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Physical exercise and the musculoskeletal system in young rats: a systematic review

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Abstract

Regular physical activity contributes to the prevention of chronic diseases, such as obesity, diabetes, and cardiovascular disease. However, the increasingly precocious entry of young people into competitive activities raises concern regarding the effects promoted on the musculoskeletal system during the growth phase. This systematic review addressed experimental studies using physical training protocols in young rats that analyzed the animals' bones and muscles. Searches were conducted based on the period between 2000 and 2020 in the SciELO, PubMed, LILACS, BVS, and Google Scholar databases. A predominance of male Wistar rats submitted to aerobic and strength training was observed. The positive effects of physical exercise on bone mineral density were highlighted, especially in trabecular bones. Based on the analyzed studies, the evaluation of the epiphyseal growth zone in young rats undergoing high-intensity physical training programs was put into perspective.

Keywords: rats, exercise, muscles, bones

INTRODUCTION

On account of the increasingly early entry of children and adolescents in sports-related activities, even while still in the growth phase, it is important

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that studies be carried out evaluating the impacts caused by physical training on the bones of these individuals. Therefore, this systematic review sought to investigate the scientific knowledge on the effects of high-intensity physical exercise on the musculoskeletal system of young rats.

Regular physical activity has been shown to promote several health benefits throughout life, from growth and development in children and adolescents to a better quality of life for the elderly, providing their independence[1]. According to Bull *et al.* (2020)[2], some of the beneficial effects provided by physical activity include improvements in serum levels of lipidemic and glucose biomarkers, blood pressure, body composition, bone density, and cardiorespiratory and musculoskeletal fitness. Considering the pediatric and hebiatric population, in particular, 60 minutes of daily physical activity with moderate to vigorous intensity is recommended, as well as vigorous muscle strength activities three times per week[2,3]. The World Health Organization (WHO)[4] published alarming data prior to the COVID-19 pandemic that revealed a high prevalence of sedentary lifestyles in the young population. Meanwhile, there were also reports regarding precocity in sports initiation. This fact has been evidenced more frequently in recent years with the entry of young individuals in sports aiming at achieving goals related to better results in competitions or tournaments[5].

Thus, it is imperative that studies be deepened concerning the effects of high-intensity physical exercise on the musculoskeletal tissue of animals for further understanding the changes that may arise in humans. Is what happens to bones and muscles when subjected to aerobic training and muscle strength protocols particularly important in the young age group because of their growth spurt? The scientific community has been discussing the human body's adaptations, especially regarding musculoskeletal tissue, in relation to the practice of physical exercise, as well as its duration and intensity, and the impacts on motor development in young individuals[6].

In face of the deadlock between the need to investigate the histomorphological effects of physical exercise on musculoskeletal tissue and the impossibility of carrying out such experiments on humans, animal models are then used, namely rodents, to understand such adaptations[7,8]. In this sense, the scientific literature has provided a variety of studies that not only detect changes in bone and muscle growth, but also suggest factors that might explain such changes in different types of physical exercise[9].

METHODS

The present systematic review was conducted based on the recommendations proposed by the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), as described by Galvão (2015)[10].

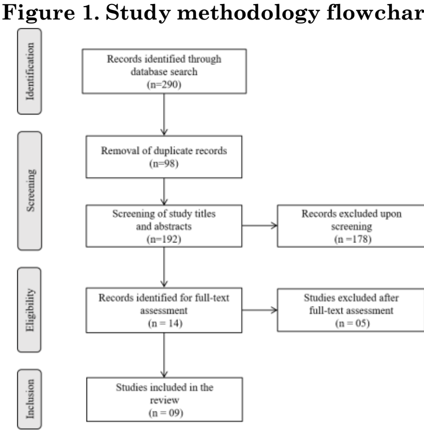
The first step of our analysis consisted of the selection of articles, in which a systematic search was carried out for studies considered to be potentially relevant, published between 2000 and 2020, and that are freely available in the full versions of the following databases: SciELO, the National Library of Medicine – the National Institutes of Health (PubMed), the Latin American Literature on Health Sciences (LILACS), the Virtual Health Library (BVS), and Google Scholar. The descriptors used in the databases were: "exercise(s)", "rats", "muscle(s)", and "bone(s)", all of which constitute descriptors in health sciences (DeCs) and Medical Subject Headings (MeSH). The Boolean operator "AND" was used for linking the cited terms. Duplicate studies were not accounted for, and review articles, editorials, expert opinions, case reports, and texts in languages other than English were excluded.

