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The Effect of Moderate- Versus High-Intensity Resistance Training on Systemic Redox State and DNA Damage in Healthy Older Women

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Abstract

This study investigated effects of a 16-week progressive resistance training program (RTP) with elastic bands at two different intensities on systemic redox state, DNA damage, and physical function in healthy older women. **Methods:** Participants were randomly assigned to the high-intensity group (HIGH; $n = 39$), moderate-intensity group (MOD; $n = 31$), or control group (CG; $n = 23$). The exercise groups performed an RTP twice a week with three to four sets of 6 (HIGH) or 15 (MOD) repetitions of six overall body exercises at a perceived exertion rate of 8–9 on the OMNI-Resistance Exercise Scale for use with elastic bands. Thiol redox state was determined by reduced glutathione (GSH), oxidized glutathione (GSSG), and GSSG/GSH in blood mononuclear cells. Degree of DNA damage was assessed by presence of the oxidized DNA base molecule 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OHdG) in urine. Physical function monitoring was based on the arm curl, chair stand, up and go, and 6-min walk tests. **Results:** The HIGH group showed a significant increase in 8-OHdG (+71.07%, effect size [ES] = 1.12) and a significant decrease in GSH (−10.91, ES = −0.69), while the MOD group showed a significant decrease in 8-OHdG levels (−25.66%, ES = −0.69) with no changes in thiol redox state. GSH levels differed significantly between the HIGH and CG groups posttest. The exercise groups showed significant improvements in physical function with no differences between groups. **Conclusion:** RTP at a moderate rather than high intensity may be a better strategy to reduce DNA damage in healthy older women while also increasing independence.

Keywords

strength training, oxidative stress, urine 8-oxo-dG, GSSG/GSH, randomized controlled trial

Human aging is characterized by a progressive decline in the neuromuscular system, with marked decreases in skeletal muscle mass, muscle strength, and physical function beginning in the sixth decade in life (Delmonico et al., 2009; Manini & Clark, 2011). It has been hypothesized that one of the causes of these changes may be the deleterious and cumulative effects of reactive oxygen species (ROS) along with a decrease in endogenous antioxidants in older adults (Bouzid, Hammouda, Matran, Robin, & Fabre, 2014). These effects are especially marked in older women because they are exposed to particular risk due to the loss of the antioxidant effects of estrogen during menopause (Moreau & Hildreth, 2014) and the high levels of sarcopenia and dynapenia seen in women compared to men (Brady, Straight, & Evans, 2014).

Chronic oxidative stress (OS) has also been associated with the loss of skeletal muscle mass and muscle strength (Cesari et al., 2012; Howard et al., 2007). The production of excess ROS can cause chronic OS, affecting several different organic molecules, including nucleic acids, and provoking DNA damage. One of the most abundant and potentially mutagenic

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lesions in DNA is the production of the oxidized DNA nucleoside 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OHdG; Wilson, Sofinowski, & McNeill, 2003).

Over the last two decades, several reports have demonstrated that the prescription of physical activity among older adults is important in the management of chronic illness, OS, and loss of strength (de Souto Barreto, Cesari, Andrieum, Vellas, & Rolland, 2017; Padilha et al., 2015). The promotion of activity among community-dwelling older people is a crucial task for primary care nurses (Goodman, Davies, Dinan, See Tai, & Iliffe, 2011), and as such, in their recent report, the International Association of Gerontology and Geriatrics—Global Aging Research Network recommends that nurses provide a report on "Recommendations on Physical Activity and Exercise for Older Adults Living in Long-Term Care Facilities" (de Souto Barreto et al., 2016). The majority of published data on the effects of exercise and associated changes on OS and antioxidant enzymes are derived from studies involving endurance training (Bouzid et al., 2014) or young people (Nordin, Done, & Traustadóttir, 2014) or those analyzing only acute effects (Çakır-Atabek, Özdemir, & Çolak, 2015). Although resistance training is a safe and effective method for increasing muscle strength, physical function, and muscle mass in older adults (Liu & Latham, 2009; Peterson, Rhea, Sen, & Gordon, 2010), and this effect is supported by Category A evidence (Chodzko-Zajko et al., 2009), only a few studies have described redox state changes that are provoked by strength training in healthy older adults (Padilha et al., 2015; Parise, Brose, & Tarnopolsky, 2005; Ribeiro et al., 2017; Soares et al., 2015; H. K. Vincent, Bourguignon, & Vincent, 2006), and the results of these studies were contradictory.

It should be noted that adaptations in OS biomarkers and endogenous antioxidants in older adults as a result of resistance training may be dependent on appropriately manipulating the parameters of training programs including training volume and intensity (Azizbeigi, Azarbayjani, Atashak, & Stannard, 2015; Çakir-Atabek, Demir, PinarbaŞili, & Gündüz, 2010; Çakir-Atabek et al., 2015; Carteri et al., 2015; Parker, McGuckin, & Leicht, 2014), as previously demonstrated with muscle mass, muscle strength, and physical function (Borde, Hortobágyi, & Granacher, 2015; Liu & Latham, 2009; Peterson et al., 2010). Heterogeneity in the doses applied in different older adult training protocols may be one of the causes of the different antioxidant enzyme levels obtained in these studies. Is not clear whether variation in the intensities of exercise can generate changes in such markers, but Dixon, Robertson, Goss, and Timmer (2006) and Çakır-Atabek, Özdemir, and Çolak (2015) hypothesized that there is an exercise intensity threshold beyond which OS increases.

Therefore, in the present study, we examined how OS responds to different exercise intensities during a 16-week resistance training program (RTP) with elastic bands in older women in order to improve our understanding of the dose–response relationship of exercise intensity to OS. We aimed to identify the most suitable intensity for improving physical function and redox state in this population, while also considering that changes in the neuromuscular system and thiol redox state during aging are strongly associated with disability, frailty, and mortality (Cesari, Kritchevsky, Leeuwenburgh, & Pahor, 2006). Our findings should be of great interest to nurses, therapists, practitioners, and clinicians.

