopherol succinate supplementation (60 mg/kg/day) was carried out for 6 weeks. Data were analyzed using one-way analysis of variance at $P < 0.05$ level. α-Tocopherol succinate supplementation increased serum total antioxidant capacity (TAC) in SS, CES and IES groups. CK, LDH, and OGG1 levels increased significantly in CE and IE groups; however, α-tocopherol succinate supplementation reduced these factors dramatically in CES and IES groups. In addition, 8-OHdG level was remarkably lower in CES and IES groups. Taken together, α-tocopherol succinate supplementation can modify oxidative damage to genomic structures induced by intensive exercise training.

Keywords Intermittent exercise training · Continuous exercise training · α-Tocopherol succinate · 8-Oxoguanine DNA glycosylase · 8-Hydroxy-2′-deoxyguanosine · Creatine kinase · Lactate dehydrogenase

Introduction

Low to moderate exercise training has many positive effects on various organelles of body and acts as a protective approach against diseases [1]. Paradoxically, it is also obvious that free radicals induced by exercise training, especially exercise training with high intensity, can result in oxidative damage to cellular constituents as a result of increased oxygen consumption [2, 3]. A larger generation of radicals during intense exercise training increases lipid peroxidation and leads ultimately to the release of intracellular contents, i.e., creatine kinase (CK) and lactate dehydrogenase (LDH), into the intercellular space [4, 5]. In addition, free radicals generated by contracting skeletal muscles penetrate into the mitochondria and the nucleus and eventually result in oxidative damage to genomic constituents [1–5].

8-hydroxydeoxyguanosine (8-OHdG) is one of the most frequently generated oxidative base lesions due to lower redox potential of guanine as compared with other nucleic acid bases [6–10]. Unrepaired 8-OHdG can lead to transversion of G:C to T:A and cause mutation. 8-OHdG level increases in the course of several diseases such as cancer, atherosclerosis, diabetes, and Alzheimer's disease [1, 2, 4, 9]. To cope with such detrimental complications, cells are equipped with DNA repair system to reduce the effects of these oxidative DNA damages. 8-oxoguanine DNA glycosylase (OGG1) is the major mammalian DNA glycosylase used to recognize and cleave oxidized guanine from DNA [8, 9]. Many factors can affect OGG1 and 8-OHdG levels

✉ Hossein TaheriChadorneshin
h.taheri@ub.ac.ir

[1] Department of Sport Sciences, University of Bojnord, Bojnord, North Khorasan 9453155111, Iran

[2] Department of Clinical Biochemistry, Gonabad University of Medical Sciences, Gonabad, Iran

[3] Department of Sport Sciences, University of Birjand, Birjand, Iran

including maximum oxygen consumption (VO_2max) [10], body mass index (BMI) [11], exercise training [3, 12], and antioxidant supplementation [13, 14].

Exercise training at low intensity is reportedly with no significant effect on 8-OhdG and acetylated OGG1 levels [12]; however, maximal stretch–shortening contractions [15] and overtraining increase 8-OhdG and OGG1 levels in different tissues of young and old rats [3, 15]. Furthermore, both running on treadmill [9, 16] and swimming [7] with moderate intensity increase OGG1 activity in the red type of skeletal muscle [9], the liver [16], and the subcellular compartments, i.e., the nucleus and mitochondria [7]. Increased OGG1 activity is greater in slow-twitch than fast-twitch muscle fibers after exercise training with moderate intensity [9]. In contrast, these increases return to baseline levels after detraining [7]. The effect of different types of exercise training, particularly intensive continuous and intermittent training, is not well-documented. In reality, greater oxidative stress occurs during intensive exercise training due to activation of NADPH oxidase [17], xanthine oxidase [18], and hypoxic conditions [19]. Moreover, many people fail to exercise because of limited time, and it is necessary to examine the effects of exercise training intensity on health improvement, especially DNA repair system adaptations.

Antioxidant supplementation is another approach to reducing genomic damage in addition to DNA repair system. In this context, accumulating evidence by the comet assay method has shown that vitamin E supplementation significantly reduces DNA breakage in peripheral white blood cells induced by exhaustive exercise [20, 21]. Concerning DNA oxidation, a reduction is reported in 8-OHdG level in plasma [13] and gastrocnemius and heart muscle [14] after L-cysteine [13] and astaxanthin [14] supplementation. In addition, vitamin E acetate supplementation attenuates 8-OHdG in the liver [22] and in the tibialis anterior muscle [15] induced by 4 weeks running on treadmill [22] and chronically loaded muscles [15], respectively. Nevertheless, other studies have shown no significant change in 8-OHdG levels after vitamin E acetate supplementation along with acute [23] and chronic exercise training [24]. In the serum, the relationship between 8-OHdG levels and antioxidant capacity is not clear upon intensive exercise training. In addition, it has been shown that vitamin E supplementation attenuates lipid peroxidation [15, 22]. In turn, there is evidence of induced mitochondrial DNA damage by lipid peroxidation [25, 26]. Thus, we propose that serum 8-OHdG levels during intensive exercise training may also be inhibited by vitamin E supplementation. Thus far, the effect of vitamin E supplementation, especially its succinate isoform, on DNA oxidation and its repair system upon intensive continuous and intermittent exercise training has not been sufficiently studied. Therefore, the aim of the present study was to investigate (i) how serum 8-OHdG and OGG1 levels respond to intensive continuous and intermittent exercise training and (ii) how α-tocopherol succinate affects serum 8-OHdG and OGG1 levels induced by these exercise trainings.

