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Original research

Periodized exercise performed in aquatic or dry land environments improves circulating reactive species and 8-isoprostane levels without any impact on total antioxidant capacity in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: The aim was to compare the impact of acute exercise and periodized training performed in aquatic and dry land environments on oxidative status, evaluating reactive species levels, macromolecules damage and antioxidant defense systems in diabetes mellitus type 2 (T2DM) patients.
Methods: Twelve weeks of individualized exercise including walking or running in a swimming pool (aquatic group) or in a track (dry land group) were performed. Blood samples were collected before and after the first and last exercise sessions. Reactive species content, lipid peroxidation (8-isoprostane and water-soluble fluorescent substances), and protein oxidative damage were quantified in plasma, while total antioxidant potential and antioxidant enzyme activities, specifically superoxide dismutase, catalase and glutathione peroxidase, were evaluated in erythrocytes.
Results: Periodized aerobic exercise performed in both environments acutely reduced reactive species and 8-isoprostane levels in sedentary conditions (after first session) and after 12 weeks of training (after last session) in T2DM patients. In addition, our exercise protocol performed in both environments reduced antioxidant enzymes activities; however total antioxidant capacity was unchanged.
Conclusions: Our results suggest that periodized training in both aquatic and land environments improves acutely circulating oxidative stress, specifically reactive species and 8-isoprostane levels, without any effect on total antioxidant capacity, in sedentary and trained T2DM patients.

1. Introduction

Exercise has been widely considered as a non-pharmacological approach to prevent and treat diabetes mellitus type 2 (T2DM) reducing morbidity and health-care costs (Warburton et al., 2006; Newsholme et al., 2009; Colberg et al., 2010), however little is known about the training frequency, mode and intensity that are needed to optimize the outcomes. Besides, there are few studies investigating the impact of periodized training protocols, which are characterized by increases in intensity over time considering individual performance in T2DM.

Previously, our group demonstrated that periodized training performed in both water and dry land has positive effect in T2DM, since it was able to improve plasma glucose control and reduced cardiometabolic risk factors; specifically decreased glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL) cholesterol, plasma angiotensin (ANG) II and C-reactive protein (CRP) levels were found (Delevatti et al., 2016). In addition, acute and periodized exercise in both environments impacts similarly circulating epigenetic and inflammatory parameters, respectively, histone desacetilase activity and Interleukin-10 (IL-10) levels, an anti-inflammatory cytokine (Korb et al., 2018).

Although several studies have demonstrated the relationship between diabetes-induced hyperglycemia and redox imbalance, as well as it has been suggested that antioxidant and pro-oxidant machineries are

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involved with exercise effects (Newsholme et al., 2009; Maiese, 2015; Rochette et al., 2014), to our knowledge, studies about oxidative stress as a biochemical mechanism of periodized training has not been performed.

Several studies described that aerobic exercise can reduce lipid peroxidation, specifically thiobarbituric acid reactive substances (TBARS) in T2DM (Iborra et al., 2008; Nuttamonwarakul et al., 2014; Wycherley et al., 2008). In this context, a study conducted by Nuttamonwarakul et al. (2014) comparing the effect of water or land-based aerobic exercise in older woman with T2DM observed that plasma malondialdehyde, a lipoperoxidation index, decreased only in the water group after 12 week of exercise. Another study showed that 18-week of aerobic exercise training was able to reduce TBARS levels in plasma only in the diabetes group while a single exercise session did not influence TBARS levels (Iborra et al., 2008).

Although, plasma fluorescent adducts formed by peroxidation-derived aldehydes and proteins have been linked to T2DM (Vehkala et al., 2013), to our knowledge, there are no studies reporting the exercise impact on water-soluble fluorescent substances in patients with diabetes. It is interesting to note that Brinkmann et al. (2012) demonstrated a time-dependent effect of a single bout of exercise on lipid peroxidation products in overweight/obese diabetic patients, since 8-iso-prostaglandin F2α and isoprostanes levels were increased during exercise and decreased during recovery. In this context, it has been hypothesized that beneficial exercise effects are related to training-induced adaptations in antioxidant status, since acute exercise could increase reactive species content (Fisher-Wellman and Bloomer, 2009), resulting in an upregulation of antioxidant enzymes (Gomez-Cabrera et al., 2008). Conversely, Akova et al. (2001) demonstrated decreases in superoxide dismutase (SOD) and glutathione peroxidase (GPX) activities post-exercise in erythrocyte from healthy women.