The specific aims of this study, then, were to examine the effects of a 16-week progressive elastic band RTP at different intensities (high vs. moderate) on DNA damage (8-OHdG), thiol redox state (glutathione [GSH], oxidized glutathione [GSSG], and the GSSG/GSH ratio), and physical function (30-s arm curl test, 30-s chair stand test, 8-foot up-and-go test [TUG], and 6-min walk test [6MWT]) in healthy older women. Based on previous findings, we hypothesized that (a) 16 weeks of progressive resistance training with elastic bands at high intensity would increase OS, detected as an increase in the concentration of 8-OHdG, while the moderate-intensity routine would produce a reduction of the values in this parameter; (b) resistance training at both intensities would produce similar increases in the concentration of thiol redox state parameters; and (c) the experimental groups would increase their physical function values by similar amounts.

Material and Method

Participants

Healthy, Caucasian, and untrained older women (aged 60–75 years) volunteered to participate in this study after reading an advertisement containing the study information that was publicly posted at several Municipal Physical Activity Centers for Older People in Valencia, Spain. The inclusion criteria were as follows: (a) age $\geq$60 years, (b) sedentary lifestyle (less than 1 hr of physical activity or exercise a week during the previous 6 months), (c) medical certificate of suitability or fitness to practice resistance training activities, (d) no plans to leave the area during the intervention, (e) cognitive ability to understand and follow the instructions, and (e) free of any antioxidant supplements for at least 6 weeks before the start of this study. The exclusion criteria were as follows: (a) presence of cardiovascular, musculoskeletal, or neuromuscular disorders that would prevent the participant from performing the exercises; (b) body weight changes $\geq$10% in the previous year; (c) intake of prescription medications that were expected to alter the results of the study (ergogenic or dietary aids); (d) a history of malignant neoplasms; and (e) engagement in regular strength training (more than once a week) during the previous 6 months.

Before being included in the study, all potential participants were comprehensively informed about the study purpose and procedures as well as the benefits, risks, and discomfort that might result from participation. Each participant provided informed consent and was free to withdraw from the study at any time. The study was conducted according to the Helsinki Declaration (1964; revised in 2001), and the experimental protocol was approved by the University of Valencia (Spain) ethics committee (H1395923230221).

Experimental Design

To examine the effects of 16 weeks of supervised, progressive resistance training with elastic bands at different intensities, we randomly assigned the participants to the high-intensity group (HIGH; $n = 39$), moderate-intensity group (MOD; $n = 31$), or control group (CG; $n = 23$) using a computer-generated random permutation procedure. The researcher who generated the random allocation sequence also enrolled the participants. The sample sizes differ because both men and women were originally recruited, and more men were randomly assigned to the control and MOD groups than the HIGH group. However, the total number of men recruited was insufficient, so we eventually excluded them from our analysis. In writing this article, we adhered to the Consolidated Standards of Reporting Trials guidelines (Schulz, Altman, & Moher, 2010).

Variables and Testing Procedures

The exercise intervention was carried out at two Municipal Physical Activity Centers for Older People in Valencia from November 2014 to February 2015. The urine and blood samples used to evaluate DNA damage and the thiol redox state, respectively, were obtained by nurses at the Dr. Peset University Hospital (Valencia) at baseline and after 16 weeks in the experimental groups. Because the biochemistry data (blood samples) are logistically difficult, invasive, and expensive to collect and analyze, and in accordance with previous studies in which CGs comprising similar populations did not exhibit changes in DNA damage or thiol redox state over a period of time similar to that of the present study (Azizbeigi et al., 2015; Soares et al., 2015), we used the baseline data as a single reference for the CG, as has been done in previous studies (Monzo-Beltran et al., 2017). Biological samples for testing the thiol redox state and levels were processed at the Oxidative Pathology Unit in the Department of Biochemistry and Molecular Biology in the Faculty of Medicine at Valencia University and by the Clinical Analysis Service at University Hospital Dr. Peset–FISABIO. Anthropometric measurements (height and weight) and the tests for evaluating physical function in older adults were carried out with the three groups before and after the experimental period in the Performance Laboratory in the Faculty of Physical Activity and Health Sciences at Valencia University.

The assessments were performed 24–72 hr before and after the intervention period on 2 different days. Urine and blood samples were taken during Session 1, and the anthropometric measurements and physical status tests were carried out 48 hr later. All participants were asked to maintain their normal daily routines and eating habits, avoid nutritional supplements that might affect their body composition or performance, and refrain from beginning new exercise programs or any other type of physical exercise for the duration of the study. All the tests were supervised by the same investigators and clinicians using the same protocols. Each participant was familiarized with all the physical testing procedures, and we provided verbal encouragement during all the tests.

Urine collection. Ten to fifteen milliliter of spot urine (first urine in the morning) were collected in polyethylene bottles and transferred to glass tubes. Urine samples were centrifuged at 3,000 rpm for 5 min to precipitate and remove impurities. Different aliquots were separated and stored at −80°C until use.

Blood sample collection and separation of plasma and peripheral blood mononuclear cells (PBMc). After participants fasted for 12 hr, we extracted venous blood samples (10–15 ml) from seated participants between 8:00 and 10:00 a.m., collecting the samples in ethylenediaminetetraacetic acid (EDTA) tubes. These samples were kept in a refrigerator at 2–4°C until they were processed, which always occurred within 4 hr of extraction. Separation was carried out by density-gradient centrifugation with Histopaque (Sigma H-1077) at 1,700 rpm for 30 min (at 12°C). The resulting yellow top layer (plasma) along with the ring of PBMc found between the first and second layers were transferred to Eppendorf tubes, gently resuspended, and stored at −80°C until use. The same procedure was carried out to obtain only the plasma layer which was also stored at −80°C until use. Prior to their use in the study assays, the samples were sonicated for 3–5 s (Monzo-Beltran et al., 2017).

DNA oxidation: 8-OHdG assay in urine by high-pressure liquid chromatography-electrochemical detection (HPLC-EC). The method we used to measure DNA oxidation was modified from that described by Espinosa et al. (2007). Specifically, 1 ml of urine was defrosted and 100 µl of 3 mol/L Tris–EDTA solution (pH 8.6) were added and vortex mixed for 30 s. Then, 1 ml of the solution was applied to a Bond Elute C18(OH)SPE (3 ml) column preprepared with 3 ml methanol and 3 ml distilled water (HPLC grade). The column was washed with 3 ml water followed by 3 ml of 2.5% acetonitrile and 1.5% of methanol in 10 mmol/L borate (pH 7.9). The sample was then eluted with 3 ml of the same buffer and applied to a Bond Elute strong cation exchange column (3 ml) prepared with 3 ml of methanol and 3 ml of borate buffer (pH 7.9). The 8-OHdG was then eluted with 2 ml of acetonitrile/methanol buffer in borate and adjusted to pH 6.0 with 1 mol/L HCl. About 4 ml of 50:50 dichloromethane:propane-2-ol was added to the 2 ml of eluent and it was vortex mixed for 30 s. The samples were then centrifuged for 10 min at 3,500 rpm, the upper aqueous layer aspirated off, and 3 ml of organic layer were dried by evaporation in a vacuum chamber (Concentrator plus; Eppendorf AG, 2331 Hamburg) at 50°C. Finally, the samples were reconstituted in 1 ml HPLC running buffer as above, but without acetonitrile, and 50 µl was injected into the HPLC column.