Materials and methods

Animals

Forty-two pathogen-free adult (3 months old and initial body mass of 282 ± 14 g) male albino Wistar rats were obtained from the bearing and multiplying laboratory at Mashhad University of Medical Sciences (Iran). The animals were accustomed to laboratory conditions for 2 weeks before the experiment, and were subsequently allocated into seven equal groups ($n = 6$) of sedentary control (SC), sedentary vehicle (SV), sedentary supplementation (SS), continuous exercise (CE), continuous exercise + supplementation (CES), intermittent exercise (IE), and intermittent exercise + supplementation (IES) via simple allocation method. They had free access to water and food (Javaneh Khorasan Company, Iran) and were kept in a room with 25 ± 2 °C and a 12 h light/12 h dark cycle. All animal experiments conformed to the guidelines for the use and care of laboratory animals ("Principles of laboratory animal care", NIH publication No. 86-23. Revised 1996), and the study was approved by the ethics committee of Birjand University of Medical Sciences (Iran).

Exercise training protocols

Exercise training was performed on a 12-line treadmill because the intensity and duration of exercise could be easily controlled [25]. The animals were familiarized with running on a motor-driven treadmill (5 days at 10 min/day at a speed of 10 m/min) [27, 28]. Continuous and intermittent exercise trainings were performed on the basis of an overload principle for 6 weeks, 6 sessions each. One session of continuous training consisted of 3-min warm-up at 16 m/min, followed by continuous running at 27 m/min and 3-min cool-down. These intensities correspond to 68 and 80% maximal oxygen uptake (VO_2max), respectively. The duration of continuous running at the first session was 20 min and increased with 2 min per day until 60 min was achieved by the 4th week. The duration was maintained for the next 2 weeks [27]. On even days, the intermittent exercise protocol consisted of 3-min warm-up at 16 m/min, followed by intervals of running at 40 m/min for 3 min (corresponding to 95% VO_2max), alternated with active rest for 60 s at 16 m/min, and completed with 3-min cool-down at 16 m/min. The interval in the first session was 2 and increased to 6 repetitions in the 4th week and was maintained for the following 2 weeks [27, 28]. On odd days, intermittent exercise protocol consisted of

3-min warm-up at 16 m/min, followed by intervals of running at 54 m/min for 30 s (corresponding to 100% VO_2max), alternated with active rest for 60 s at 16 m/min, and completed with 3-min cool-down at 16 m/min. The interval in the first session was 3 and increased to 20 repetitions in the 4th week and was maintained for the next 2 weeks [27, 28]. The rats were motivated to run by electrical current (0.5 mA, 1 Hz) [28] on treadmill and by gentle prodding using a sponge [7]. Each animal was assigned to a fixed lane and all the activities were performed in the respective lane during the entire training program. The rats of the sedentary groups were transported daily to the training room, were exposed to the same environment as the exercising group, and were placed on treadmill without running for the matched period [2, 3].

α-Tocopherol succinate preparation

α-Tocopherol succinate (25 g) was purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA) and was dissolved in sesame oil (60 mg/mL) [28]. Rats in the SS, CES and IES groups were supplemented orally by α-tocopherol succinate (60 mg/kg body weight) for 6 weeks, 6 days/week, 3 h before exercise training [28]. In addition, rats in the SV group were supplemented orally by sesame oil (1 mL/kg body weight) for 6 days/week.

Sample collection and biochemical estimations

At the end of the training programs, 48 h after the last exercise training session, fasting rats were euthanized under deep anesthesia (ketamine, 60–80 mg/kg and xylazine, 8 mg/kg; IP). Blood samples were taken via cardiac puncture and serum stored at − 80 °C for further analysis.

DNA damage was assessed by 8-OHdG assay. The serum levels of OGG1, 8-OHdG (Cusabio Biotech CO., LTD. Sino-American), CK and LDH (Parsazmoon Co., Karaj, Iran) were determined using commercial kits. In addition, 96-well colorimetric assay kit was used to measure the levels of total antioxidant capacity (TAC) in the serum (BiocoreDiagnostik Ulm, German). All analyses were performed in accordance with the manufacturers' recommendations.