In order to provide quality of care for diabetes patients, it is important to be aware that they are at higher risk for exercise-induced osteomuscular disorders. In this context, our group previously demonstrated that aquatic training can avoid these injuries (Delevatti et al., 2015). Besides, recently clinical studies have showed similar metabolic, cardiorespiratory and functional benefits after training in both environments (aquatic or dry-land) in patients with T2DM (Delevatti et al., 2016, 2017a; Johnson and Boulé, 2017).

The purpose of this study was to investigate the effects of periodized exercise performed in aquatic and land environments on reactive species levels, macromolecules damage and antioxidant defense systems, indicating the oxidative stress, in T2DM patients. It is important to note that reactive species content was quantified using a probe (Driver et al., 2000); lipid oxidative damage, also called lipid peroxidation, was detected by isoprostane levels which are generated nonenzymatically by free radicals attack on arachidonic acid and has been considered among the best oxidative stress markers (Masako et al., 1985; Weinberger et al., 2015). Additionally, water-soluble fluorescent substances like lipofuscin were quantified given that it was demonstrated high levels in diabetic patients (Thérond et al., 2000). Protein oxidative changes were estimated by intrinsic specific residues fluorescence (Guzow et al., 2002; Bondy, 1996). In addition, total antioxidant capacity, evaluated by the TRAP assay, and antioxidant enzyme activities, specifically superoxide dismutase, catalase and glutathione peroxidase were performed. Moreover, we also investigated the time course of the exercise effects specifically acute and chronic effects of periodized exercise.

2. Materials and methods

2.1. Participants

The subject recruitment was performed by advertisement in a newspaper of general circulation. Eligible subjects were sedentary with no regular physical activity and diagnosed with T2DM. In total, 35 patients (15 men and 20 women) were originally included in the study and were allocated to aquatic (n = 17) or dry land group (n = 18) through a blinded randomization performed by blocks and stratified by sex. As described in Korb et al. (2018), three and seven participants in aquatic and dry land groups respectively dropped out of the study. The factors for dropping out included family or work demands (3 in aquatic and 2 patients in land group); medical conditions (depression, accident and joint injuries respectively 1, 1 and 2 patients in the land group) and one participant of land group did not report the reason for withdrawn. Fourteen patients completed the training protocol in aquatic group, three participants exhibited low compliance (< 80% of presence in exercise sessions) with the exercise sessions. In the dry land group, eleven patients completed the training protocol, and one exhibited low compliance with the exercise sessions. The remaining patients (aquatic group, n = 11 and dry land group, n = 10; mean age of 57.87 ± 8.5 years) were included in the per-protocol analysis. They did not change their pharmacological therapy during the study.

2.2. Ethical procedures

A written informed consent for study participation was provided by all participants after the volunteers were informed of all the risks, discomforts, and benefits of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. The Local Ethics Committee (CEP/UFRGS) approved the study protocol (nr. 108997). Trial registration number NCT01956375.

2.3. Experimental design and training

Patients underwent three a week during 12-week training programs. The exercise consisted of interval aerobic-training programs involving deep-water walking or running in a swimming pool with a life vest (aquatic group) or walking or running on a track (land group).

Both groups underwent exercise programs that consisted of periodized training in four mesocycles of three weeks as detailed in Korb et al. (2018). The training was conducted three times per week (Monday, Wednesday and Friday), and the sessions were divided into a warm-up period (5 min), a main training program (35 min) and a cool-down section (5 min) (Johnson and Boulé, 2017). The exercise intensity was prescribed according to the anaerobic threshold (ATHR) through individual's heart rate deflection point (Johnson and Boulé, 2017). The measures of the heart rate deflection point in the sixth week of the training protocol were performed to ensure the maintenance of the prescribed intensity throughout the intervention. However, this parameter was not yet altered from the baseline. The heart rates (HR) were evaluated by themselves using HR monitors (RSX 300, Polar) under the supervision of at least three teachers. It was adopted the interval method of aerobic training, with intensity of the stimulus increasing of 85–100% of the ATHR along of the intervention. The interval training sessions had 7 blocks of 5 min with stimulus: recovery relation of 1,5:1 (mesocycle 1 = 3 min of stimulus and 2 min recovery per block) in first three weeks and 4:1 (mesocycles 2,3 and 4 = 4 min of stimulus and 1 min of recovery per block) (Korb et al., 2018; Delevatti et al., 2017b). The cardiorespiratory and functional effects of this training protocol were reported in previous study (Delevatti et al., 2017b).