Running conditions and EC detection were the same as those described for plasma samples; 8-OHdG values were expressed as the ratio to millimole per mole creatinine quantified with the Cayman Creatinine (urine) Colorimetric Assay kit (no. 500701) as described by Borrego et al. (2013). We followed the calibration procedures described by Espinosa et al. (2007). An HPLC-grade water solution of 8-oxo-dG >98% (thin-layer chromatography [TLC]) purchased from Sigma-

Aldrich Chemical Company, St. Louis, MO (ref. number H5653), was used as a standard sample. Each working day, six different samples with known low and high concentrations of 8 8-OHdG were run twice; the intra- and interday calculated variability coefficient was 5% (Borrego et al., 2013).

Assay of reduced and oxidized GSH in PBMc. The total oxidized and reduced GSH levels were analyzed by spectrophotometry following the respective Cayman total GSH and GSSG assay kit procedures (no. 703002). The GSSG/GSH ratio was calculated and expressed as a percentage (Monzo-Beltran et al., 2017).

Anthropometric measurements. Prior to anthropometric measures and physical status tests, participants fasted for 3–4 hr, refrained from ingesting stimulants (e.g., caffeine) for 8 hr, and avoided practicing intense exercise for 24 hr but were allowed to hydrate freely.

Height (meter) was measured to the nearest 0.1 cm using a portable stadiometer (SECA model 217, Seca GmbH & Co. KG, Hamburg, Germany). Total body weight (kg) and percentage body fat (%) were measured to the nearest 0.1 kg using an electrical bioimpedance analyzer (Tanita® model BC-418 MA, Tokyo, Japan). The participants were advised to wear light clothes and remove metal items that could disrupt the electrical current during the measurement. Body mass index (kilogram per square meter) was calculated by dividing the body mass (in kilogram) by the square of the body height (in meter).

Physical function measurements. Physical function was evaluated using the following standardized tests from the Rikli and Jones battery (Rikli & Jones, 2013; the 30-s arm curl test [Arm Curl], 30-s chair stand test [Chair Stand], 8-foot up-and-go test [TUG], and 6MWT). Protocols for each of these tests have been previously described (Flandez et al., 2017).

Elastic Band RTP

The supervised intervention program included 2 weekly sessions of 55 min to 1 hr performed on nonconsecutive days (separated by 48 hr) for 16 weeks. As recommended by the American College of Sports Medicine, each exercise session was divided into three components: a 10-min general warm-up, 35–40 min of resistance exercises, including three upper limb exercises (upright rowing, incline rowing, and elbow curl) and three lower limb exercises (narrow stance squat, lunge, and standing hip abduction), and a 10-min cooldown routine. Primarily multijoint exercises were chosen to emphasize both major and minor muscle groups (Garber et al., 2011). Each session was performed in a group, and each participant always performed the exercises in the same order, alternating between the upper and lower limbs (Romero-Arenas, Pérez-Gómez, & Alcaraz, 2011). Elastic bands (TheraBand®, Akron, OH, USA) and chairs were used as the equipment.

The HIGH group performed six submaximal repetitions equivalent to 85% of the one-repetition maximum (1RM) per exercise, while the MOD group performed 15 submaximal repetitions equivalent to 70% of 1RM throughout the training period. The perceived exertion level on the OMNI Resistance Scale (Colado, Garcia-Masso, Triplett, et al., 2012) progressed from 6–7 (somewhat hard) in the first 4 weeks to 8–9 (hard) in the remaining 12 weeks for both experimental groups. Control of the intensity by this method (which takes into account the grip width, band color, and number of bands) has been previously validated in young adults (Colado et al., 2010), middle-aged adults (Gargallo et al., 2014), and older adults (Martín et al., 2016). The number of sets per exercise progressed from three in the first 8 weeks to four in the remaining 8 weeks in both groups, with 120 or 60 s of active recovery (slow rhythmic swinging of the extremities without the use of elastic bands) between sets in the HIGH and MOD groups, respectively; 90 s of rest was allowed between exercises in both groups. The speed of execution of the exercises was controlled using a metronome marking the cadence (2 s of concentric contraction and 2 s of eccentric contraction).

The subjects performed two sessions of preintervention familiarization to (a) select the color, grip width, and number of bands; (b) adapt the rate of perceived exertion; and (c) learn the correct technique for the exercises. The loads were adjusted every week to maintain the appropriate training intensities by adapting the color and number of elastic bands along with the grip width. Training attendance was recorded at every session. All the training sessions were performed at the same time of the day (10–11 a.m.) and took place in two Municipal Physical Activity Centers for Older People located in Valencia, under the supervision of a qualified and experienced sports scientist, nurses, and physiotherapists to ensure safety and compliance. The experimental design is shown in Figure 1.

Statistical Analysis

The data distribution was tested with the Kolmogorov–Smirnov test and with a box plot analysis. A Wilcoxon signed-rank test was used for data with a nonnormal distribution to compare the results within each pre- and posttraining data group. To compare the variables between groups, a Kruskal–Wallis test followed by Mann–Whitney U test was used for nonnormally distributed variables. A two-way analysis of variance for repeated measures followed by Bonferroni corrections was used for within- and between-group comparisons for variables with a normal distribution (GSH and TUG). The ES was calculated as the posttraining mean minus the pretraining mean divided by the pooled standard deviation of the pre- and posttraining data (Cohen, 1988). An ES of less than .2 was considered a trivial effect, .20–.49 a small effect, .50–.79 a moderate effect, and in excess of .80 a large effect (Cohen, 1988). The $\Delta\%$ was calculated with the standard formula: change (%) = [(posttest score − pretest score)/pretest score] × 100. A 95% confidence level (significance $p \leq .05$) was accepted as statistically significant. The statistical analyses were performed using commercial software (SPSS, Version 20.0; SPSS Inc., Chicago, IL). All data are reported as the means ± the standard deviations.

