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Dose-and gender-specific effects of resistance training on circulating levels of brain derived neurotrophic factor (BDNF) in community-dwelling older adults

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ABSTRACT

Background: BDNF is known to induce neuroplasticity and low circulating levels have been related to neuronal loss in older persons. Physical exercise is thought to trigger BDNF-induced neuroplasticity, but conflicting observations have been reported regarding the effects of resistance training on circulating BDNF in the elderly. These conflicting observations might reflect dose-and gender-specific differences.
Method: Fifty-six apparently healthy elderly (68 ± 5 years) participants were randomized to 12 weeks of resistance training (3×/week) at either high-resistance (HIGH, 8 Males, 10 Females, 2 × 10–15 repetitions at 80% 1RM), low-resistance (LOW, 9 Males, 10 Females, 1 × 80–100 repetitions at 20% 1RM), or mixed low-resistance (LOW+, 9 Males, 10 Females, 1 × 60 repetitions at 20% 1RM followed by 1 × 10–20 repetitions at 40% 1RM). Serum was collected for BDNF assay at baseline and after 12 weeks (24 h–48 h after the last training).
Results: 12 weeks of LOW+ exercise significantly increased BDNF levels in male (from 34.9 ± 10.7 ng/mL to 42.9 ± 11.9 ng/mL, time × group interaction $p = 0.013$), but not in female participants. No significant change was observed in HIGH or LOW, neither in male nor female subjects.
Conclusion: Our results show that only the mixed-low-resistance training program with a very high number of repetitions at a sufficiently high external resistance was able to increase circulating BDNF in older male participants. Training to volitional fatigue might be necessary to obtain optimal results. Additional studies are needed to unravel the underlying mechanisms, as well as to confirm the observed gender difference.

1. Introduction

Brain derived neurotrophic factor (BDNF) is a member of the neurotrophic growth factor family and described in the literature as a contraction-regulated myokine (Pedersen and Febbraio, 2012). BDNF has been associated with neuronal protection and survival, axonal and dendritic growth and remodeling, neuronal differentiation and synaptic plasticity (Coelho et al., 2013; Knaepen et al., 2010; Voss et al., 2013). It is implicated in many neural processes and can prevent or delay neurodegenerative diseases. In addition, BDNF is also involved in energy homeostasis and cardiovascular regulation (Golden et al., 2010) as well as in enhancing lipid oxidation in skeletal muscle via activation of AMP activated kinase (Pedersen and Febbraio, 2012).

Circulating BDNF levels have been shown to be affected by a host of factors including gender, age, body weight and nutritional status. The concentrations of BDNF change with increasing age, and neuronal loss in older persons have been shown to be related to low peripheral BDNF levels (Ziegenhorn et al., 2007; Lommatzsch et al., 2005). In addition, Lommatzsch et al. (Lommatzsch et al., 2005) found gender differences in platelet BDNF but not in plasma BDNF levels. Higher BDNF concentration in females compared to males has been reported (Trajkovska et al., 2007; Golden et al., 2010) while others found no gender differences (Ziegenhorn et al., 2007; Gustafsson et al., 2009). Furthermore, depression and neurodegenerative diseases have been linked with a decrease in BDNF levels in older persons (Pereira et al., 2013; Frazzitta et al., 2014; Baker et al., 2010; Laske et al., 2010) and in frailty (Coelho et al., 2012).

Apart from improving physical fitness, physical exercise also plays an important neurobiological role through enhanced brain plasticity (Voss et al., 2013). To understand the exercise-induced changes in