The Abstracts of the studies identified in the search were evaluated according to the aforementioned criteria; those that met the criteria or generated doubt were retained for further full-text analysis. Studies that did not meet the specifications for young rat models without pathologies or covered irrelevant topics for this investigation were excluded. Two reviewers took part in the search process independently. In case of disagreement, the final decision involved a third reviewer.

RESULTS

The systematic review process, which was conducted according to PRISMA criteria[10], is detailed in Figure 1. Methodological differences were observed regarding the used physical training protocols in 12 of the analyzed articles, and included weekly frequency, number of series, and type of physical activity.

Figure 1. Study methodology flowchart.



Therefore, due to such methodological diversity, it was impossible to carry out a meta-analysis based on the results obtained in the selected studies, which are described in Table 1.

Table 1 - Analysis of the selected articles.

AUTHORS	**ANIMALS**	**PHYSICAL TRAINING**	**BONE ANALYSIS**	**MUSCLE ANALYSIS**
OZAKI *et al.*[23]	40 Wistar rats, 21 weeks old.	Aerobic training in water and on a treadmill, resistance training in water and on a treadmill. Duration: 4 weeks, 3 times a week.	-	HIS- Hypertrophy of the soleus muscle: resistance training; Hypertrophy of the extensor digitorum longus muscle: resistance training by climbing and aerobic swimming.
SPAGNOL *et al.*[24]	15 male Wistar rats, 90 days old.	Resistance and strength training in water. Duration: 8 weeks, 3 times a week for 30 minutes.	-	HIS- Hypertrophy of the soleus muscle fibers.
NEBOT *et al.*[14]	20 male Wistar rats, 5 weeks old.	Strength training: motorized treadmill with weights in a bag tied with a rope to the tail. Duration: 12 weeks.	pQCT; µCT- Beneficial effect on cancellous bone microarchitecture. Association with hypogonadism.	-
IWAMOTO *et al.*[15]	20 female Wistar rats, 6 weeks old.	Treadmill running. Frequency: 5 times a week with gradual increase in speed.	DXA- Increased tibial and femoral bone mass with stimulation of longitudinal bone growth.	WE- The weight of the gastrocnemius muscle lacked statistical significance in the two training protocols.
LIU Z, GAO J, GONG H.[16]	48 male Sprague-Dawley rats, 5 months old.	Treadmill running. Frequency: 5 times a week for 4 weeks, 30 minutes/day.	µCT- Microarchitectural analysis of the left femur revealed an increase in bone mass with 12-min exercise.	TT- Mechanical properties of the soleus muscle were increased after exercise and treadmill.
BOTT *et al.*[17]	19 male Sprague-Dawley rats. Between 51-53 days old.	Treadmill running with 10% inclination and gradual increase in speed (from 18 m/min for 30 min to 25 m/min for 1h). Frequency: 7 times a week for 8 weeks.	µCT; DXA- Analysis showed that endurance running resulted in superior bone structure in the proximal tibia compared to the control group.	-
HAMANN *et al.*[18]	36 female Sprague-Dawley rats, 6 weeks old.	Running on a level treadmill and a 20º slope. Frequency: 5 days a week, 30 minutes/day, divided into 2 times per day (morning and afternoon), for 6 weeks.	pQCT; µCT; HIS- Increased trabecular bone mineral density in the femoral metaphysis. Superior osteogenic stimulus in the femoral epiphysis.	-
HUANG *et al.*[28]	32 male Wistar rats, 7 weeks old.	Running on a treadmill. Frequency: 5 days a week for 8 weeks. Daily training time with a gradual increase from 20 to 60 min.	DXA- There was no significant difference in bone mineral content and bone mineral density among the trained groups, although some animals showed improvements in bone	-

			mass.	
FLUCKEY *et al.*[25]	14 male Sprague-Dawley rats, 6 months old.	Resistance training with suspended tail. Duration: 11 exercise sessions over 4 weeks (2 sets of maximum 25 reps, 3 days a week).	DXA- Greater bone mass in the trained group. The cortical area of the femur was not different in the two groups.	IN VITRO - The loss of muscle mass in the soleus muscle was attenuated and protein synthesis maintained. The extensor digitorum longus muscle showed no differences.