Statistical analysis

Data were analyzed by Statistical Package for Social Sciences (SPSS Inc., Chicago, USA) software, version 16.0, and expressed as means ± standard deviation (SD). Initially, Shapiro–Wilk's and Levene's tests were performed on all dependent variables to test normality and equality of variances, respectively. Statistical significance was set at $P < 0.05$. Differences between groups were tested using one-way analysis of variance followed by Bonferroni post hoc comparison.

Results

The results indicated that α-tocopherol succinate supplementation increased serum TAC significantly in SS (376.3 ± 24.60 nmol/mL) ($P = 0.001$), CES (358.5 ± 23.8 nmol/mL) ($P = 0.001$), and IES (356.9 ± 15.4 nmol/mL) ($P = 0.001$) groups (Fig. 1). However, both the CE (214.1 ± 20.5 nmol/mL) ($P = 0.118$) and IE (218 ± 14.8 nmol/mL) ($P = 0.256$) exercise trainings had no significant effect on serum TAC with respect to the SC (252.6 ± 29 nmol/mL) group (Fig. 1).

In the context of enzymatic markers of tissue damage, our results showed that CK increased significantly in the IE (1691 ± 195 U/L) ($P = 0.001$) and in the CE (1103 ± 141 U/L) ($P = 0.001$) groups with respect to the SC group (697 ± 91 U/L), while the IE group had a greater increase in serum CK level than the CE group ($P = 0.001$) (Fig. 2a). In contrast, α-tocopherol succinate supplementation reduced serum CK levels in CES (750 ± 82 U/L) ($P = 0.001$) and IES (1314 ± 141 U/L) ($P = 0.001$) groups in comparison with the corresponding training groups (Fig. 2a). α-Tocopherol succinate supplementation had no significant impact on CK levels in the SS (581 ± 134 U/L) group with respect to the SC group ($P = 0.999$).

In addition, serum LDH increased significantly in IE (1044 ± 125 U/L) ($P = 0.001$) and CE (679 ± 95 U/L)

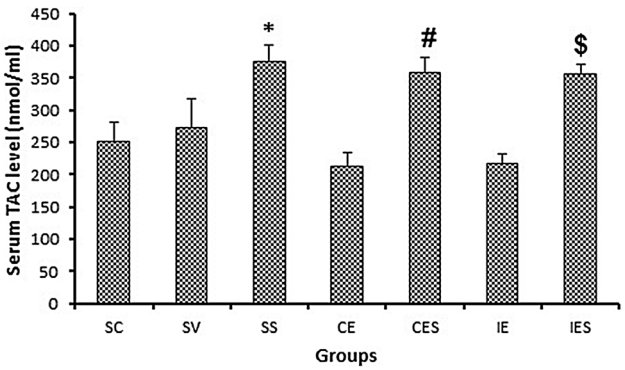

Fig. 1 Effect of continuous and intermittent exercise training and α-tocopherol succinate supplementation on serum TAC level in rats. *SC* sedentary control, *SV* sedentary vehicle, *SS* sedentary supplementation, *CE* continuous exercise, *CES* continuous exercise + supplementation, *IE* intermittent exercise, *IES* intermittent exercise + supplementation. The asterisk (*) indicates a significant increase in serum TAC in the SS group in comparison with the SC group. In addition, the hashtag (#) indicates a significant increase in the serum TAC in the CES group in comparison with the CE group. Finally, the dollar sign ($) indicates a significant increase in serum TAC in the IES group in comparison to the IE group

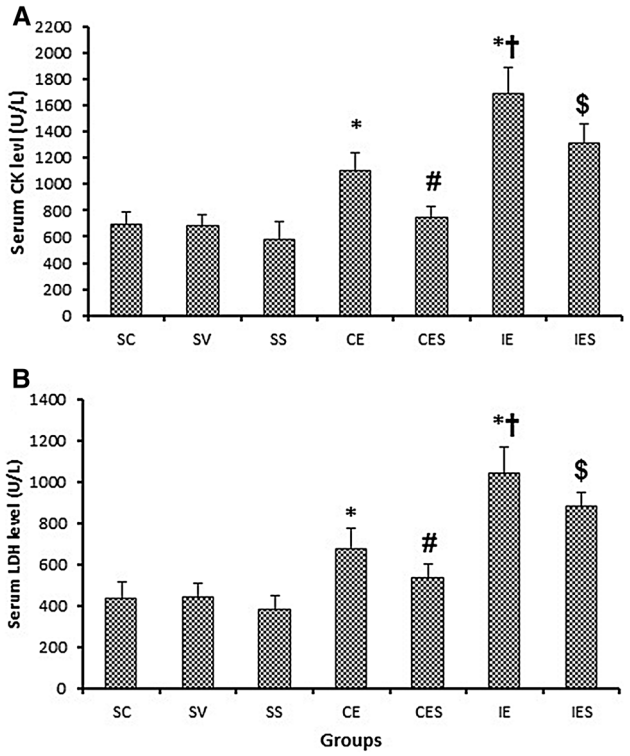

Fig. 2 Effect of continuous and intermittent exercise training and α-tocopherol succinate supplementation on serum CK (**a**) and LDH (**b**) levels in rats. The asterisk (*) indicates a significant increase in both the serum CK and LDH levels in the CE and IE groups in comparison with the SC group. In addition, the hashtag (#) indicates a significant reduction in both the serum CK and LDH levels in the CES group in comparison with the CE group. Furthermore, the dollar sign ($) indicates a significant reduction in both the serum CK and LDH levels in the IES group in comparison with the IE group. Finally, the dagger sign (†) indicates a greater increase in the serum CK and LDH levels in the IE group with respect to the CE group. Abbreviations are the same as the ones denoted in the legend of Fig. 1