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circulating BDNF-levels, one must distinguish *acute effects* (changes in concentration of circulating BDNF during and immediately following the exercise bout) and effects on *basal levels* (changes in concentration of circulating BDNF when the acute exercise-induced changes have been washed out, e.g. after an overnight resting period). In addition, current literature shows that exercise-induced changes in circulating BDNF-levels might differ according to the exercise modalities such as type (e.g. running, cycling), duration, frequency, number of repetitions (reps) and intensity (e.g. % of maximal oxygen uptake) or external resistance (e.g. % of maximum weight that can be moved once over the whole range of movement (1RM)) (Knaepen et al., 2010; Ferris et al., 2007; Szuhany et al., 2015). Available data suggest that acute aerobic, but not resistance exercise is effective in increasing, although transiently, peripheral BDNF concentrations (Knaepen et al., 2010). An acute increase in circulating BDNF following aerobic exercise has been recorded in elderly women with osteoarthritis (67 ± 4 years) (Gomes et al., 2013) and in elderly persons with major depression (aged 61 ± 7 years), but not in healthy older adults (aged 58 ± 6 years) (Laske et al., 2010). Participants with major depression showed a significantly lower basal circulating BDNF concentration prior to exercise, which immediately after exercise increased up to comparable levels as in the healthy controls and decreased back to baseline levels after 30 minute rest. Studies reporting on the acute effects following strength training in older persons are limited.

The picture is complex with regard to the effect of resistance training on the basal BDNF levels. The effects of resistance training on circulating BDNF levels in elderly persons are scarcely studied and most of the data reported in the literature are from acute aerobic exercise (Knaepen et al., 2010). Several studies that examined the effects of resistance exercise on peripheral BDNF levels failed to observe a significant acute BDNF response following a single bout of resistance training, or changes in basal levels (Forti et al., 2014; Levinger et al., 2008; Swift et al., 2012; Rojas Vega et al., 2010; Correia et al., 2010; Goekint et al., 2010). On the other hand, Coelho et al. (Coelho et al., 2012) reported higher baseline BDNF levels in non-frail compared with pre-frail elderly women. However, basal circulating BDNF increased significantly in both groups following 10 weeks of progressive resistance (3×/wk, 8 reps at 75% of 1RM) training. In line with these findings, Pereira et al. (Pereira et al., 2013) showed that 10 weeks of resistance (3×/wk at 50%–75% of 1RM), but not aerobic training, was effective in increasing basal circulating BDNF levels in older women. In contrast, we recently demonstrated that 12 weeks of intensive resistance training (3×/wk, 3 series of 10 reps at 70–80% of 1RM) did not influence basal circulating BDNF levels when compared with matched controls in community-dwelling older persons (aged >60 years) (Forti et al., 2014). Similarly, Levinger et al. (Levinger et al., 2008) and Swift et al. (Swift et al., 2012) reported no significant change in basal circulating BDNF levels in middle aged subjects (51 ± 6 years) with mixed risk factors for metabolic syndrome and in adults with type-2 diabetes with a broad age-range (30–75 years) following progressive resistance training for 10 weeks (3×/wk, initially 2 sets of 15–20 reps at 40–50% 1RM later 3 sets, 8–20 reps, at 50–85% 1RM) and 9 months (3×/wk of 10–12 reps) respectively. The report by Swift et al. (Swift et al., 2012) did not include information on the percentage of 1RM. These conflicting observations regarding the effects of resistance training on basal levels of circulating BDNF in older persons might reflect dose-and gender-specific differences. It is important to note that in the above mentioned studies mainly the external resistance was different but not the number of reps and none reported training to volitional fatigue. Strength endurance training at a high number of reps might be more comparable to aerobic training and might therefore trigger a different physiological response compared to the traditional resistance training protocols.

A number of sources for peripheral circulating BDNF have been suggested in the literature, including the brain (Rasmussen et al., 2009), platelets (Yamamoto and Gurney, 1990), vascular endothelial cells (Nakahashi et al., 2000), monocytes (Schulte-Herbruggen et al., 2005) and even muscle (Pedersen et al., 2009). In addition, the difference between arterial and internal jugular venous plasma BDNF has been demonstrated to reflect BDNF release from the brain during and following acute exercise (Rasmussen et al., 2009). In general, peripheral serum BDNF-levels are higher compared to plasma levels (which are assumed to be due to the contribution of platelets) (Cho et al., 2012; Gilder et al., 2014); however, there is not yet a consensus in the literature regarding the preferential use of serum or plasma when studying exercise-induced changes in basal circulating BDNF-levels.