HIS: histomorphometric analysis; µCT: computed microtomography; pQCT: quantitative computed tomography; DXA: dual energy x-ray absorptiometry; WE: weighing; TT: Traction test; IN VITRO: *in vitro* analysis.

DISCUSSION

The Wistar lineage was the most used animal model in the studies analyzed herein. This strain of rats was created at the beginning of the 20th century (1909) in the state of Philadelphia (USA)[7] and became very common among biomedical researchers, in addition to Sprague-Dawley rats. These animals are among the most used rodents in experimental studies due to their biological similarities with humans. Female rats reach sexual maturity early and have irregular reproductive cycles[8]. The greater use of male animals can be explained by the lower hormonal influence on the results, which may justify the preference for males in the majority of studies. According to the analyzed articles, the mean age of rats that began training protocols was 83.4 days, which characterizes the young adult rat[8].

Among the selected studies, the training protocols ranged from 4 to 12 weeks, and aerobic exercises were predominant in relation to resistance exercises. According to Hughes *et al.* (2018)[11], endurance training (aerobics) is generally practiced for an extended period of time with a moderately low load. The changes caused as a result of this type of exercise promote greater resistance to metabolic fatigue due to increased mitochondrial biogenesis and capillary density. On the other hand, strength training is performed with a high load for a shorter time period. The results obtained in the strength exercises evidence an increase in the capacity to produce strength and in muscle mass[12].

The positive effects of exercise on bones can be explained by the influence of mechanical stress on the maintenance of bone mass and strength[13]. Several studies have shown beneficial effects of aerobic and resistance training protocols on bone mineral density, particularly in the cancellous bone of long bones, such as the femur and tibia[14,15,16,17,18]. Only one of the selected studies did not present significant results regarding the resistance training protocol in increasing bone mass when compared to the sedentary control group. However, in that study, the animals were submitted to a physical training model with a long period of tail suspension, known as Flywheel.

In two of the studies, the researchers analyzed the mandible and spinal vertebrae. According to the study by Bott *et al.* (2016)[17], lower jaw volume was evidenced in the group trained using a load on the treadmill compared to the control group, postulating that there was less chewing and lower food intake than the sedentary group. Meanwhile, in the study by Iwamoto *et al.* (2004)[15], who analyzed the bone mineral density of long bones and lumbar vertebrae, no significant difference was observed between the trained and control groups. In 2010, Bouxsein *et al.*[19] published a proposal for systematization for the assessment of bone microstructure in rodents by way of computerized microtomography. Their study emphasizes the need to standardize terminologies and units, as well as the manner in which the histomorphometry technique is performed. Such systematization would enable the standardized analyses of different studies. In the present review, the technique mostly used by the authors to assess bone density was microtomography. Although the description of the results was not detailed as suggested by Bouxsein (2010)[19], the tomographic images were able to evidence the results described by the authors[14,18].

As for the analysis of muscle tissue, five studies evaluated the following muscles: extensor digitorum longus, soleus, and gastrocnemius, with the soleus muscle being addressed in four of the five studies. These three muscles are found in the animals' hind legs, with the soleus and gastrocnemius located posteriorly and the extensor digitorum longus muscle anteriorly. The soleus and gastrocnemius muscles are mainly composed of slow oxidative and fast oxidative-glycolytic fibers, respectively, and are widely used in aerobic resistance exercises and posture maintenance[20,21]. The gastrocnemius muscle is responsible for the prominence of the calf, while the soleus is essential for ankle flexion in humans. In addition to the extension of the toes, the extensor digitorum longus muscle also mediates foot dorsiflexion[22].