In the aquatic environment, the patients were immersed up to the level of the xiphoid process, and the water temperature ranged from 30 to 31 °C. The temperature ranged from 21 to 26 °C in the land environment.

2.4. Blood samples preparation

The blood samples were collected immediately before (baseline) and soon after the first and the last exercise sessions. The acute effect of single session on sedentary T2DM patients was verified. Blood was also

collected before and after last exercise session to investigate chronic effects on trained patients at resting state, without any impact of acute exercise, and to verify acute effects of last session on trained T2DM patients, respectively. Considering that all patients were sedentary, baseline values (samples obtained before the first exercise session) where considered their control values.

Blood samples were collected from the cubital vein into vacuum tubes (Vacutainer®) containing tripotassium ethylenediamine tetraacetic acid (K_3EDTA), after the samples were centrifuged at 1500 x G at 4 °C for 10 min; plasma was aliquoted and frozen at −80 °C. In addition, blood samples were collected with heparin and centrifuged as well; erythrocytes were washed 3 times with cold 0.9 N phosphate buffered saline. For enzymatic antioxidant activity analyses, 1 mM hydrochloric acid (HCl) and 4 mM magnesium sulfate (MgSO4) buffer diluted 50:500 (vol/vol) were added to erythrocytes (Delevatti et al., 2016), and the samples were frozen at −80 °C. In total, 100 µl washed erythrocytes were lysed by hypotonic shock using 1 ml distilled water to evaluate the total reactive antioxidant potential (TRAP).

2.5. Biochemical parameters

2′-7′-dichlorofluorescein diacetate (DCFH-DA) was used as a probe to evaluate reactive species content; formation of oxidized fluorescent derivative (DCF) was monitored at excitation and emission wavelengths of 488 nm and 525 nm, respectively (Driver et al., 2000).

8-Isoprostane levels and water-soluble fluorescent substance determinations estimated lipid peroxidation. 8-Isoprostane content was determined using an 8-isoprostane EIA kit (Cayman Chemical Company, USA) according to the manufacturer's instructions. Plasma fluorescent adducts comprised of peroxidation-derived aldehydes and proteins were monitored fluorometrically as described by Masako et al. (1985). The fluorescence exhibited by adducts was monitored at 350 nm excitation and 460 nm emission.

Protein oxidative modifications occur predominantly in specific residues or susceptible sequences. Intrinsic tryptophan fluorescence was determined at excitation and emission wavelengths of 280 and 345 nm (Guzow et al., 2002), respectively, and intrinsic tyrosine fluorescence excitation (277 nm) and emission (320 nm) wavelengths (Bondy, 1996).

Glutathione peroxidase (GPX) activity was quantified using tert-butyl-hydroperoxide as a substrate at 340 nm (Wendel and Feuerstein, 1981). Catalase (CAT) activity was evaluated by hydrogen peroxide decomposition at 240 nm (Aebi, 1984). Superoxide dismutase (SOD) activity was determined using a RANSOD kit (Randox Labs, USA) according to the manufacturer's instructions. Total reactive antioxidant potential (TRAP) is based on DCF oxidation induced by peroxyl radicals generated by 2,2′-azobis (2-amidinopropane) dihydrochloride (ABAP). DCF oxidation in the presence of ABAP and serum was quantified at 504 nm during 120 min. Trolox (8.4 µmol/l) was used as a standard (Valkonen and Kuusi, 1997). Protein was evaluated by the Coomassie blue method using bovine serum albumin as a standard (Bradford, 1976).

2.6. Statistical analysis

Results were expressed as mean ± S.D. Distribution normality was assessed by the Shapiro-Wilk test, and variance homogeneity was assessed using Levene's tests. When the data were not normally distributed, the results were transformed into a base-10 logarithm. The results were analyzed by two-way analysis of variance (ANOVA) with repeated measures with time and environment as factors followed by a post hoc least significant difference (LSD) assessment. In all tests, $p < 0.05$ was considered to indicate statistical significance. Baseline differences were compared using Fischer's exact test for categorical variables and an unpaired *t*-test for continuous variables. All the analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 18.0.