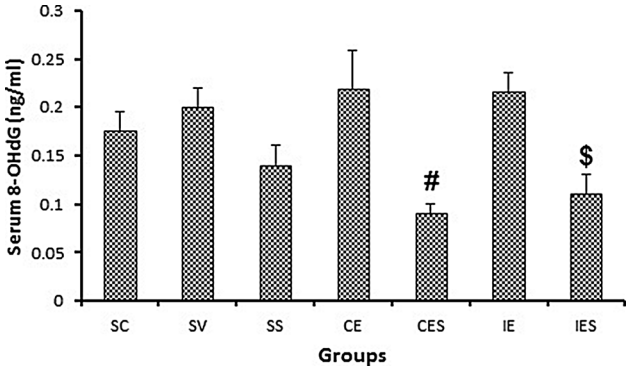

Fig. 3 Effect of continuous and intermittent exercise training and α-tocopherol succinate supplementation on serum 8-OHdG level in rats. The hashtag (#) indicates a significant reduction in 8-OHdG level in the CES group in comparison with the CE group. In addition, the dollar sign ($) indicates a significant reduction in the serum 8-OHdG level in the IES group in comparison with the IE group. Abbreviations are the same as the ones denoted in the legend of Fig. 1

($P=0.001$) groups in comparison with the SC (433 ± 81 U/L) group. However, IE resulted in a greater increase in the concentration of serum LDH than CE ($P=0.001$) (Fig. 2b). On the contrary, α-tocopherol succinate supplementation reduced serum LDH levels in the CES (538 ± 64 U/L) ($P=0.031$) and IES (884 ± 67 U/L) ($P=0.008$) groups in comparison with the corresponding training groups (Fig. 2b). α-Tocopherol succinate supplementation had no significant effect on LDH levels in the SS (384 ± 64 U/L) group with respect to the SC group ($P=0.999$).

In context of base oxidation, our finding revealed that neither CE (0.218 ± 0.04 ng/mL) ($P=0.220$) nor IE (0.216 ± 0.02 ng/mL) ($P=0.284$) had significant effect on serum 8-OHdG levels in comparison with the SC group (0.175 ± 0.02 ng/mL). In contrast, α-tocopherol succinate supplementation significantly reduced serum 8-OHdG levels in CES (0.095 ± 0.01 ng/mL) ($P=0.001$), and IES (0.115 ± 0.02 ng/mL) ($P=0.001$) groups in comparison with the corresponding training groups (Fig. 3). α-Tocopherol succinate supplementation had no significant effect on 8-OHdG levels in SS (0.148 ± 0.02 ng/mL) group with respect to the SC group ($P=0.999$).

In the context of DNA repair, serum OGG1 increased significantly in the IE (62.04 ± 12.14 pg/mL) ($P=0.001$) and CE (48.37 ± 3.62 pg/mL) ($P=0.001$) groups with respect to the SC (20.92 ± 2.60 pg/mL) group. Besides, IE induced a greater increase than CE in terms of serum OGG1 ($P=0.019$). In contrast, after α-tocopherol succinate supplementation, a significant reduction in serum OGG1 was found in CES (34.79 ± 4.56 pg/mL) ($P=0.020$) and IES (49.14 ± 9.45 pg/mL) ($P=0.033$) groups with respect to the corresponding training groups (Fig. 4). α-Tocopherol succinate supplementation had no significant effect on 8-OHdG levels in the SS (18.10 ± 3.47 pg/mL) group in comparison with the SC group ($P=0.999$).

Discussion

In recent years, there has been a growing interest in evaluating the interactive effects of exercise training and antioxidant supplementation on stress oxidative markers. Here, in an experimental animal model, it was revealed that both the intensive continuous and intermittent trainings led to significant increases in serum CK and LDH levels. However, serum levels of 8-OHdG did not change significantly after both exercise training types. OGG1, as the DNA repair protein, significantly increased after continuous and intermittent training. In contrast, α-tocopherol succinate significantly reduced CK, LDH, 8-OHdG, and OGG1 after both continuous and intermittent training types.