A possible drawback of traditional resistance training in the elderly is the impact of high external resistances on the musculoskeletal system. Therefore, there is a need to adapt the traditional high-resistance exercise protocols for the elderly. To the best of our knowledge, most studies using low-to-moderate-resistance exercise protocols only reduce the external resistance without substantially increasing the number of reps (Mendham et al., 2011; Karabulut et al., 2013; Cordova et al., 2011; Onambele-Pearson et al., 2010; Coelho et al., 2013). Considering the importance of training to volitional fatigue for optimizing muscular adaptations (Steele, 2014; Fisher and Smith, 2012; Steele and Fisher, 2014), we propose a training protocol with a reduction in the external resistance as well as a substantial increase of the number of reps (until volitional fatigue). Recently, Van Roie et al. (Van Roie et al., 2013) reported that 12 weeks of high resistance training (high external resistance and few reps) led to a higher increase in 1RM than low resistance training (low external resistance and many reps) in community-dwelling adults aged 60 and older. However, this difference disappeared when a mixed low-resistance (mixed external resistance and many reps till volitional fatigue) protocol was compared to traditional high-resistance exercise. In addition, the high, low and mixed low resistance exercise programs had a similar outcome on muscle hypertrophy.

To date, most studies examining the effects of resistance training on circulating BDNF have not focused on the effects due to increasing or decreasing the external loads and training to volitional fatigue has not been reported. Thus the main aim of this study was to evaluate the effect of 12 weeks of resistance training on circulating BDNF in older men and women randomly assigned to one of three training interventions (traditional high-resistance training (HIGH), mixed low-resistance training (LOW+), or low-resistance training protocols (LOW)).

2. Participants and methods

2.1. Participants

This study was designed as a randomized intervention study. The recruitment strategy and main study procedures have been reported in detail previously (Van Roie et al., 2013). Briefly, participants were excluded if they were involved in any structured endurance exercise and/or participated in resistance exercise during the last 6 months prior to the study, were suffering from hip or knee problems, showed unstable cardiovascular disease, neuromuscular disease or acute hernia. The presence of type-2 diabetes was recorded based on self-report. Briefly, 56 elderly volunteers were enrolled, and allocated to one of three training protocols: traditional high-resistance training (HIGH, n = 18), low-resistance training (LOW, n = 19), and mixed low-resistance training (LOW+, n = 19) (see Fig. 1). Randomization was stratified for gender, age, and baseline isometric knee extension strength (see Fig. 1). As described previously, all participants showed good functional performance as reflected by modified physical performance test scores of 35.6 ± 0.7, 35.3 ± 1.1 and 35.1 ± 1.6 for respectively HIGH, LOW+ and LOW at baseline (Van Roie et al., 2013). Due to technical issues, serum samples from only 49 out of 56 participants were available for BDNF analysis at both baseline and 12 weeks (see Fig. 1). There were no significant differences for baseline characteristics between the subjects of whom serum samples for BDNF-assay were unavailable compared to those of whom serum samples were available