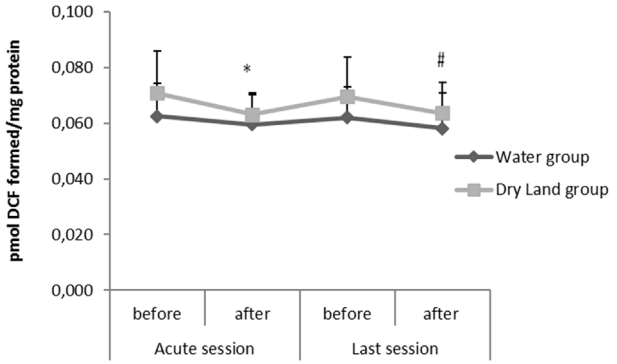

Fig. 1. Effects of periodized aerobic exercise performed in water or dry land on plasma reactive species content in T2DM patients. Repeated-measures analysis of variance (ANOVA) followed by the LSD test. *Values significantly different from baseline levels (before the first session) in both environment groups; #Values significantly different from before the last session (acute effect on chronic training) in both environment groups; $p < 0.05$.

3. Results

The baseline subject characterization was described in Korb et al. (2018).

3.1. Reactive species content

Two-way ANOVA with repeated measures showed a time effect on reactive species levels ($p = 0.02$). Reactive species content, evaluated by formed DCF, was reduced after the first session when compared with baseline levels ($p = 0.02$). The last session of periodized training acutely diminished this parameter ($p = 0.02$) (Fig. 1). Exercise performed in aquatic or dry land environments impacted similarly reactive species levels in T2DM patients.

3.2. 8-Isoprostane levels

In accordance with DCF data, ANOVA with repeated measures indicated a time effect ($p = 0.002$) on 8-isoprostane levels. Exercise performed in aquatic and dry land reduced 8-isoprostane levels after the first ($p = 0.002$) and last (0.030) exercise sessions as showed in the Fig. 2.

3.3. Plasma fluorescent adducts

Plasma fluorescent adducts levels remained unchanged after

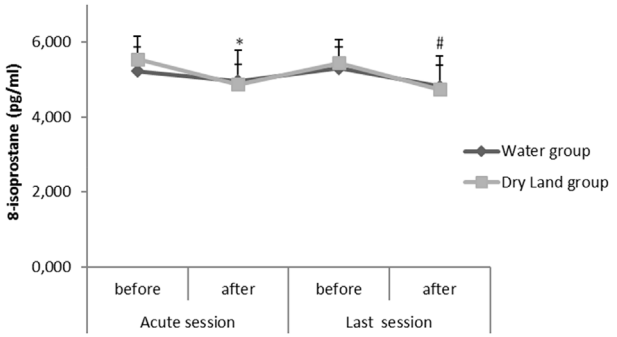

Fig. 2. Effects of periodized aerobic exercise performed in water or dry land on plasma 8-isoprostane levels in T2DM patients. Repeated-measures analysis of variance (ANOVA) followed by the LSD test. *Values significantly different from baseline levels (before the first session) in both environment groups, # Values significantly different from before the last session (acute effect on chronic training) in both environment groups; $p < 0.05$.

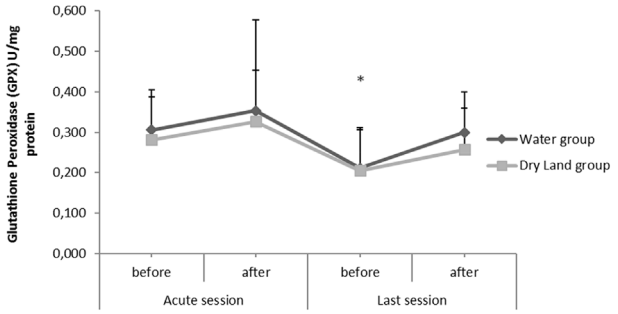

Fig. 3. Effects of periodized aerobic exercise performed in water or dry land on GPX activity in erythrocytes from T2DM patients. Repeated-measures analysis of variance followed by the LSD test. *Values significantly different from the first session (before and after); $p < 0.05$.

exercise in both environments in T2DM patients (supplementary material 1).

3.4. Tryptophan and tyrosine residues contents

Exercise performed in both aquatic and dry land environments did not change the tryptophan and tyrosine residues contents, indices of protein oxidative damage, in T2DM patients (supplementary material 2).