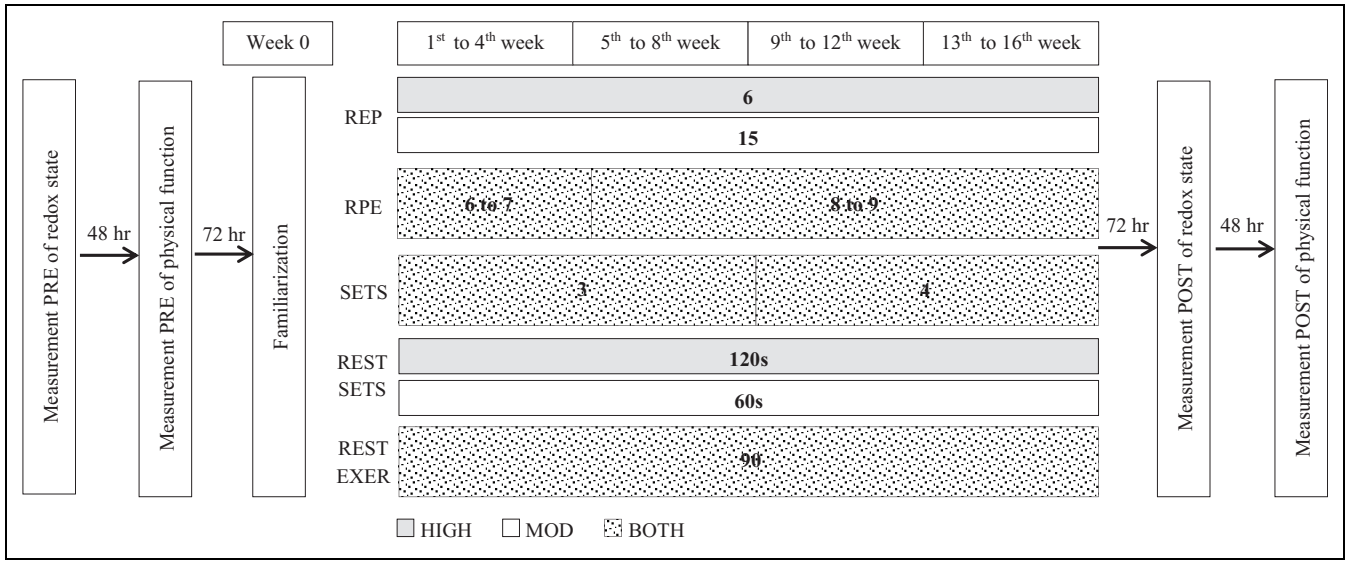

Figure 1. Experimental design. Measurement of redox state in the control group was completed at baseline only. HIGH = high-intensity group; MOD = moderate-intensity group; REP = repetitions; RPE = rate of perceived exertion (6–7 = *somewhat hard*, 8–9 = *hard*); EXER = exercise.

Results

Participant Flow and Baseline Characteristics

Details of the participant flow through the study are displayed in Figure. 2. Because the very low number of men in the HIGH group ($n = 3$) could have affected the detection of differences between groups with the level of confidence and statistical power required in the present study, and the results could be strongly influenced by chance, we decided to exclude men from the analyzes presented here. Furthermore, the unequal sample sizes between groups in the case of men (HIGH: $n = 3$; MOD: $n = 9$; and CG: $n = 14$) would dramatically affect statistical power (decreasing) and Type I error rates (increasing; Rusticus & Lovato, 2014), which was our other reason for excluding them. Additionally, because of the high cost of OS biomarker analyses, only 70 blood samples and 60 urine samples were initially collected. At the end of the intervention, blood samples were available from 63 older women (HIGH: $n = 24$, MOD: $n = 20$, and CG: $n = 19$) and urine samples from 50 (HIGH: $n = 20$, MOD: $n = 16$, and CG: $n = 14$). The samples were equally distributed among the groups according to the proportion of women who were initially assigned to each group (HIGH > MOD > CG), with the intention of also making the sample size as similar as possible between the three groups with respect to the initial proportion. None of the dropouts left the program as a result of injuries or adverse responses to the treatment.

The attendance rate for the exercise program was very similar for the two groups: 83.33% for the HIGH and 83.74% for the MOD group (30 of 36 sessions, including the familiarization sessions, in both cases), and the study adherence rate was greater than 90% in all three groups (HIGH = 92.30%, MOD = 90.32%, and CG = 91.30%). The baseline characteristics of the subjects are presented in Table 1. At baseline, the age, anthropometric characteristics, redox measurements, and TUG performance ($p > .05$) did not differ between the intervention groups (Tables 1 and 2). Comparisons between the groups revealed differences between the HIGH and CGs for the Arm Curl ($p = .008$), between both intervention groups and the CG for the Chair Stand (HIGH: $p = .002$; MOD: $p = .001$), and between training groups ($p = .015$) and MOD versus CG ($p = .029$) for 6MWT (Table 2).

DNA Damage and Thiol Redox State

In urine 8-OHdG, there was a significant increase (71.07%, $p = .010$) in the HIGH group (pre: 2.12 $\pm$ 1.34 nmol/mmol creatinine, post: 3.64 $\pm$ 1.37 nmol/mmol creatinine) with a large ES (1.12) and a significant decrease (−25.66, $p = .033$) in the MOD group (pre: 3.91 $\pm$ 1.40 nmol/mmol creatinine, post: 2.90 $\pm$ 1.54 nmol/mmol creatinine) with a moderate ES (−0.69). The baseline mean and standard deviation was 2.75 $\pm$ 1.30 for the CG. We found no significant effect between groups or for Group × Time interaction. Regarding the thiol redox state, results showed a significant decrease (−10.91%, $p = .002$) in GSH in the HIGH group (pre: 22.71 $\pm$ 3.83 nmol/mg protein, post: 20.23 $\pm$ 3.35 nmol/mg protein; ES = −0.69) and nonsignificant changes (−0.74%, $p = .857$) in the MOD group (pre: 20.84 $\pm$ 3.15 nmol/mg protein, post: 20.69 $\pm$ 4.22 nmol/mg protein; ES = −0.04). The baseline CG data were 22.46 $\pm$ 2.67 nmol/mg protein. In addition, there was a significant difference between the HIGH group and CG in this parameter after the exercise program ($p = .048$). The training groups did not show any pre/postintervention changes in GSSG (HIGH pre: 0.23 $\pm$ 0.08 nmol/mg protein, post: 0.25 $\pm$ 0.13 nmol/mg protein; $p = .903$; $\Delta\% = +7.91$; ES = 0.19. MOD pre: 0.25 $\pm$ 0.07 nmol/mg protein, post: 0.23 $\pm$ 0.09 nmol/mg protein; $p = .479$; $\Delta\% = -7.15$; ES = −0.25) or GSSG/GSH ratio (HIGH pre: 1.05 $\pm$ 0.48%, post: 1.29 $\pm$ 0.79%; $p = .375$; $\Delta\% = +12.65$; ES = −0.25. MOD pre:

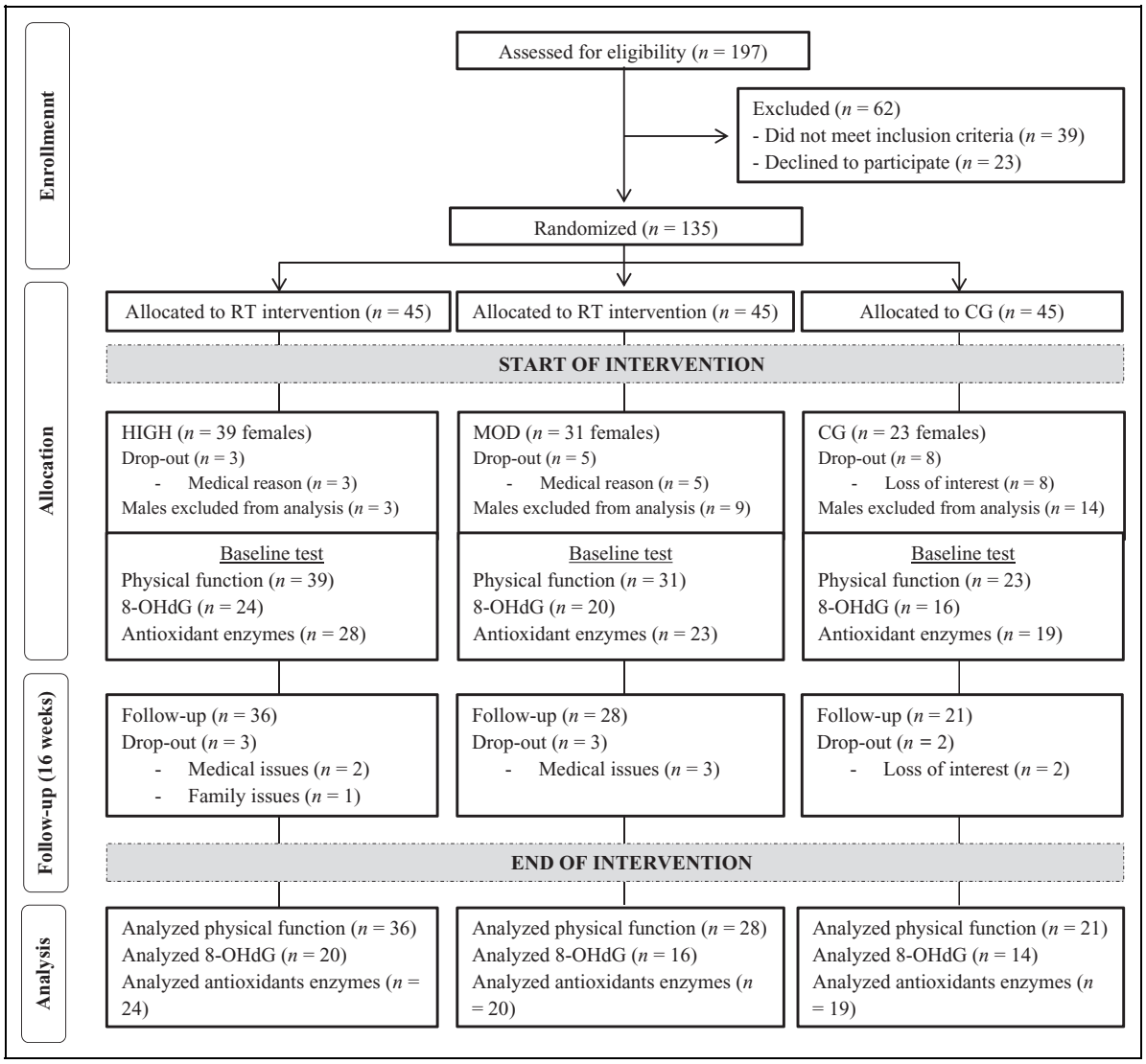

Figure 2. Flowchart of participation. Follow-up included all measures from the baseline test for the two experimental groups but only physical function for the CG, as 8-OHdG and antioxidant measures were expected to exhibit little change in this group over the study period. CG = control group; RTP = resistance training program; HIGH = high-intensity group; MOD = moderate-intensity group; 8-OHdG = 8-oxo-7,8-dihydro-2′-deoxyguanosine.

Table 1. Baseline Characteristics.

Characteristic	HIGH ($n = 39$)	MOD ($n = 31$)	CG ($n = 23$)
Age (years)	71.10 ± 5.30	68.74 ± 6.05	70.46 ± 8.10
Weight (kg)	64.67 ± 10.12	67.35 ± 10.68	66.73 ± 8.63
Height (m)	1.52 ± 0.04	1.53 ± 0.06	1.52 ± 0.04
BMI (kg/m^2)	28.10 ± 4	29.20 ± 4.80	29.13 ± 3.95
Fat mass (%)	36.56 ± 6.31	38.48 ± 6.53	39.27 ± 5.61

Note. Data are presented as the mean ± standard deviation. BMI = body mass index; CG = control group; HIGH = high-intensity group; MOD = moderate-intensity group.

1.25 ± 0.40%, post: 1.19 ± 0.57%; $p = .717$; $\Delta\% = -4.18$; ES = −0.15). Baseline GSSG data in the CG were 0.23 ± 0.10 nmol/mg protein and the GSSG/GSH ratio was 1.08% ± 0.59%. There were no significant differences between groups in these parameters. Figure 3 shows the redox activity results by group at the different time points in the study.

