The Effects of Physical Exercise on Insulin-Like Growth Factor I in Older Women: A Systematic Review

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ABSTRACT

Castro JBP, Aguiar RS, Venturini GRO, Santos AOB, Silva GP, Lima TP, Principe VA, Vale RGS. The Effects of Physical Exercise on Insulin-Like Growth Factor I in Older Women: A Systematic Review. JEPonline 2019;22(7):88-99. The purpose of this study was to evaluate the effects of chronic physical exercise (PE) on insulin-like growth factor-1 (IGF-1) serum levels in older women. We conducted a systematic review in PubMed, Embase, and Cochrane. Search terms included insulin-like growth factor I, exercise, and aged, and their synonyms. Only randomized controlled trials (RCTs) were included. Seven RCTs met our inclusion criteria. The interventions of the studies included land resistance training (with weight machines, free weights or elastic bands), water resistance training (with or without aquatic accessories), aerobic training (on a treadmill or ergometer), and taekwondo. The intervention period ranged from 12 to 24 wks. Most of the studies showed a significant increase in IGF-1 levels after the intervention with PE (P<0.05). Therefore, the practice of PE appears to be an effective intervention to improve IGF-1 levels in elderly women. However, further studies are needed with higher methodological quality to reduce the risk of bias. Some variables such as sleep time and stress levels should be considered in future studies.

Key Words: Elderly, Exercise, Female, IGF-1, Older Adults
INTRODUCTION

The hormonal profile tends to be negatively affected by advancing age. Insulin-like growth factor I (IGF-1) is one of the anabolic hormones that usually decreases during the aging process (3,20). Skeletal muscles and bones can synthesize this peptide hormone, although it is mainly produced in the hepatic cells after stimulation of the growth hormone (GH) receptor (9,31). IGF-1 is present in several biocompartments (such as blood, interstitial fluid, bone, muscle, and nerve tissue), and is a significant metabolic biomarker related with numerous outcomes associated with health and exercise (32). This hormone contributes to a series of important physiological processes, like enhance protein synthesis, attenuate protein degradation, and facilitate glucose and free fatty acid uptake (30).

Lower levels of IGF-1 have been associated with elevated rates of cardiovascular diseases, increased mortality (9), enlarged susceptibility to sarcopenia, loss of functional autonomy (27,29), reduced synthesis of protein, and body fat increase (33). On the other hand, elevated IGF-1 concentrations have been related to many positive health outcomes. For instance, improvements in physical fitness (40), muscle hypertrophy, preservation of lean body mass (48), better bone mineral density (BMD) and longevity (8). Conversely, high IGF-1 levels have also been linked with increased risk for some types of cancer and shrank longevity (2,26,39). Modifications in the IGF-I axis have also been allied with diverse pathological conditions, such as obesity and type II diabetes (38).

With regards to a low level of IGF-1, the uninterrupted practice of physical exercise (PE) can be considered a non-pharmacological possibility to mitigate age-related health harm (21). Hence, several scientific studies have reported that exercise training is a beneficial intervention that improves IGF-1 in older adults (5,13,43,45). On the other hand, it is interesting that some studies did not address significant IGF-1 modifications after a period of training (4) or found a reduction in serum total IGF-1 (3) after the intervention.

Among these interventions, there is a large range of PE types, training intensity, volume (duration and frequency), sample size, physical characteristics, health profile of the sample, and individuals with established diseases. As a result, the effects of PE on IGF-1 levels, especially in elderly people, remain controversial. Hence, an increase in information about the hormonal impact of PE may help to verify the effectiveness of training programs for maintenance or improvement of IGF-1 levels and to determine the potential effects of PE on IGF-1 levels in older adults (12). Thus, the aim of this systematic review was to evaluate the effects of PE on IGF-1 serum levels of older women.

METHODS

This systematic literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28).

Study Eligibility and Inclusion Criteria
We included experimental, randomized controlled trials (RCTs) that used PE as a chronic intervention to evaluate responses in IGF-1 serum levels in women 60 yrs-of-age or older. Studies that were excluded in this review included cross-sectional studies, studies with animals, with individuals who presented some disease (e.g., diabetes, cancer, hypertension
or hyperlipidaemia), with young participants in the sample, those without a control group (CG) or written in another language other than English, Portuguese or Spanish.

Search Strategy
A systematic search without time or language filters was performed using the electronic databases PubMed, Embase, and Cochrane, with the last update on August 2019. The descriptors and their synonyms *insulin-like growth factor I*, *exercise*, and *aged*, available in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), were used. The search sentence was developed with the Boolean operators [OR] (between synonyms) and [AND] (between descriptors). The references of the selected studies and other sources were checked to maximize the search.