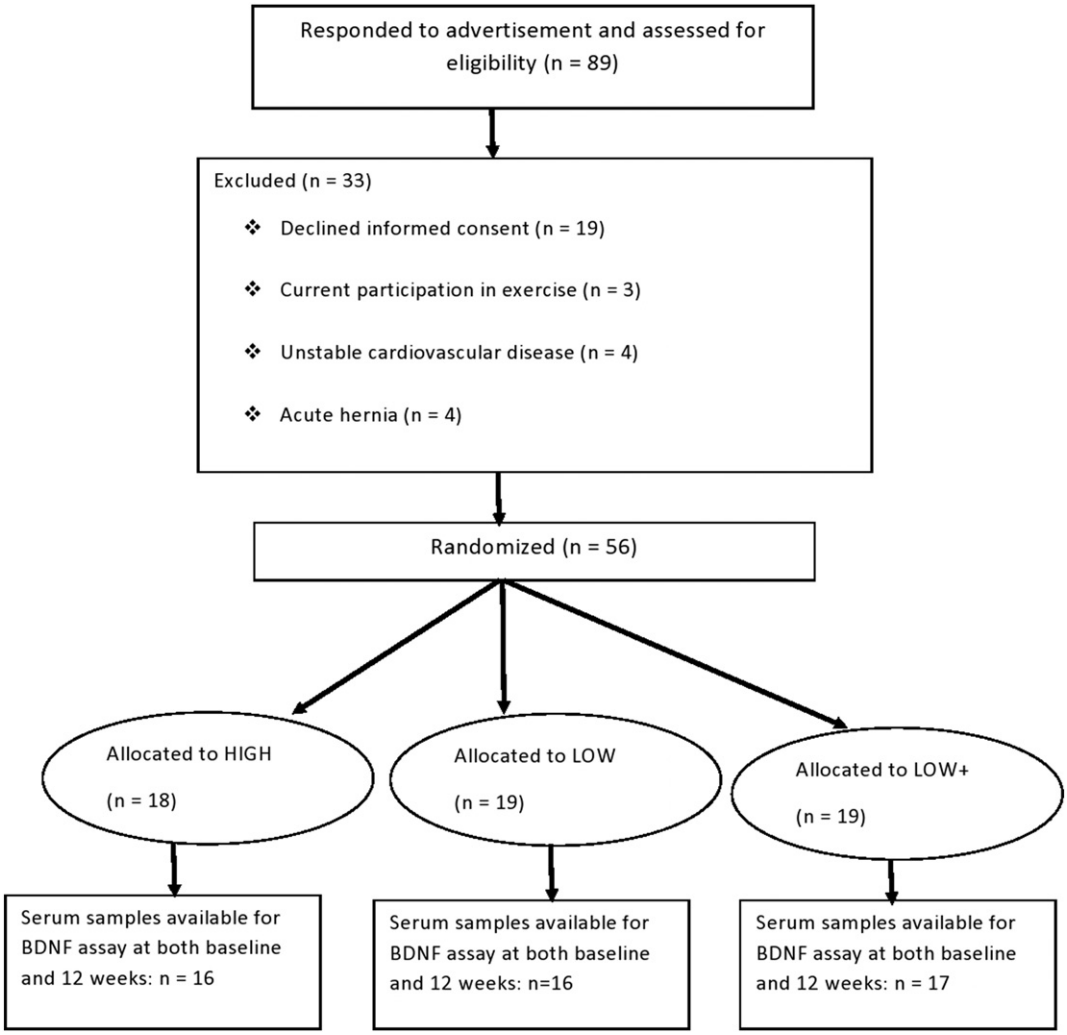

Fig. 1. Flowchart of study participants.

(data not shown). Each participant gave written informed consent after reading and understanding the risks and benefits associated with the study. The study protocol was approved by the local ethical committee in accordance with the Declaration of Helsinki.

2.2. Resistance training protocol

The resistance training program took place at a local fitness and health center for a duration of 12 weeks. The training program has been previously reported (Van Roie et al., 2013). Briefly, after an initial familiarization session in which training techniques were explained and demonstrated, participants exercised 3 times weekly on nonconsecutive days for 12 weeks (total of 36 sessions). The exercises (leg press, leg extension and seated row) were performed on Technogym™ (Gambettola, Italy) devices, designed for resistance training. Each exercise session started with a brief warm-up (10 min) on a cycle ergometer (Technogym Bike Excite, Gambettola, Italy) or on a treadmill (Technogym Run Excite, Gambettola, Italy). Exercises were performed at a moderate speed with rest periods of 2 min in between and the training was closely monitored by qualified fitness instructors.