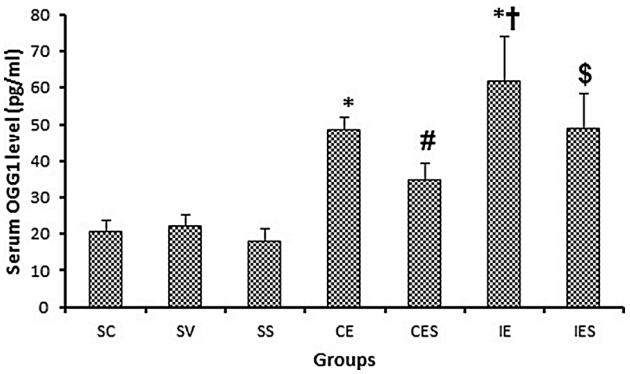

Fig. 4 Effect of continuous and intermittent exercise training and α-tocopherol succinate supplementation on serum OGG1 level in rats. The asterisk (*) indicates a significant increase in serum OGG1 level in the CE and IE groups in comparison with the SC group. In addition, the hashtag (#) indicates a significant reduction in OGG1 level in the CES group in comparison with the CE group. Furthermore, the dollar sign ($) indicates a significant reduction in the serum OGG1 levels in the IES group in comparison with the IE group. Finally, the dagger sign (†) indicates a greater increase in the serum OGG1 levels in the IE group with respect to the CE group. Abbreviations are the same as the ones denoted in the legend of Fig. 1

Creatine kinase and LDH are released into blood when the cell membrane is destructed by oxidative stress. Therefore, changes in the serum CK and LDH levels can be used as markers of membrane damage resulting from oxidative stress. In this context, we showed that both the continuous and intermittent training types raised serum CK and LDH levels. Our finding is consistent with other studies that showed increased levels of CK and LDH after short-term running training on treadmill [29], down-hill running [30], up-hill running [31], and endurance swimming [32]. Moreover, the intermittent exercise training resulted in a greater increase in the levels of CK and LDH than those of continuous exercise training. Compared with continuous exercise training, intermittent exercise training may lead to further shear stress on endothelial cells, and subsequently more activation of NADPH oxidase [27]. Interestingly, it has been shown that ischemia and blood re-perfusion at the beginning and end of each set of severe intermittent exercise training increase the xanthine oxidase enzyme activity [33]. The combination of these factors leads to greater production of ROS, and consequently, more oxidative damage after intensive intermittent training. Conversely, α-tocopherol succinate supplementation significantly reduces serum levels of CK and LDH. In reality, the results of the current study illustrate the effect of α-tocopherol succinate supplementation on the reduction of oxidative stress caused by intensive exercise training. Along with the results of our study, it has been reported that short-term vitamin E acetate supplementation can reduce the leakage of CK and LDH after 6 successive days of endurance running [29] and down-hill running [30].

Reactive oxygen species plays an important role in physiological processes at moderate levels [4]; at large concentrations, however, ROS oxidizes lipid, protein, and genomic structures [1, 4]. With respect to CK and LDH, evidence has suggested that 8-OHdG is excreted into the serum and urine as the repair process. Hence, it is thought that 8-OHdG elimination reflects DNA damage and repair [22]. In this regard, two previous studies have reported that over-training [3] and maximal stretch–shortening contractions [15] significantly increase 8-OHdG levels in the liver [3] and in the tibialis anterior muscle [15]. Nevertheless, our findings show no significant changes in serum 8-OHdG levels after intensive continuous and intermittent exercise training. In addition, increased levels of urine 8-OHdG have been reported after strenuous work in cold weather at moderate altitude [24]. On the other hand, our findings are supported by studies that have reported no significant changes in serum and tissue 8-OHdG levels after acute [23] and chronic strenuous exercise training [22, 34, 35].

OGG1, as a DNA repair enzyme, expresses in significantly different levels in all kinds of tissue, and recognizes and cleaves oxidized guanine from DNA [34]. Although it has been shown that 8-week swimming [2] and running on treadmill [12] at low to moderate intensity have no significant impact on rat's hippocampus OGG1 levels, our results reveal a dramatic increase in serum OGG1 levels after both intensive continuous and intermittent exercise training. This observed increase in the current study may be largely attributed to increased gene and protein OGG1 expression that releases into bloodstream after tissue damage. Accordingly, an increased content of OGG1 in different tissue regions have been demonstrated after over-training [2], endurance [35], and sprint exercise training [34]. Moreover, OGG1 activity increases after running on treadmill [16] and swimming exercise training [7]. Currently, evidence also indicates that high-intensity exercise training [36], voluntary wheel running [37], and swimming exercise training [38] increase the antioxidant enzymes' activity. Collectively, these findings indicate that unchanged levels of 8-OHdG following intensive exercise training, at least partially, may be associated with higher levels of OGG1 activity [9, 16], higher levels of antioxidant activity [36–38], and higher content of OGG1 protein, as shown in the current study. Lastly, the existing reports indicate that inter-individual variation, nutritional conditions [11], mental state [39], age [8], and VO_2max [10] may all be important contributors to regulating 8-OHdG and OGG1 levels. Therefore, the current animal model study set out to reduce the influential effect of the mentioned variables. Hence, it can be claimed that the observed changes in OGG1 and 8-OHdG are exclusively due to intensive continuous and intermittent exercise training.