Physical Function

Changes in physical function at the different time points of the study are presented in Table 2. There was a significant main effect of time ($p < .05$) for all the physical function tests in both training groups, but no significant effects for Group × Time interactions were found between the HIGH and MOD groups. The improvements obtained after the RTP in both groups for the Arm Curl, Chair Stand, and TUG had large ESs. For the 6MWT, the improvements had a small ES in the case of the MOD group and a moderate ES in the case of the HIGH group. However, we did find a significant effect for the Group × Time interaction for the Arm Curl between the MOD and CGs. The

Table 2. Intervention Effects on Physical Function.

Physical Function	Group	Baseline	Posttest	*p* Value (Time)	Δ%	Effect Size *d*
Arm Curl (rep)	HIGH ($n = 36$)	15.06 ± 3.48§	23.92 ± 3.91§	.000	+58.85	2.39
	MOD ($n = 28$)	16.71 ± 4.28	26.21 ± 5.18§	.000	+56.83	1.99
	CG ($n = 21$)	18.32 ± 5.82	20.77 ± 5.92	.002	+13.39	0.42
Chair Stand (rep)	HIGH ($n = 36$)	12.50 ± 2.58§	19.39 ± 3.33§	.000	+55.11	2.31
	MOD ($n = 28$)	11.93 ± 2.72§	18.57 ± 3.80	.000	+55.68	2.01
	CG ($n = 21$)	15.45 ± 5.24	16.91 ± 7.11	.176	+9.41	0.23
TUG (s)	HIGH ($n = 36$)	6.60 ± 0.90	5.96 ± 0.69	.000	−9.71	−0.80
	MOD ($n = 28$)	7 ± 1.00	5.83 ± 0.64	.000	−16.74	−1.39
	CG ($n = 21$)	6.51 ± 1.37	6.26 ± 1.89	.339	−3.84	−0.15
6MWT (m)	HIGH ($n = 36$)	486.66 ± 47.82*	514.50 ± 54.42	.002	+5.71	0.54
	MOD ($n = 28$)	529.67 ± 59.85§	548.82 ± 59.98§	.000	+3.61	0.32
	CG ($n = 21$)	464.59 ± 101.39	477.40 ± 98.90	.266	+2.75	0.23

Note. Data are presented as the mean ± standard deviation. Δ% = percentage change from pre- to posttest; 6MWT = 6-min walk test; arm curl = 30-s arm curl test; CG = control group; chair stand = 30-s chair stand test; HIGH = high-intensity group; MOD = moderate-intensity group; rep = repetitions; TUG = 8-foot up-and-go test.
*Significantly different from MOD ($p \leq .05$); §significantly different from CG ($p \leq .05$).

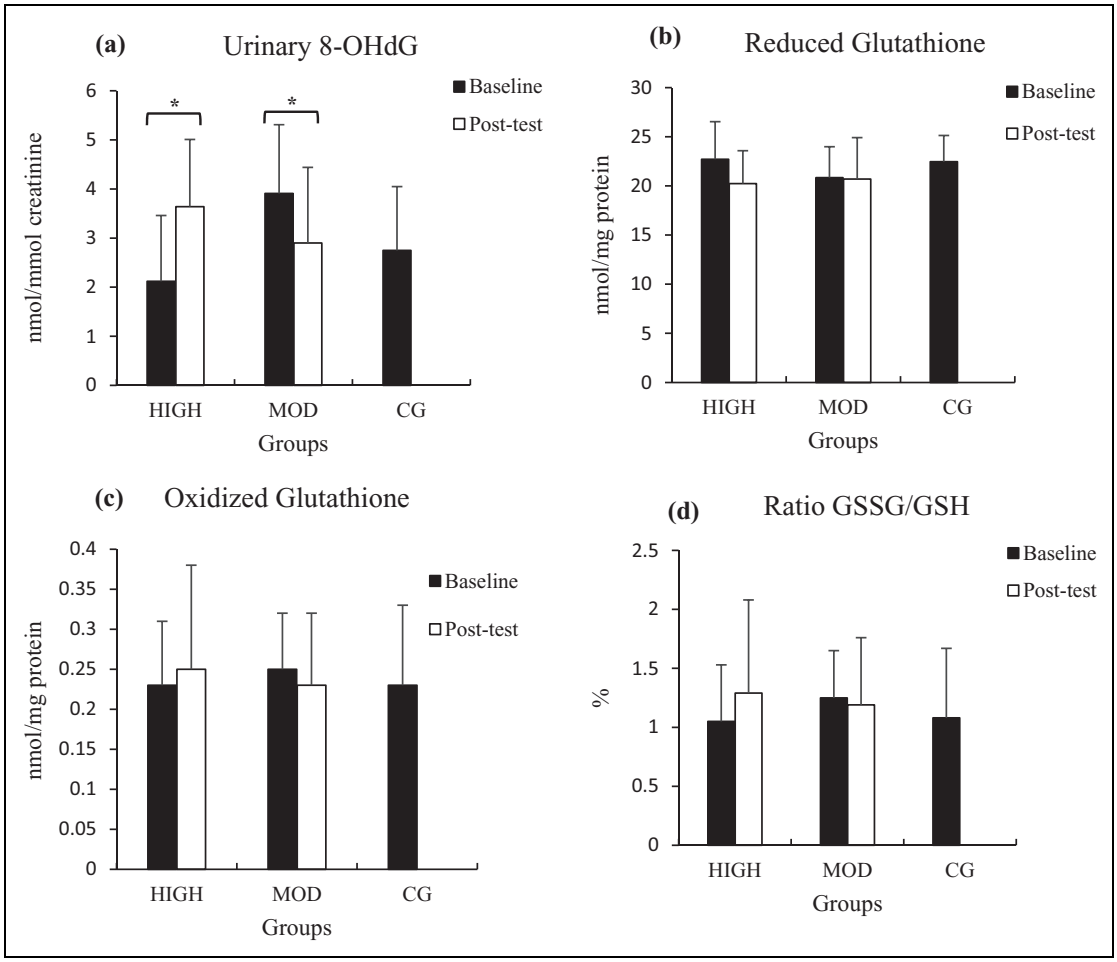

Figure 3. Markers of DNA damage and redox state in the high-intensity (HIGH), moderate-intensity (MOD), and control (CG) groups at baseline and after the training period. (a) Urinary 8-OHdG, (b) reduced glutathione, (c) oxidized glutathione, and (d) ratio GSSG/GSH. Data are expressed as mean ± standard deviation. *Significant difference from pre- to posttests ($p \leq .05$); §significant difference from CG ($p \leq .05$).