The HIGH resistance protocol (2 sets separated by 1 min interval of 10–15 reps at 80% of 1RM) was based on ACSM's guidelines for resistance training (Thompson et al., 2013). In the LOW resistance group, participants were instructed to complete 1 set of 80–100 reps at 20% of 1RM. Participants in the LOW + group were instructed to complete first 60 reps at 20% of 1RM, and immediately afterwards (no rest), the external resistance was increased to 40% of 1RM and participants were instructed to perform 10–20 additional reps. In all intervention groups, participants were solicited to continue the exercise if maximal effort was not attained after the requested number of reps. External resistance was adjusted if participants performed reps beyond the prescribed training zone, as well as if the rate of perceived exertion dropped below 6. This strategy was used to ensure that maximal effort was reached at the end of each exercise set (Van Roie et al., 2013). As described previously (Van Roie et al., 2013), adherence (number of training sessions attended as a percentage of the total number of training sessions) to the program was 95.7% in HIGH, 95.8% in LOW and 95.3% in LOW +, with no significant differences between groups.

2.3. BDNF assay

At baseline and at the end of the 12 week resistance-training program (at least 24 h and maximum 48 h after the last training session) serum samples were collected from all participants and stored at −80 °C until assayed (simultaneously for all time points). BDNF was analyzed by an investigator blinded for group allocation using a commercially available ELISA kit (ChemiKine™ BDNF ELISA kit, Millipore™, Temecula, CA, USA) following the manufacturer's instructions. The ELISA kit has a detection range from 7.8 to 500 pg/mL. The intra-assay coefficient of variation was ±3.7%. The baseline and 12 week samples from the same participants were run on the same plate to reduce

variability. Samples were measured at a wavelength of 450 nm against a reference filter set at 650 nm using a Bio-Rad iMarkmicroplate reader.

2.4. Statistical analysis

The distribution of the data was verified using the Kolmogorov–Smirnov Goodness of Fit test, which revealed that BDNF followed a normal distribution ($p > 0.05$). One-way ANOVA and Fisher's exact test was used to test for baseline differences between the intervention groups. Interaction between group assignment and changes over time was assessed with Repeated Measures ANOVA using time as within-subjects factor and group as between-subjects factor. When a significant main effect was detected Bonferroni post hoc tests were subsequently performed. To detect within groups changes (baseline vs. 12 weeks), paired sample t-tests were employed. Statistical analysis was performed using IBM SPSS version 22.0. Differences were considered to be significant for two-sided $p < 0.05$. All data are presented as mean (±standard deviation) except otherwise indicated.

3. Results

The baseline characteristics of the 49 participants enrolled in this study are shown in Table 1. No significant differences among groups were detected. We observed no significant difference in BDNF concentrations between the intervention groups when stratified according to gender at baseline.

No significant change in BDNF concentration in the different intervention groups was observed ($p = 0.347$; Fig. 2). Similarly, no time × group interaction was observed. To further evaluate the influence of gender, we stratified our participants according to gender. A significant time × group interaction effect was shown in males only ($p = 0.013$). Twelve weeks of LOW + exercise significantly increased BDNF levels in male (from 34.9 ± 10.7 ng/mL to 42.9 ± 11.9 ng/mL; Fig. 3), but not in female ($p = 0.992$; Fig. 4) participants. Bonferroni post hoc analysis showed a significant difference in change over time between LOW + and both HIGH ($p = 0.022$) and LOW ($p = 0.048$), but not between LOW and HIGH ($p = 1.00$). No significant change in BDNF was observed in HIGH or LOW, neither in male nor female subjects.

4. Discussion

The main aim of the present study was to compare the effects of 12 weeks of resistance training using three different external loads (HIGH, LOW + or LOW) on circulating BDNF in elderly persons (older than 60 years). The key finding in this study was that 12 weeks LOW + exercise significantly increased BDNF levels in male, but not in female participants. No significant change was reported for those who exercised either in the HIGH or LOW group.