Unlike antioxidant enzymes, non-enzymatic antioxidants are not made in the body and should be obtained

principally through the diet. TAC refers to the total amount of non-enzymatic antioxidants in the body [40]. Results of the present study are in line with other studies that report no significant change in serum TAC in response to endurance swimming [32], eccentric exercise training [41], and running at moderate intensity [31]. Moreover, it has been shown that resting TAC levels in aerobically and anaerobically trained athletes and untrained individuals are not different [42]. However, α-tocopherol succinate supplementation increased serum TAC levels in the current research. In this regard, several lines of evidence have suggested that alpha-tocopherol [43], vitamin C [32], and L-cysteine supplementation [13] raise TAC levels. Hence, the nutritional status, and in particular, the use of antioxidant supplements rather than exercise training, affects TAC levels [32].

Currently, there is evidence that astaxanthin supplementation can attenuate exhaustive exercise-induced genomic damage in mouse gastrocnemius muscle and heart [14]. Furthermore, L-cysteine supplementation in basketball players reduce plasma 8-OHdG induced by forced training [13]. Moreover, our findings showed that α-tocopherol succinate reduced serum 8-OHdG levels after intense continuous and intermittent exercise training. In this context, vitamin E acetate supplementation for 4 weeks is reported to attenuate 8-OHdG levels induced by strenuous running on treadmill in the rat liver [22]. Intriguingly, 8-OHdG levels increase in the tibialis anterior muscles of aged and young adult animals with repetitive loading (maximal stretch–shortening contractions), but DL-alpha tocopheryl acetate and L-ascorbic acid supplements attenuate this increase [15]. Conversely, our findings are inconsistent with other studies because of their short-term vitamin E supplementation period (2 weeks) and the type of consumed vitamin E (alpha-tocopherol isomer), whereby the increased levels of 8-OHdG induced by intense exercise did not alter [23, 24]. Vitamin E as the most important antioxidant is mainly accumulated in the membranes of cells. However, the addition of acetate and succinate to it will increase its entry to the cytosol and mitochondria of the cell [15, 22]. Therefore, vitamin E succinate/acetate mediates 8-OHdG levels by direct scavenging of superoxide and hydroxyl radicals that diffuse out of the mitochondria into the cytosol [22, 44, 45]. In addition, vitamin E inhibits free radical production by reducing the expression [44] and activity [45] of superoxide dismutase (SOD) and increasing the activity of catalase (CAT) [15, 22], which in turn reduces oxidative damage in genomic structures [15, 22]. Lastly, 8-OHdG low concentration in the rat skeletal muscle after vitamin E supplementation has been attributed to the reduced levels of malondialdehyde [15]. In this context, Niedernhofer et al. have pointed out to mutagenic aspects of malondialdehyde in human cells [26]. Similarly, work by Almeida et al. showed that mitochondrial DNA damage is associated with lipid peroxidation of the mitochondrial membrane [25].

Conclusion

Although widespread and direct evidence is not available in support of this notion, it appears that continuous and intermittent exercise training can modify 8-OHdG levels through increases in OGG1 levels. In addition, α-tocopherol succinate can reduce oxidative stress damage induced by intensive continuous and intermittent exercise training.

Acknowledgements We thank the staff of the biochemistry laboratory at Gonabad University of Medical Sciences for their valuable assistance with us in carrying out the biochemical assays.

Author contributions HT, SH-AE, and ZN and conceived the study and its design and coordination. All authors were involved in the data collection, data analysis, and drafting of the manuscript. In addition, all authors read and approved the final version of the manuscript, and agreed with the order of presentation of the authors.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All methods performed in the study were in accordance with ethical standards of the national research committee and with 1964 Helsinki Declaration.

Informed consent There is no informed consent for this study scince the study was not conducted on humans.

References

1. Gandhi G, Gunjan G (2009) Exercise-induced genetic damage: a review. Int J Hum Genet 9(2):69–96
2. Ogonovszky H, Berkes I, Kumagai S, Kaneko T, Tahara S, Goto S et al (2005) The effects of moderate-, strenuous-and over-training on oxidative stress markers, DNA repair, and memory, in rat brain. Neurochem Int 46(8):635–640
3. Ogonovszky H, Sasvári M, Dosek A, Berkes I, Kaneko T, Tahara S, Nakamoto H et al (2005) The effects of moderate, strenuous, and overtraining on oxidative stress markers and DNA repair in rat liver. Can J Appl Physiol 30(2):186–195
4. Radak Z, Chung HY, Goto S (2008) Systemic adaptation to oxidative challenge induced by regular exercise. Free Radic Biol Med 44(2):153–159
5. Radak Z, Toldy A, Szabo Z, Siamilis S, Nyakas C, Silye G et al (2006) The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. Neurochem Int 49(4):387–392