3.5. Erythrocyte antioxidant enzymes activities

Periodized exercise (without any acute interference) reduced GPX activity when performed in both environments (two-way ANOVA with repeated measures; $p = 0.002$) as showed in the Fig. 3. In addition, the single session ($p = 0.027$) and the last session ($p = 0.048$) reduced CAT activity in both environments, as well as the SOD activity (respectively, $p = 0.041$ and $p = 0.010$) (Figs. 4 and 5).

3.6. Total reactive antioxidant potential (TRAP)

The erythrocyte total reactive antioxidant potential remained unchanged when exercise was performed in both evaluated environments by T2DM patients (supplementary material 3).

4. Discussion

Our results revealed that the periodized protocol can optimize the exercise-induced improvement on blood oxidative stress in T2DM patients. Interestingly, regular exercise protocols at long-term were needed to improve metabolic and oxidative status profiles (Arikawa et al., 2013). In accordance, 12 months of aerobic exercise decreased

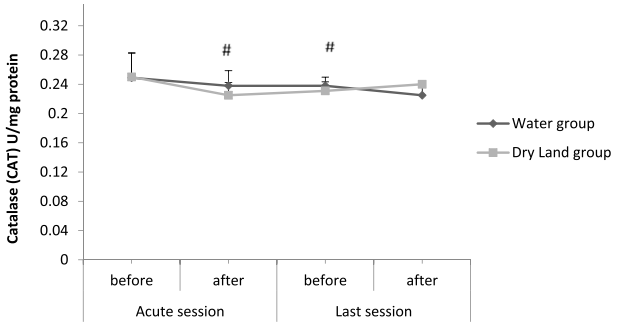

Fig. 4. Effects of periodized aerobic exercise performed in water or dry land on CAT activity in erythrocytes from T2DM patients. Repeated-measures analysis of variance ANOVA followed by the LSD test. #Values significantly different from baseline (before the first session); $p < 0.05$.

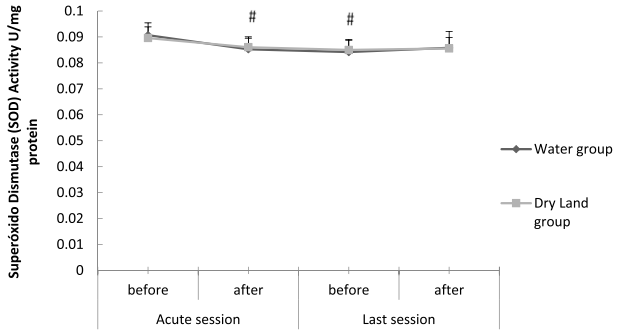

Fig. 5. Effects of periodized aerobic exercise performed in water or dry land on SOD activity in erythrocytes from T2DM patients. Repeated-measures analysis of variance (ANOVA) followed by the LSD test. #Values significantly different from baseline (before the first session); $p < 0.05$.

isoprostane levels in sedentary older women (Campbell et al., 2010). Gordon et al. (GordonL et al., 2008) described that 6 months of aerobic training reduced lipid peroxidation without any effects after 12 weeks (3 months) of exercise in T2DM patients. Meanwhile our periodized protocol of 12 weeks was enough to achieve a significant impact on metabolic (Korb et al., 2018) and oxidative status marks.

Another remarkable finding that emerged from our study was that exercise performed in water and dry land with similar training periodization (time, intensity and frequency) may reduce oxidative stress markers, specifically isoprostane and reactive species levels. This result is relevant because aquatic environment can be used to minimize injuries and ulcerations in T2DM patients given that the biochemical effects were comparable to land ones (Åsa et al., 2012; Nuttamonwarakul et al., 2012). On the other hand, we cannot exclude different beneficial effects of aquatic exercise, since the immersion *per se* leads to an augmentation of the central blood flow, as a result of blood redistribution and extracellular fluid (Watenpaugh et al., 2000). Moreover, immersion promotes a suppression of the renin-angiotensin system, which includes an important role on development and progression of T2DM (Goossens, 2012; Rodriguez et al., 2011). Accordantly, Nuttamonwarakul et al. (2014) reported that exercise performed in water environment improves endothelial function in older women with T2DM.