Currently, data are scarce concerning the effect of resistance training at different loads on circulating BDNF levels in the elderly. The effects of an *acute* resistance exercise or graded exercise test on the levels of BDNF have been described in the literature. Different exercise protocols of low moderate or high external load have demonstrated to increase levels of BDNF. Yarrow et al. (Yarrow et al., 2010), Goekint et al. (Goekint et al., 2010),Zoladz et al. (Zoladz et al., 2008) and Ferris et al. (Ferris et al., 2007) used an acute resistance exercise, endurance training program and graded exercise test to investigate the exercise induced effect on BDNF respectively. Following two types of exercise protocols, Yarrow et al. (Yarrow et al., 2010) observed similar elevated serum BDNF levels up to 32% following resistance (4 sets of 6 reps at 53% 1RM both concentrically and eccentrically) and eccentric enhanced (3 sets of 6 reps at 40% 1RM concentrically and 100% 1RM eccentrically) exercise, though this was gradually reduced to 41% below resting levels 60 min post-exercise. There was no difference in outcome with respect to the load of the exercise when participants from both groups were matched for exercise volume. This is in support to the report by Ferris et al. (Ferris et al., 2007), who demonstrated an intensity-dependent association (graded exercise test: two 30 min exercise bouts on a cycle ergometer at a power output corresponding to ventilator threshold plus 10% (high intensity) or minus 20% (low intensity)). Likewise, Zoladz et al. (Zoladz et al., 2008) demonstrated that moderate intensity exercise in young, healthy and physically active men (mean age 22.7 ± 0.5 years) was effective in increasing acute BDNF concentrations. In contrast, Goekint et al. (Goekint et al., 2010) found no acute effect in healthy young participants following resistance training with high external load (six resistance exercises of 3 × 10 reps at 80% of 1RM).

In a previous study, we could not demonstrate any significant change in *basal* circulating BDNF concentration in older community dwelling individuals following 12 week intensive resistance training (load was progressively increased by 10% of 1RM every two sessions from 50% up to 70–80% of 1RM) (Forti et al., 2014). Despite the high external load, the number of reps during the training sessions might not have been sufficiently high compared to the LOW + group in our current study. In the same respect, Levinger et al. and Swift et al. (Swift et al., 2012; Levinger et al., 2008) observed no significant change in basal circulating BDNF levels in middle aged subjects (51 ± 6 years) with mixed risk factors

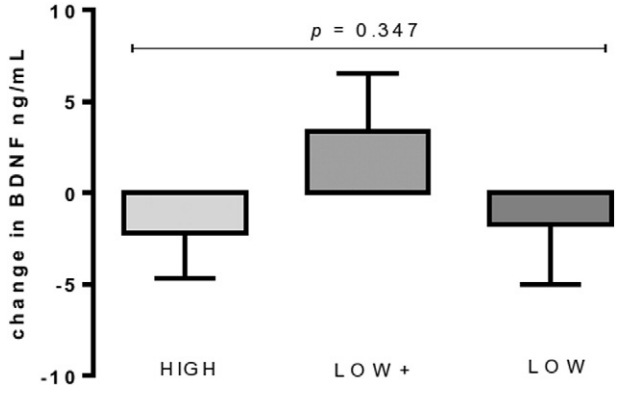

Fig. 2. Change in BDNF Concentrations between baseline and after 12 weeks exercise of the different intervention groups (HIGH, LOW, and LOW+). There was no significant change in BDNF in none of the groups at 12 weeks compared to baseline (p = 0.347).

Table 1
Overview of participant characteristics at baseline stratified accordingly to gender.

Variable	Male				Female			
	HIGH (n = 8)	LOW (n = 7)	LOW + (n = 9)	p[a]	HIGH (n = 8)	LOW (n = 9)	LOW + (n = 8)	p[a]
Age (years)	67.45 ± 5.80	69.88 ± 3.99	68.05 ± 6.49	0.69	67.93 ± 2.88	68.05 ± 6.31	67.17 ± 5.87	0.92
Weight (kg)	79.69 ± 10.40	86.77 ± 12.92	86.64 ± 8.52	0.33	65.10 ± 7.31	66.83 ± 11.38	68.17 ± 6.27	0.74
Height (m)	1.74 ± 0.05	1.73 ± 0.06	1.73 ± 0.05	0.96	1.62 ± 0.06	1.58 ± 0.07	1.61 ± 0.05	0.36
BMI (kg/m^2)	26.38 ± 2.87	28.94 ± 3.19	28.96 ± 3.27	0.19	24.87 ± 2.74	26.90 ± 4.97	26.48 ± 2.50	0.43
Type-2 diabetes (n)	0	2	1	0.26	1	0	0	0.64
BDNF (ng/mL)	35.05 ± 13.67	35.48 ± 11.94	34.86 ± 10.74	0.99	37.60 ± 13.78	36.76 ± 13.32	39.54 ± 9.97	0.89