6. Radák Z, Apor P, Pucsok J, Berkes I, Ogonovszky H, Pavlik G et al (2003) Marathon running alters the DNA base excision repair in human skeletal muscle. Life Sci 72(14):1627–1633
7. Radak Z, Atalay M, Jakus J, Boldogh I, Davies K, Goto S (2009) Exercise improves import of 8-oxoguanine DNA glycosylase into the mitochondrial matrix of skeletal muscle and enhances the relative activity. Free Radic Biol Med 46(2):238–243
8. Radak Z, Bori Z, Koltai E, Fatouros IG, Jamurtas AZ, Douroudos II et al (2011) Age-dependent changes in 8-oxoguanine-DNA glycosylase activity are modulated by adaptive responses to physical exercise in human skeletal muscle. Free Radic Biol Med 51(2):417–423
9. Radak Z, Kumagai S, Nakamoto H, Goto S (2007) 8-Oxoguanosine and uracil repair of nuclear and mitochondrial DNA in red and white skeletal muscle of exercise-trained old rats. J Appl Physiol 1985 102(4):1696–1701
10. Loft S, Astrup A, Buemann B, Poulsen HE (1994) Oxidative DNA damage correlates with oxygen consumption in humans. FASEB J 8(8):534–537
11. Kasai H, Iwamoto-Tanaka N, Miyamoto T, Kawanami K, Kawanami S, Kido R et al (2001) Life style and urinary 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage: effects of exercise, working conditions, meat intake, body mass index, and smoking. Jpn J Cancer Res 92(1):9–15
12. Koltai E, Zhao Z, Lacza Z, Cselenyak A, Vacz G, Nyakas C et al (2011) Combined exercise and insulin-like growth factor-1 supplementation induces neurogenesis in old rats, but do not attenuate age-associated DNA damage. Rejuvenation Res 14(6):585–596
13. Tsakiris S, Parthimos T, Parthimos N, Tsakiris T, Schulpis KH (2006) The beneficial effect of L-cysteine supplementation on DNA oxidation induced by forced training. Pharmacol Res 53(4):386–390
14. Aoi W, Naito Y, Sakuma K, Kuchide M, Tokuda H, Maoka T et al (2003) Astaxanthin limits exercise-induced skeletal and cardiac muscle damage in mice. Antioxid Redox Signal 5(1):139–144
15. Ryan MJ, Dudash HJ, Docherty M, Geronilla KB, Baker BA, Haff GG, Cutlip RG, Alway SE (2010) Vitamin E and C supplementation reduces oxidative stress, improves antioxidant enzymes and positive muscle work in chronically loaded muscles of aged rats. Exp Gerontol 45(11):882–895
16. Nakamoto H, Kaneko T, Tahara S, Hayashi E, Naito H, Radak Z et al (2007) Regular exercise reduces 8-oxodG in the nuclear and mitochondrial DNA and modulates the DNA repair activity in the liver of old rats. Exp Gerontol 42(4):287–295
17. Haram PM, Kemi OJ, Lee SJ, Bendheim M, Al-Share QY, Waldum HL et al (2009) Aerobic interval training vs. continuous moderate exercise in the metabolic syndrome of rats artificially selected for low aerobic capacity. Cardiovasc Res 81(4):723–732
18. Kostaropoulos I, Nikolaidis M, Jamurtas A, Ikonomou G (2006) Comparison of the blood redox status between long-distance and short-distance runners. Physiol Res 55(6):611–616
19. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E et al (2009) Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 94(10):1062–1069
20. Mastaloudis A, Yu TW, O'donnell RP, Frei B, Dashwood RH, Traber MG (2004) Endurance exercise results in DNA damage as detected by the comet assay. Free Radic Biol Med 36(8):966–975
21. Sardas S, Omurtag GZ, Monteiro IF, Beyoglu D, Tozan-Beceren A, Topsakal N (2012) Assessment of DNA damage and protective role of vitamin E supplements after exhaustive exercise by comet assay in athletes. J Clinic Toxicol S 5:2161-0495
22. Kinoshita S, Tsuji E (2008) Vitamin E supplementation attenuates strenuous exercise induced DNA damage and lipid peroxidation of the liver in rats. Kawasaki J Med Welf 14:1–7
23. Bloomer RJ, Goldfarb AH, McKenzie MJ (2006) Oxidative stress response to aerobic exercise: comparison of antioxidant supplements. Med Sci Sports Exerc 38(6):1098–1105
24. Chao WH, Askew EW, Roberts DE, Wood SM, Perkins JB (1999) Oxidative stress in humans during work at moderate altitude. J Nutr 129(11):2009–2012
25. Almeida AM, Bertoncini CR, Borecký J, Souza-Pinto NC, Vercesi AE (2006) Mitochondrial DNA damage associated with lipid peroxidation of the mitochondrial membrane induced by Fe^{2+}-citrate. An Acad Bras Cienc 78(3):505–514
26. Niedernhofer LJ, Daniels JS, Rouzer CA, Greene RE, Marnett LJ (2003) Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. J Biol Chem 278(33):31426–31433
27. TaheriChadorneshin H, Cheragh-Birjandi S, Ramezani S, Abtahi-Eivary SH (2017) Comparing sprint and endurance training on anxiety, depression and its relation with brain-derived neurotrophic factor in rats. Behav Brain Res 329:1–5
28. Sarir H, Emdadifard G, Farhangfar H, TaheriChadorneshin H (2015) Effect of vitamin E succinate on inflammatory cytokines induced by high-intensity interval training. J Res Med Sci 20(12):1177–1181
29. Itoh H, Ohkuwa T, Yamazaki Y, Shimoda T, Wakayama A, Tamura S et al (2000) Vitamin E supplementation attenuates leakage of enzymes following 6 successive days of running training. Int J Sports Med 21(05):369–374
30. Kyparos A, Sotiriadou S, Mougios V, Cheva A, Barbanis S, Karkavelas G et al (2011) Effect of 5-day vitamin E supplementation on muscle injury after downhill running in rats. Eur J Appl Physiol 111(10):2557–2569
31. Salimeh A, Mohammadi M, Mohaddes G, Badalzadeh R (2011) Protective effect of diosgenin and exercise training on biochemical and ECG alteration in isoproterenol-induced myocardial infarction in rats. Iran J Basic Med Sci 14(3):264
32. Vesali-Akbarpour L, Samavati-Sharif MA (2016) The effect of endurance swimming plus vitamin c supplement on oxidative stress and muscles damage indices in male Wistar rats. Avicenna J Med Biochem 4:e34241
33. Lamprecht M, Greilberger J, Oettl K (2004) Analytical aspects of oxidatively modified substances in sports and exercises. Nutrition 20(7–8):728–730
34. Afroozi-Gerow E, Afzalpour ME, TaheriChadorneshin H, Abtahi-Eivary SH (2016) Effect of high intensity interval training on 8-oxoguanine DNA glycosylase and 8-hydroxy-2′-deoxyguanosine contents in the brain and liver of rats. J Appl Pharm Sci 6(10):170–173
35. Afzalpour ME, TaheriChadorneshin H, Abtahi-Eivary SH, Afroozi-Gerow E (2016) Effect of intensive endurance training on rat brain and hepatic 8-oxoguanine DNA glycosylase and 8-hydroxy-2′-deoxyguanosine levels. J Appl Pharm Sci 6(12):110–113
36. Cunningham P, Geary M, Harper R, Pendleton A, Stover S (2005) High intensity sprint training reduces lipid peroxidation in fast-twitch skeletal muscle. JEP Online 8(6):18–25
37. Judge S, Jang YM, Smith A, Selman C, Phillips T, Speakman JR et al (2005) Exercise by lifelong voluntary wheel running reduces subsarcolemmal and interfibrillar mitochondrial hydrogen peroxide production in the heart. Am J Physiol Regul Integr Comp Physiol 289(6):R1564–R1572
38. Jolitha A, Subramanyam M, Devi SA (2006) Modification by vitamin E and exercise of oxidative stress in regions of aging rat brain: studies on superoxide dismutase isoenzymes and protein oxidation status. Exp Gerontol 41(8):753–763
39. Forlenza MJ, Miller GE (2006) Increased serum levels of 8-hydroxy-2′-deoxyguanosine in clinical depression. Psychosom Med 68(1):1–7