Once references were extracted using the search terms, they were exported to a shared Endnote library. Two authors completed the search, the removal of duplicates, the analysis of titles and abstracts, and the screening of the full articles. Any divergences in the analysis were sent to a third author. Then, the full version of the articles that were more relevant for the present work was read, and any articles not meeting the inclusion/exclusion criteria were removed.

Methodological Quality Evaluation
The Jadad scale was used to evaluate the methodological quality of the studies (24). This scale was applied by two independent and qualified researchers. In the case of discordant assessments, a third researcher was requested to decide. The following methodological criteria were considered: 1a) the study was described as randomized; 1b) the randomization was properly performed; 2a) the study was a double-blind trial; 2b) the blinding was properly performed; and 3) the sample loss was described. In case the items 1a, 2a, and 3 were observed, the study got 1 point per item. If the items 1b and 2b were met, the study received another point per item. Moreover, in the case of items 1b and 2b were not met, the study lost 1 point regarding items 1a and 2a, respectively. In this scale, the scores ranged from 0 to 5. Studies with score ≤3 were considered at a high risk of bias.

Bias Analysis
The Cochrane Collaboration tool was used to assess the risk of bias in each study included in this systematic review (10). Two independent and experienced evaluators analyzed the risk of bias in the included RCTs. Discordant assessments were evaluated by a third researcher. The study is classified as high risk, uncertain risk or low risk if at least one domain had a high risk, uncertain risk or if no domain had a high or uncertain risk of bias, respectively.

Data Collection Process
We extracted following data from the selected studies: (a) country; (b) number of participants in each group; (c) age; (d) intervention protocol; and (e) results related to IGF-1 levels.

RESULTS
In total, 1098 studies were found following the proposed search methodology (PubMed = 373; Embase = 598; Cochrane = 127) and three articles were manually included. After using the selection criteria, seven RCTs were included in this review (Figure 1).
Table 1 shows the descriptive and methodological characteristics, and the main results of the studies included in the present review.

### Table 1. Data Extracted from the Included Studies.

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Groups (n) / Age (yrs)</th>
<th>Intervention Protocol</th>
<th>Duration (wks)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banitalebi et al., 2018 (Iran)</td>
<td>RT after AT (n = 9); RT prior to AT (n = 10); Interval RT/AT (n = 12); CG (n = 9); Age: 67.35 ± 1.40</td>
<td>AT: cycle ergometer, 3x/wk, 50'; 60–90% HRmax; RT: machines, 40–75% 1RM, 8–18 rep</td>
<td>12</td>
<td>All interventions: ↑ IGF-1 (P=0.07); pre- to post-test: RT after AT (P=0.04) and RT prior to AT (P=0.02)</td>
</tr>
<tr>
<td>Cho &amp; Roh, 2019 (Korea)</td>
<td>TKD (n = 19; 68.89 ± 4.16); CG (n = 18; 69.00 ± 4.41)</td>
<td>5x/wk, 60', 50–80% HRmax</td>
<td>16</td>
<td>TKD ↑ IGF-1 pre-to post-test (P&lt;0.05) and vs. CG (P&lt;0.01)</td>
</tr>
<tr>
<td>Cunha et al., 2019 (Brazil)</td>
<td>RT SS (n = 21; 70.09 ± 5.95); RT MS (n = 20; 68.60 ± 4.44); CG (n = 21; 68.04 ± 4.38)</td>
<td>RT: machines and free weights; 3x/wk, 8 exercises, 10–15RM; SS: 1 set/exercise, ~15'/session; MS: 3 sets/exercise, ~45'</td>
<td>12</td>
<td>RT SS and MS ↑ IGF-1 pre- to post-test, and vs. CG (P&lt;0.05)</td>
</tr>
<tr>
<td>Ha &amp; Son, 2018 (Korea)</td>
<td>CE (n = 10; 73.80 ± 3.16); CG (n = 10; 74.60 ± 2.84)</td>
<td>3x/wk, 60', RT elastic band (20'), 1x15 rep, intensity ↑ from yellow–red–green, OMNI-RES scale 4 to 6 (easy to hard) +</td>
<td>12</td>
<td>CE ↑ IGF-1 (P&lt;0.01)</td>
</tr>
</tbody>
</table>
walking (30’), 1st 4wks: 40–50% HRR; 5–9wks: 50–60%; 9–12 wks: 60–70%

Hofmann et al., 2016 (Austria)
RT (n = 33; 82.9)
RT + NS (n = 28; 83.9)
CG (n = 30; 84.5)
RT: elastic band, 2×/wk, ~60’, 1st 4wks: 1×15 rep, yellow Thera-Band®; other wks: intensity ↑ from yellow–red–black, 2×15 rep

