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Could sestrins 2 be the secret of resistance exercise benefiting dialytic patients?

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It has been previously observed that the beneficial role of exercise depends, at least in part, on the bioavailability of sestrins, which are evolutionarily conserved between species and are expressed through different stress conditions [1]. Sestrin modulates the expression of genes that are related to mitochondrial bioenergetics, probably guaranteeing biological functions linked to cell and tissue recovery [2, 3].

Physical exercise is a natural stress mode that was prominent throughout the evolutionary process of human beings [4]. Recently, regular exercise was shown to improve mitochondrial biogenesis and reduce cell damage from oxidative stress and inflammatory agents [5]. This condition is highly present in end-stage renal disease (ESRD), in which mitochondrial function can play a key role in treatment, reducing morbidity and mortality in this population [6]. Furthermore, evidence suggests that sestrin 2 promotes some metabolic actions on the muscle, such as the improvement of insulin resistance, inflammation and autophagy [7–9].

In experimental models, knockout of the gene that expresses sestrin dramatically limits the metabolic and physical fitness benefits promoted by exercise [1]. In this regard, we believe that sestrins are evolutionarily conserved proteins inducible by exercise, and considered mediators of its effects. Therefore, as patients with ESRD need to reestablish mitochondrial function, strategies to increase sestrins in these patients may play a key role in nonpharmacological treatment. However, to the best of our knowledge, it has not yet been established whether resistance training (RT) can induce the expression of sestrin 2 in this population. This article reports the effect of 6 months of RT at low to moderate intensity on systemic levels of sestrin 2 in patients under maintenance hemodialysis (glomerular filtration rate <15 mL/min/1.73 m^2; all dialysis dependent). A total of 202 patients were randomized into two groups by simple randomization by a researcher using a random number generator. After randomization, 101 patients were allocated to the control (CTL) and RT groups. In the CTL group we lost 25 patients for personal reasons, while in the RT group we lost 20 patients for the same reason. Thus our total sample size was 157 patients (CTL, $n = 76$; RT, $n = 81$).

The RT group completed 24 weeks of training, with sessions held 3 times per week on alternate days. The volume of 3 sets of 8 to 12 repetitions. The rest interval between sets and between exercises was 120 s. The patients performed predialysis exercise ~1 h before the start of the hemodialysis session. Each training session consisted of 12 exercises that included chest press, squat [they used only body weight and were encouraged to complete only a few repetitions (four repetitions) at the beginning of the program], unilateral row, unilateral knee extension, unilateral knee flexion, unilateral shoulder press, hip thrust, unilateral biceps curl, unilateral hip adduction, unilateral hip abduction, unilateral elbow extension with dumbbells and seated calf raise. The training load was monitored using the OMNI (omnibus) rating of perceived exertion (RPE) scale [10]. Participants initially trained with a load corresponding to eight repetitions at an RPE of 5–6 for the first 12 weeks and 7–8 over the final 12 weeks. When the RPE indicated the load was too easy, we first increased the number of repetitions and, if the participant exceeded 12 repetitions, the load was increased. Age, body mass and body mass index were recorded 48 h pre- and postintervention. The Kruskal–Wallis test followed by Dunn's *post hoc* analysis revealed that patients did not differ in age from baseline (CTL 63.3 ± 3.9 versus RT 67.3 ± 3.2, $P = 0.099$). They also did not decrease body mass (CTL 73 ± 15 versus 73 ± 16 kg, $P = 0.87$; RT 74 ± 17 versus 72 ± 14 kg, $P = 0.87$) nor body mass index (CTL 27 ± 3versus 27 ± 3 kg/m^2, $P = 0.54$; RT 27 ± 4versus 26 ± 3 kg/m^2, $P = 0.54$) from pre- to postintervention. In order to measure the effect of 6 months of RT intervention on serum sestrin 2 concentration, blood samples were collected pre- and post-RT. Serum sestrin 2 levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (SESN2 ELISA kit, USCN Life, Wuhan, China; limit detection 0.06 ng/mL).