40. Lodovici M, Giovannelli L, Pitozzi V, Bigagli E, Bardini G, Rotella CM (2007) Oxidative DNA damage and plasma antioxidant capacity in type 2 diabetic patient with good and poor glycaemic control. Mutat Res 683(1–2):98–102
41. Theodorou AA, Nikolaidis MG, Paschalis V, Koutsias S, Panayiotou G, Fatouros IG et al (2011) No effect of antioxidant supplementation on muscle performance and blood redox status adaptations to eccentric training. Am J Clin Nutr 93(6):1373–1383
42. Park SY, Kwak YS (2016) Impact of aerobic and anaerobic exercise training on oxidative stress and antioxidant defense in athletes. J Exerc Rehabil 12(2):113–117
43. Karajibani M, Hashemi M, Montazerifar F, Dikshit M (2010) Effect of vitamin E and C supplements on antioxidant defense system in cardiovascular disease patients in Zahedan, southeast Iran. J Nutr Sci Vitaminol (Tokyo) 56(6):436–440
44. Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M et al (2009) Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci USA 106(21):8665–8670
45. Strobel NA, Peake JM, Matsumoto A, Marsh SA, Coombes JS, Wadley GD (2011) Antioxidant supplementation reduces skeletal muscle mitochondrial biogenesis. Med Sci Sports Exerc 43(6):1017–1024