Except for gender, data are mean ± SD; High = High resistance training; LOW + = Mixed low-resistance training; LOW = Low resistance training; BDNF = Brain-derived neurotrophic factor; BMI = Body mass index.
[a] One-way ANOVA or Fisher's Exact test.

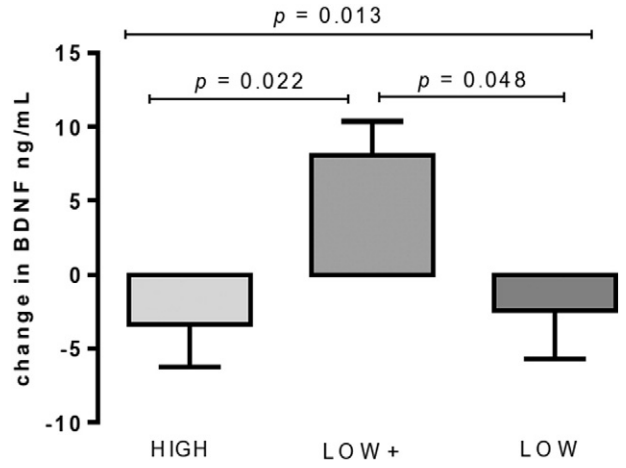

Fig. 3. Change in BDNF Concentrations between baseline and after 12 weeks exercise of the different intervention groups (HIGH, LOW, and LOW+) in males. There was a time X group interaction ($p = 0.013$). A significant change (increase) in BDNF levels was observed in the LOW+, but not in the LOW and HIGH groups in males. Bonferroni post hoc analysis showed a significant difference in change over time for LOW+ with HIGH ($p = 0.022$), and with LOW ($p = 0.048$), but not between LOW and HIGH ($p = 1.00$).

for metabolic syndrome and in adults with type-2 diabetes with a broad age-range (30–75 years) following resistance training for 10 weeks (3×/wk, initially 2 sets of 15–20 reps at 40–50% 1RM later 3 sets, 8–20 reps, at 50–85% 1RM) and 9 months (3×/wk of 10–12 reps) respectively.

Few studies have investigated the effect of gender difference on circulating BDNF levels following exercise. Swift et al. (Swift et al., 2012) found no significant difference in BDNF levels based on gender in a group of type 2 diabetic patients (aged 30–75 years) who were randomized to an aerobic (50% to 80% of maximal oxygen consumption), resistance (3×/wk of 10–12 reps) or combination of both forms of exercise for a period of nine months. In support of this finding, Ziegenhorn et al. (Ziegenhorn et al., 2007) in a large cohort of 465 participants (aged 70–103 years) were unable to report any difference as a result of gender. We suppose that the sufficient amount of external resistance combined with a large number of reps (resulting in a longer time that the muscles are under tension) in the LOW+ group could account for the increase in BDNF concentration in our present study. But the reason for the lack of a significant change in peripheral BDNF in females in our study is unclear. Animal studies show that BDNF is positively modulated by estrogen; if this is also the case in humans it can be hypothesized that the decline in estrogen levels in women as a result of menopause may