24 All interventions: ↑ IGF-1 (P<0.05 vs. CG)

Santos et al., 2010 (Brazil)
RT (n = 26; 68.52 ± 4.68)
CG (n = 26; 67.52 ± 7.34)
3×/wk, 50’, free weights, 3×8 rep, 75–85% 1RM, OMNI-RES scale 7.82 ± 2.52

12 RT ↑ IGF-1 pre- to post-test (P=0.028) and when compared to CG (P=0.045)

Vale et al., 2017 (Brazil)
RT Land (n = 10; 66.10 ± 2.77)
RT Water (n = 10; 67.10 ± 3.54)
CG (n = 10; 68.80 ± 5.41)
RT: 3×/wk, ~50’, 1st 4wks: OMNI-RES scale 3 to 5 (light to middle intensity); other wks: 5 to 8 (strong intensity); RT Land: machines, 1st 4wks: 3×15 rep, 50% 1RM; other wks: 3×8–10 rep, 75–85% 1RM; RT Water: pool, 1st 4wks: 3×15–20 rep no AC, other wks: 3×8–10 rep with AC, 75–85% 1RM

12 IGF-1 ↑ RT Land (P=0.004) pre- to post-test and when compared to RT Water (P=0.002) and CG (P=0.0001)

n: sample size; yrs: years; RT: resistance training; AT: aerobic training; CE: combined exercise; CG: control group; TKD: taekwondo; 1RM: one repetition maximum; wk: week; wks: weeks; *: minutes; ~: approximately; reps: repetitions; HRmax: maximum heart rate; HRR: heart rate reserve; AC: aquatic accessories; IGF-1: insulin-like growth factor 1; SS: single-set; MS: multiple-sets; NS: nutritional supplementation; ↑: increase

Tables 2 and 3 presents the studies’ methodological quality and the risk of bias through the Jadad scale and the Cochrane collaboration tool, respectively.

Table 2. Methodological Quality of the Included Studies through the Jadad Scale.

<table>
<thead>
<tr>
<th>Studies</th>
<th>1a</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
<th>3</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banitalebi et al. (4)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cho &amp; Roh (15)</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cunha et al. (16)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ha &amp; Son (22)</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hofmann et al. (23)</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Santos et al. (41)</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vale et al. (46)</td>
<td>1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1a: randomized study; 1b: adequate randomization; 2a: double-blind study; 2b: proper blinding; 3: description of the sample loss
Table 3. Risk of Bias Analysis through the Cochrane Collaboration Tool.

<table>
<thead>
<tr>
<th>Studies</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banitalebi et al.</td>
<td>Low</td>
<td>Uncertain</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Uncertain</td>
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<tr>
<td>Cho &amp; Roh</td>
<td>Low</td>
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<td>Low</td>
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<td>Low</td>
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<td>Low</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

1: Randomization; 2: Allocation of randomization; 3: Blinding of participants; 4: Blinding of the evaluators; 5: Incomplete outcomes; 6: Report on selective outcome; 7: Other sources of bias

DISCUSSION

The purpose of this systematic review was to evaluate the effects of chronic PE on IGF-1 serum levels in elderly women. The analysis of the seven controlled and randomized experiments (4,15,16,22,23,41,46) showed that the practice of PE at least twice a week for a period of three months or more improves the IGF-1 levels of older women (P<0.05). However, the findings of these RCTs should be interpreted with caution, especially since they were classified with a high risk of bias. The full-text of six RCTs included in the present review was written in English and one was in Portuguese (41). Although we did not use any time filter, the years of the publications varied from 2010 to 2019.

Concerning the interventions, six studies used resistance training (RT). Four studies used traditional weight machines and/or free weights (4,16,41,46). The other two used elastic bands as resistance (22,23). However, only one (23) described the brand of the accessory. The other just mentioned the intensity related colors. Additionally, one of these studies (46) performed the RT in water, adding aquatic accessories after 4 wks of training. Combined with RT, Banitalebi et al. (4) submitted the sample to aerobic training, alternating the order of the training in the three intervention groups. Similarly, Ha & Son (22) included aerobic training to the program in conjunct with the RT. On the other hand, none of the RCTs used exclusively aerobic exercises as an intervention. A RCT by Chen et al. (14) also investigated the influence of RT, aerobic training, or a combination of both training interventions in elderly men and women with sarcopenic obesity (65 to 75 yrs). After 8 wks of intervention, the blood IGF-1 concentration was significantly higher in the trained groups, especially in the RT group when compared to the CG.