It is interesting to comment that Arikawa et al. (2013) described that four months of aerobic exercise reduced isoprostane levels in sedentary young women who had the highest quartile of baseline isoprostanes, suggesting a significant effect only in individuals with their elevated levels. This information is important since T2DM patients normally have high isoprostane levels (Kaviarasan et al., 2009). In addition, it has been suggested that isoprostane levels are related to glycemic control in T2DM (Kaviarasan et al., 2009; Davì et al., 1999), taken together it is possible infer that the metabolic exercise effects in diabetes (Maiese, 2015) are linked to isoprostane levels.

Although isoprostanes are generated mainly through non-enzymatic oxidation of arachidonic acid by reactive species, supporting their role as oxidative status biomarkers, these compounds can also be partially derived from the cyclooxygenase pathway (Galano et al., 2013). Considering that the inflammation role has been widely suggested in T2DM (Krause et al., 2014), it is impossible to exclude the exercise-induced modulation on inflammatory status and consequently isoprostane levels in patients with diabetes.

It is important to note that the data here described disagree with the hypothesis that acute exercise can increase reactive species content (Fisher-Wellman and Bloomer, 2009), at least in diabetic patients. In this context, a study conducted by Fayh et al. (2018) demonstrated that high-intensity acute exercise was not able to increase the lipoperoxides production as evaluated by TBARS and F2-isoprostanes in plasma of patients with type 2 diabetes.

Surprisingly, a positive effect of periodized exercise on oxidative

status was acutely observed, reducing reactive species and isoprostane levels in plasma of both sedentary (first session) and trained (last session) conditions. On the other hand, this result can open a new perspective, once the idea of acute exercise increases free radical levels and induces adaptations in the cellular antioxidant system is based on strenuous protocols, inducing excessive stress (cortisol levels) and oxidative stress (Jin et al., 2015) and periodized protocol with an individualized program seems to be unable to impact hypothalamic pituitary adrenal axis, assessed by cortisol levels (Agostinho et al., 2017). In addition, it is possible to suggest that declines on reactive species content induced by exercise are related to a reduction in their generation, instead of altering the antioxidant system given that acute exercise did not improve the total antioxidant capacity.

Previous reports suggest a rather complex relationship between exercise benefits on antioxidant capacity and diabetes. Atalay et al. (1997) demonstrated that moderate exercise (VO_2 60% for 40 min) did not alter antioxidant enzyme activity in erythrocytes of young men with diabetes. However, acute and chronic exercise on a cycle-ergometer increased antioxidant enzyme activities (Kostić et al., 2009; Oliveira et al., 2012). Our exercise protocol consisting of periodized training for 3 months reduced GPX, SOD and CAT activities in T2DM patients without any effect on the total antioxidant capacity, evaluated by the TRAP assay. It is relevant to note that increased unidentified antioxidant compounds levels might mask reductions on tested antioxidant enzymes, since TRAP levels were unchanged. This method evaluates enzymatic and non-enzymatic defenses (Evelson et al., 2001), indicating total antioxidant concentrations (Desmarchelier et al., 1997), which is important because a substantial amount of antioxidants may be composed of unidentified compounds (Evelson et al., 2001). Besides downregulating antioxidant enzymes induced by our periodized exercise can be related to adaptations to reduced reactive species content here observed. As described above, previous findings reporting higher antioxidant enzyme activities in strenuous exercise protocols can be related to stress response (cortisol levels), while our individualized program seems to be unable to induce psychological or physical stress.

Considering that exercise in both environments had similar effects on metabolic, epigenetic, inflammatory and oxidative status and, as described in Korb et al. (2018), exercise performed in dry land environment induced more adverse effects and dropout rates comparing to aquatic group, we could suggest that exercise performed in water is more suitable than on land for T2DM patients.

It is important to note that the lack of a control group is one limitation of our work; however, since exercise is usually accepted as a treatment for T2DM patients, an untreated control group could be considered an unethical issue. The baseline values (samples obtained before the first exercise session) were considered as control ones. Additionally, an adequate control group would need to achieve similar characteristics of the exercise groups, except for exercise, including being T2DM patient with adherence to visit three time a week our university during 12 weeks and their motivation and social interaction.

Despite the limitations of this study it is important to highlight that our periodized exercise protocol performed in water and dry land environments was able to improve acutely oxidative stress, specifically reactive species and 8-isoprostane levels, in sedentary and trained T2DM patients. Further studies are required to investigate the molecular mechanisms involved in these responses.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2019.100102.

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