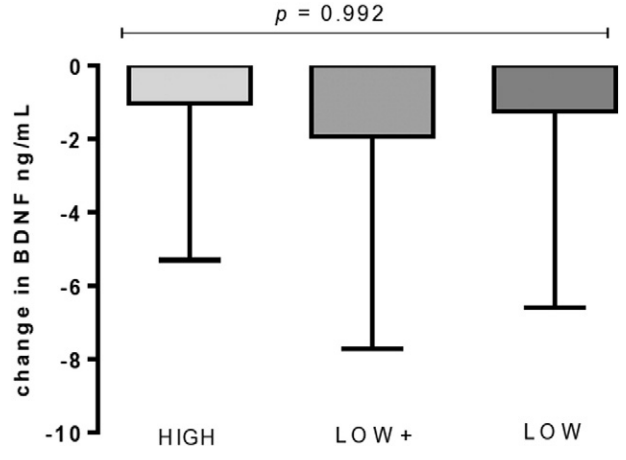

Fig. 4. Changes in BDNF Concentrations between baseline and after 12 weeks exercise of the different intervention groups (HIGH, LOW, and LOW+) in females. There was no significant change in BDNF in all groups at 12 weeks compared to baseline ($p = 0.992$).

lead to lower BDNF production (Simpkins et al., 1997). On the other hand, there might be an optimal range of circulating basal BDNF which could vary from men to women, and physical exercise could contribute to either restore or stabilize this optimal BDNF level. Though not statistically significant, females tended to show higher baseline levels compared to males in our study. Interestingly, Golden et al. (Golden et al., 2010) observed significantly higher BDNF levels in female participants than in males. In addition, a significant correlation between BDNF with bioavailable testosterone and sex hormone binding globulin was reported. The authors further demonstrated that males with higher BDNF levels tended to have lower sex hormone binding globulin and aging is associated with a decrease in bioavailable testosterone and an increase in sex hormone binding globulin. However, we did not measure bioavailable testosterone and sex hormone binding globulin in our current study since it was beyond the scope of the study.

Recently, increase in BDNF concentration has been suggested to be a compensatory mechanism in the pathogenesis of metabolic disorders (Levinger et al., 2008). This author reported increase in BDNF concentration to be positively correlated with risk factors for metabolic disorders in middle aged persons. Our participants were apparently healthy and only 4 showed self-reported type 2 diabetes (among which only 1 male in the LOW+ group). Thus we postulate that the increased BDNF concentration reported here is as a result of the training induced changes.

Current evidence points to the direction that physical training, including resistance exercise, can improve cognitive functioning in older adults (Iuliano et al., 2015). Although the exact pathways remain speculative, it is assumed that exercise-induced changes in BDNF are involved (Knaepen et al., 2010; Komulainen et al., 2008; Babaei et al., 2013). Unfortunately, data on cognitive functioning were not available in our participants and therefore it remains unclear whether the observed effects on BDNF were accompanied by improvements in cognition.

The strengths of this study are twofold; firstly, the study design is robust in nature (randomized intervention study design). Secondly, compared with prior research on the effects of resistance training on basal BDNF levels, this study addresses a gap in the literature by systematically comparing resistance training protocols at high external load (few reps until volitional fatigue) to those at low external load (many reps until volitional fatigue). However, this study is not without limitations, since there was no control group that did not perform any exercise, which might have masked some benefits resulting from the exercise intervention per se. Secondly, although similar to other reports on the effects of resistance training in elderly persons (Levinger et al., 2008; Coelho et al., 2012), the sample size was relatively small and even though there were significant effects, one cannot exclude that a type II error might have occurred. Thirdly, caution is warranted when interpreting our results since our participants are still relatively young (aged 68 ± 5 years) and might not be representative for all the community-dwelling older persons, especially those aged 80 years and over. However, other studies investigating the effect of physical exercise and peripheral BDNF levels in older adults reported included participants with similar age range as in our current study (Coelho et al., 2013). Finally, changes in cognitive function (e.g. memory) were not measured and correlation with changes in serum BDNF levels need to be investigated in future studies.

5. Conclusion

Our results show that a mixed-low-resistance training program can increase circulating BDNF in older male participants. Training to volitional fatigue with a very high number of reps at a sufficiently high external resistance might be necessary to obtain optimal results. Additional studies are needed to unravel the underlying mechanisms, as well as to confirm the observed gender difference.

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