CG showed a significant improvement in upper limb strength but no significant changes for the other tests.

Discussion

To the best of our knowledge, this study is the first to investigate the effects of a long training program (16 weeks of progressive resistance training) with elastic bands at different intensities on DNA damage and GSH, GSSG, and GSSG/GSH status in older adults. The main and novel finding of the present study was that high-intensity progressive resistance training increases OS, as shown by the increase in urine 8-OHdG concentrations and decrease in the antioxidant tripeptide GSH. However, the progressive resistance training at moderate intensity results in a decrease in DNA damage with no significant changes in GSH or the GSSG/GSH ratio. The two intensities were equally effective for improving physical function in older women, since there were no significant differences between training groups in physical function parameters. We had hypothesized that the high-intensity resistance training would increase OS, detected as an increase in the concentration of 8-OHdG, while the moderate-intensity routine would reduce this parameter. This hypothesis was partially refuted because we found no significant difference between the effects of the two intensities on this marker, though 8-OHdG did increase significantly in the HIGH group and decrease significantly in the MOD group. Next, we had hypothesized that resistance training at both intensities would produce similar increases in the concentration of thiol redox state parameters, which our findings refuted because neither of the two intensities improved the antioxidant molecule levels. Our final hypothesis was that the experimental groups would increase their physical function values by similar amounts. Our findings confirmed this hypothesis, as we found no difference in the improvements in physical function parameters between the two intensities.

To date, few studies have investigated the effect of resistance training on OS biomarkers, and more specifically on DNA damage. The results obtained in the present study are consistent with those of Parise, Brose, and Tarnopolsky (2005), which showed that in older individuals (mean age 71 years), 14 weeks of circuit resistance training 3 times a week at 50–80% of their 1RM significantly reduced their urinary levels of 8-OHdG while producing no change in GSH. In addition, our results in the MOD group are in agreement with those obtained by Soares et al. (2015), which showed that 16 weeks of resistance training 3 times a week at 75% of 1RM significantly decreased DNA damage. However, our results contrast with those of Rall, Roubenoff, Meydani, Han, and Meydani (2000) who found that 12 weeks of resistance training in older adults with rheumatoid arthritis 2 times a week at 50–80% of 1RM did not result in any significant change in urinary 8-OHdG, although their finding may have been due to their small sample size. Franzke et al. (2014) showed that, after completion of a 6-month RTP with elastic bands twice a week, DNA damage increased in very old institutionalized adults. However, the authors did not specify the intensity at which their participants worked and so the discrepancy between our findings and theirs may be related to exercise intensity and the fact that the relationship between exercise and OS is complex and multifactorial. The exercise intensity, training duration, number of exercises, previous training status, and population type—all factors that can modify the OS biomarker response—varied among all of these studies. Furthermore, some of the discrepancies in findings may be related to the time that elapsed after the exercises were performed before 8-OHdG was measured. Several acute metabolic changes resulting from exercise can persist for at least 72 hr after exercise (Çakir-Atabek et al., 2010), which is why we collected the blood samples from the participants 72 hr after their last training session. In addition, the use of different biomarkers of DNA damage across studies further confounds comparisons.

The results we obtained in the present study correspond to those of previous studies where very intense or very long exercise regimes induced increased chromosomal damage (Schiffl, Zieres, & Zankl, 1997), but lower intensities, even the practice of Tai Chi, produced significantly lower DNA damage (Goon, Noor Aini, Musalmah, Yasmin Anum, & Wan Ngah, 2008). Radak, Zhao, Koltai, Ohno, and Atalay (2013) pointed out that a moderate level of OS is essential for adaptive responses to exercise, but very prolonged or exhausting exercise or exercise to which the person is unaccustomed can impair the balance between ROS production and the antioxidant defense system. This observation was clearly manifested in the present study, where resistance training at a moderate intensity generated a beneficial adaptive response to OS, while the high intensity produced an imbalance in favor of ROS production and a decrease in antioxidant enzymes. A possible explanation for this response might be that, as aging progresses, humans gradually become less adaptable to increases in ROS when undergoing high-intensity training, thus increasing their susceptibility to OS (Ji, 2001).

Regarding the thiol redox state, the present results provide preliminary data that redox activity is dose dependent in older adults, depending on the intensities applied. The significant decrease in GSH activity (-10.91%) together with the increase in GSSG ($+7.91\%$) produced by high-intensity resistance training in the HIGH cohort could be interpreted as evidence of insufficient antioxidant defenses to cope with the enhanced free radical production resulting from the intervention. In contrast, the reduction in GSSG (-7.15) along with the absence of changes in GSH resulting from moderate-intensity resistance training shows that moderate levels would be the optimal training intensity for older women because it produces the necessary stimulus to produce effective adaptive changes in the enzymatic antioxidant system while reducing levels of DNA damage. Our results regarding GSH contrast with those of previous studies, which have suggested that GSH increases after a resistance training exercise program in elderly subjects aged between 60 and 83 years (K. R. Vincent, Vincent, Braith, Lennon, & Lowenthal, 2002).

Interestingly, a compensatory balance appears to exist among the various components contributing to the overall

antioxidant defense system in blood (Kłapcińska et al., 2000). This balance seems to result from the fact that antioxidant enzymes work in networks, where a decrease in a particular antioxidant can be compensated for by an increase in another one, as can be observed in the present study. As with OS biomarkers, their response seems to be conditioned by the training dose. Previous publications have reported very mixed results regarding antioxidant defense in physically active versus less active older adults (Traustadóttir et al., 2012).

Few studies have examined the effects of RTPs on antioxidant activity in older adults. Superoxide dismutase, catalase, and glutathione peroxidase are the most commonly analyzed enzymes, and in general, studies have shown that resistance training results in their increase (Çakir-Atabek et al., 2010; Padilha et al., 2015; Ribeiro et al., 2017; Soares et al., 2015) or produces no changes (Çakir-Atabek et al., 2015; Shahar et al., 2013; Valls et al., 2014). Our results contrast with those of Çakir-Atabek, Demir, PinarbaŞili, and Gündüz (2010) who found no acute alterations in GSH after a single resistance training session in untrained men followed by significant improvements in this parameter after 6 weeks of resistance training that was independent of the training intensity (70–85% of 1RM). On the other hand, Peters et al. (2006) reported that, after 6 weeks of isometric exercise training, OS markers significantly decreased and the whole blood GSH/oxidized GSH ratio increased (+61%) in hypertensive adults. Therefore, further research should be undertaken to investigate the effects of resistance training on the tissue content of GSH and GSSG in order to understand the response of these enzymes to different types of resistance training parameters.