Resistance training is a well-known ally for a healthy and functional life for elderly people (1). This type of training can improve physical performance and muscle quality even in very old institutionalized women (23). This is important because, as the years go by, there is a tendency to experience a decrease in lean muscle mass and strength, which can cause dependence even in the performance of trivial tasks of daily living (17,47). Moreover, women are most affected by these losses and their functional declines can be seen more severely during menopause when hormonal secretions start to reduce substantially (42). Hence, with
aging, mainly in women, there is a reduction in the growth hormone (GH) levels, which stimulates IGF-1 production (29). In this sense, PE may be a strategy to stimulate IGF-1 secretion, mainly because it presents, through RT, a high positive correlation with an increase in serum IGF-1 (33).

All the interventions with the resistance exercise of the RCTs analyzed in the present systematic review are in accordance with the American College of Sports Medicine guidelines for older adults (1), which includes a frequency of at least 2 d·wk⁻¹, intensity between moderate- (5 to 6) and vigorous- (7 to 8) on a scale of 0 to 10, and a progressive weight training program or weight-bearing calisthenics (8 to 10 exercises involving the major muscle groups of 8 to 12 repetitions for each exercise).

Age tends to negatively impact the strength and physical performance in elderly women. For healthy aging, the development of muscle strength should be prioritized (35). Muscle strength has a high correlation with IGF-1 (49) and can be increased through a resistance exercise program as occurred in the studies of Banitalebi et al. (4), Cunha et al. (16), Ha & Son (22), Hofmann et al. (23), Santos et al. (41), and Vale et al. (46). Likewise, Vale et al. (44) found significant (P<0.05) increases in both muscle strength and IGF-1 levels by performing high-intensity resistance exercise activities 3 times·wk⁻¹ for 12 wks in 12 sedentary elderly women when compared to an aerobic group (n=13) and a CG (n=10). Thus, RT may provoke anabolic effects in elderly individuals.

However, RT is not considered a motivational activity for every elderly woman. Therefore, other exercise modalities should be analyzed for this growing population. Only one RCT (15) used a combat sport as an intervention alternative. The women who practiced taekwondo achieved a significant increase in IGF-1 serum levels after 16 wks. As mentioned before, IGF-1 levels have been related to BMD. Higher BMD and the practice of physical activity tend to prevent osteoporosis, which is related to the risk of fractures and falls in older adults (7). Middle and high-impact combat sports can promote osteogenesis due to microfractures in bone tissue (6). Jati et al. (25) conducted an intervention with adapted capoeira in 28 postmenopausal women and measured BMD through dual-energy x-ray absorptiometry (DXA). The authors found improvement in BMD measures after 24 wks. This result may be associated with increases in IGF-1 levels since it has been related to BMD (36).

The interventions with aerobics exercises of the RCTs analyzed are also in accordance with the ACSM recommendations, which involves accumulate at least 30 or up to 60 (for greater benefit) min·d⁻¹ in bouts of at least 10 min each to total 150 to 300 min·wk⁻¹ for moderate-intensity activities, or at least 20 to 30 min·d⁻¹ or more of vigorous-intensity activities to total 75 to 150 min·wk⁻¹, an equivalent combination of moderate and vigorous activity. Still, according to ACSM, the type of exercise can be any modality that does not impose excessive orthopedic stress, such as walking, aquatic exercise, and/or a stationary cycle exercise (1).

**Limitations in this Study**

The present study has some limitations that should be highlighted. First, the search was conducted in three electronic databases. Although PubMed, Embase, and Cochrane index a large number of scientific journals worldwide, it may be that some articles published in other journals that address this issue were not included in this review. However, we performed a
manual search to mitigate this limitation. Furthermore, limitations in the analyses should also be observed. The methodological quality of the studies was low and, thus presented a high risk of bias while none RCT presented a low risk of bias. For that reason, the findings of the present review should be analyzed with caution. Another important point noted was the lack of investigations with other exercises as intervention, such as Pilates, which has become a popular modality in recent years, especially among older women (37). Therefore, more research should be conducted with more methodological control, more detailed description of the protocols that used different types of exercises.

CONCLUSIONS

Land resistance training appears to be the most effective intervention to improve IGF-1 levels in elderly women. However, further studies are needed with higher methodological quality to reduce the risk of bias, and with different periods of intervention. In addition, some variables such as sleep time and quality should be considered in future studies since total sleep deprivation or restriction can alter blood hormones, including IGF-1 (18). Furthermore, stress levels, anxiety, and/or the psychological state of the individuals should be analyzed (11,19,34).

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