A significant increase in sestrin 2 (pre- versus postintervention) was observed for ESRD patients after performing

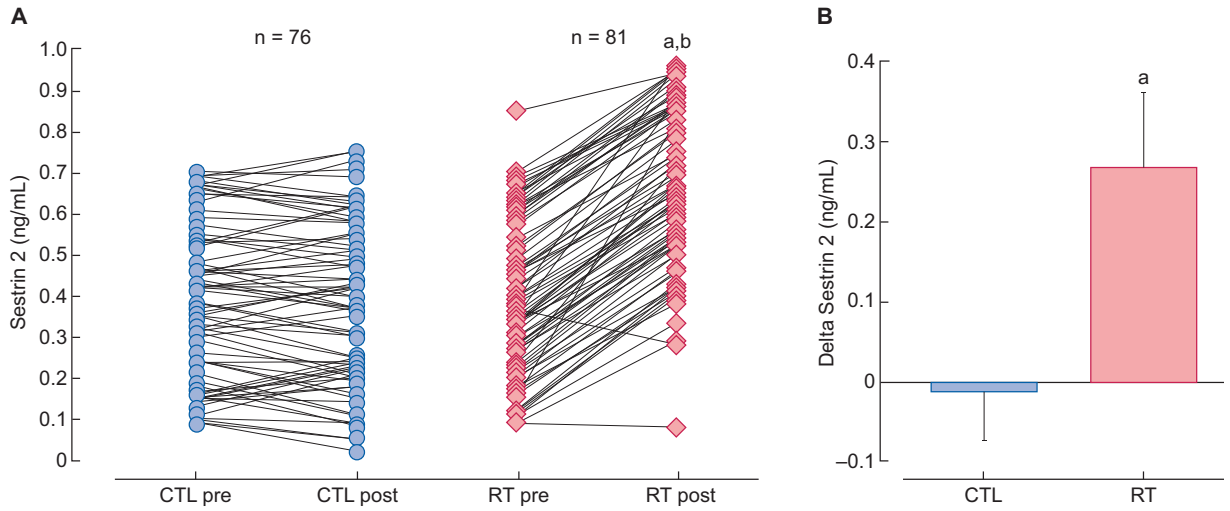

FIGURE 1: Serum sestrin 2 after 6 months of RT. (**A**) The Kruskal–Wallis test followed by Dunn's *post hoc* analysis was applied to compare groups: (a) $P < 0.0001$ versus pre-RT; (b) $P < 0.0001$ versus post-CTL. (**B**) Mann–Whitney U test was applied to compare the deltas of groups: (a) $P < 0.0001$ versus CTL.

RT (0.40 ± 0.18 versus 0.67 ± 0.19 ng/dL, $P < 0.0001$) but not for the CTL patients (0.40 ± 0.19 versus 0.40 ± 0.2 ng/dL, $P > 0.05$) (Figure 1A). Taken together, 6 months of RT increased serum sestrin 2 in maintenance hemodialysis patients. It is possible that the already known benefits promoted by RT in this population [11] could be explained, at least in part, by the increase in sestrin 2. The absence of skeletal muscle biopsy analysis limited our results once the analysis of 5' adenosine monophosphate–activated protein kinase, p-53 and mammalian target of rapamycin complex 1 are truly relevant to understand the sestrin 2 pathway. However, our results provide insights about sestrin 2 in attenuating the comorbidities associated with premature aging. However, further studies will be needed to test this hypothesis.

ETHICS APPROVAL

This study was approved by the local ethical committee from the Catholic University of Brasilia (registration no. 23007319.0.0000.0029). This study is registered in the Brazilian Clinical Trials registry (http://www.ensaiosclinicos.gov.br/; identifier: RBR-3gpg5w).

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AUTHORS' CONTRIBUTIONS

H.L.C., R.V.P.N., L.A.D., A.L.R., M.R.M. and T.S.R. performed the experiments. H.L.C., R.V.P.N., H.G.S., J.P. and T.S.R. analyzed the data. H.L.C., R.V.P.N., L.A.D., A.L.R. and T.S.R. designed the study. H.L.C, R.V.P.N., L.A.D., A.L.R., H.G.S., J.P., J.W.N., M.R.M. and T.S.R. wrote and reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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