Regarding the physical function results, after 16 weeks of the intervention, both the HIGH and the MOD groups showed improved performance in all of the physical function tests, and this improvement did not differ significantly between the two intensities. As expected, we observed no change in physical performance in the CG, except in the Arm Curl test, in which this group showed significantly improved results. A possible explanation for this unexpected result is that mere participation in this study subconsciously motivated the CG participants to improve, along with the intrinsic motivation of wanting to produce a better result than they achieved in their baseline measurement.

The improvements we observed in the dynamic strength tests (Arm Curl and Chair Stand) were practically identical for both experimental groups. However, for the agility/dynamic balance test (TUG), the MOD group achieved the greatest improvements, while in the aerobic capacity test (6MWT), the HIGH group showed the most improvement, which also reached clinical significance (28 m) according to the previously established 24–54-m threshold for older adults (Holland et al., 2010; Mangione, Craik, et al., 2010). Improvements in the TUG for the MOD group were also clinically relevant, according to the 1.09-s threshold established by Mangione, Miller, and Naughton (2010) after they reviewed 12 studies with a total of 691 participants who performed progressive resistance training.

Our results on physical function are consistent with previously published studies, suggesting that high-intensity resistance training is better than training at low intensities for strength outcomes but may not be required for improvement of functional outcomes, where lesser intensities may suffice (Borde et al., 2015; Peterson et al., 2010), especially when the older adults in question are not frail and do not present relevant comorbidities (Raymond, Bramley-Tzerefos, Jeffs, Winter, & Holland, 2013). One possible explanation for the lack of difference in functional outcomes is that there may be a threshold above which strength gains do not lead to further functional improvements (Steib, Schoene, & Pfeifer, 2010). Another frequently used argument is that the relatively high training volume of low- or moderate-intensity training (10–15 repetitions) compared with high-intensity training (4–8 repetitions) might considerably impact adaptation when the number of sets and exercises is equal between groups (Steib et al., 2010), as was the case in the present study. Furthermore, in agreement with our findings, previous studies that used similar protocols, methods, and training devices (Colado et al., 2010; Colado, Garcia-Masso, Rogers, et al., 2012; Colado & Triplett, 2008; Flandez et al., 2017; Uba-Chupel et al., 2017) also reported improvements in physical functioning in older adults after using elastic materials (Franzke et al., 2014; Shahar et al., 2013).

The baseline values for the physical function tests in the present study were low on average when compared to reference values for maintaining physical independence at the age of our participants (Rikkli & Jones, 2013). Specifically, the HIGH group showed a range of values in the Chair Stand, 6MWT, and TUG tests equivalent to reference values for an 80- to 84-year-old age-group, while the MOD group showed Chair Stand and TUG results equivalent to an 85- to 89-year-old age-group. The CG actually showed results that most closely approached the reference values for their age-group except for in aerobic capacity, where the values were more typical for women aged 80–84 years. In contrast, after completion of the RTP, the values for the upper and lower limb dynamic strength tests in both experimental groups were equivalent to those of women aged less than 60 years. In addition, the results for the HIGH and MOD groups for the TUG and 6MWT at the end of the study were very similar to those of their respective corresponding real age groups. Such improvements are relevant to older adults because they are associated with a better quality of life and functional independence (Aparicio, Carbonell-Baeza, & Delgado-Fernández, 2010) as well as a lower risk of death (Rossi et al., 2017).

Finally, the present investigation has some limitations that must be considered when attempting to draw evidence-based conclusions. The results reported in this experiment are specific to healthy older women; thus, they should not be extrapolated to other populations. Moreover, assaying activities of endogenous antioxidants such as catalase, superoxide dismutase, and glutathione peroxidase enzyme might have better reflected the antioxidant system adaptation induced by resistance training in this setting. In addition, the small sample size

of the groups was another limitation. Finally, we did not control for or evaluate daily physical activity levels or nutritional intake, although our subjects were asked to maintain their regular daily activities of living throughout the study period and not to change their nutritional habits.

Conclusion

Our results show that a 16-week progressive RTP with elastic bands with twice-weekly exercise sessions at a moderate intensity can improve OS by decreasing the DNA damage in healthy older women, while a similar high-intensity RTP produces the opposite effect. These findings reveal a possible dose–response relationship, though we found no significant differences between the two intensities. Further research in this regard is warranted. In addition, we noted a significant decrease in GSH for high-intensity resistance training but no changes in antioxidant enzymes for moderate-intensity resistance training, confirming that resistance training at a moderate intensity produces better OS metabolism results than high-intensity resistance training in the study population. Furthermore, improvements in physical function occurred independently of the resistance training intensity. Thus, implementing RTPs at a moderate intensity may be the best strategy for reducing DNA damage and increasing independence in older women. From a clinical point of view, nurses and other professionals could use these ROS markers, combined with a simple and inexpensive RTP, as a novel, minimally invasive, and low-cost diagnostic tool (8-OHdG assay in urine) to prevent OS and dynapenia in older women. Further investigation is required to evaluate the relationship between intensity and OS in RTPs, to analyze the effects in older men and subjects with different baseline training statuses, to track other antioxidant enzymes and OS biomarkers, and to verify the dose–response relationship between redox activity and RTP prescription variables.

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Authors' Contribution

P. Gargallo and J.C. Colado contributed to conception, design acquisition, analysis, and interpretation of data; drafted the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. A. Juesas contributed to conception, design, acquisition, analysis, and interpretation of data; critically revised the manuscript for important intellectual content; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. A. Hernando-Espinilla contributed to conception, acquisition, analysis, and interpretation of data; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. N. Estañ-Capell contributed to conception, acquisition, analysis, and interpretation of data; critically revised the manuscript for important intellectual content; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. L. Monzó-Beltran contributed to conception, analysis, and interpretation of data; critically revised the manuscript for important intellectual content; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. P. García-Pérez contributed to conception, analysis, and interpretation of data; critically revised the manuscript for important intellectual content; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. O. Cauli contributed to conception, analysis, and interpretation of data; drafted the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. G.T. Sáez contributed to conception, design, acquisition, analysis, and interpretation of data; drafted the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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