Considering muscle hypertrophy, the types of exercises to which the animals were submitted interfered with the described results, which differed according to exercise modality: level treadmill, swimming, climbing, jumping in water with weight, and tail suspension. In the study by Ozaki *et al.* (2018)[23], the training protocol used involved climbing with a weight load. According to the authors, the obtained results were compared with resistance training and aerobic exercise, with hypertrophy being observed in all protocols. When analyzing the soleus muscle, aerobic training by swimming generated greater hypertrophy than aerobic training on a treadmill. Meanwhile, resistance training by climbing was more efficient in promoting hypertrophy than resistance training in water. In the extensor digitorum longus muscle, resistance training in water led to greater hypertrophy when compared to resistance training by climbing. In the study by Spagnol *et al.*

(2012)[24], the authors used the concurrent training method, which involved aerobic swimming and weight-loaded swimming exercises. According to their findings, an increase in soleus muscle fibers was noted.

In the two aforementioned studies, muscle histomorphometry analysis was conducted, both using n-hexane solution and freezing in nitrogen. Five-millimeter sections were made using a cryostat microtome, and the slides were stained with hematoxylin-eosin (HE). After staining, the sections were observed under a microscope and photomicrographed. In both studies, there was an increase in the cross-section of the muscle, *i.e.*, muscle hypertrophy occurred with all training methods used.

The study by Iwamoto *et al.* (2004)[15] did not present significant results regarding the weight of the gastrocnemius muscle among the evaluated groups. Meanwhile, Liu *et al.* (2019)[16] conducted a traction test on the soleus muscle, which was prepared with saline solution to keep the muscle moist. When performing the test, the researchers used a speed of 2 mm/min until the muscle ruptured. Even without significant results among groups, the exercise group that sustained a speed of 12 m/min (EX12) presented maximum load and minimum final displacement in the traction test, evidencing that adequate intensity is relevant for the mechanical properties of the muscle. In the study by Fluckey *et al.* (2002)[25], an *in vitro* evaluation of muscle protein synthesis using muscle strips in cold (non-radioactive) and radiolabeled phenylalanine solution was carried out. This procedure was performed both on the soleus muscle and the extensor digitorum longus muscle. Their results showed that resistance training in the proposed model attenuates soleus muscle atrophy and maintains muscle protein synthesis. However, no effect was found on muscle mass and protein synthesis in the extensor digitorum longus muscle. The authors used this muscle as a control in performing the flywheel exercise.

As for the evidence of changes in bone tissue with physical exercise, it is important to mention the histological parameters of this tissue. Bone tissue is in constant renewal, with resorption and bone formation occurring simultaneously due to enzymes and enzymatic cofactors. Hydroxylase enzymes participate in the activation of Vitamin D, and micronutrients are part of the composition of the mineralized extracellular matrix. Elements such as calcium, phosphorus, magnesium, potassium, boron, selenium, zinc, and iron are considerably relevant to bone health[26].

Regarding the analysis of these elements in the bone matrix, three studies were identified in this literature review. In Nebot *et al.* (2017)[14], the authors performed biochemical analyses in blood and urine samples obtained from Wistar rats. They also assessed the calcium (Ca), magnesium (Mg), and zinc (Zn) content in their bones and the Ca content in their feces. As a result, it was identified that plasma concentrations of Ca and testosterone were lower in the group of trained animals when compared to the sedentary group (14% and 65%, respectively). Glucocorticoids induce a sex hormone deficiency and alter vitamin D metabolism, which might explain the influence on bone modeling, with effects on growth and skeletal integrity[27].

According to the study by Huang *et al.* (2008)[28], blood samples collected for the measurement of alkaline phosphatase (ALP), calcium, and phosphorus showed no significant differences among the three trained groups. Bone remodeling markers, important indicators of gain or loss of bone mass, and intact serum osteocalcin and bone alkaline phosphatase better represent the bone formation process, while pyridinolines and carboxy and amino-terminal telopeptide fragments of type I collagen better reflect bone resorption[29]. Nebot *et al.* (2017)[14] analyzed specific markers of bone remodeling and noted a reduction in osteocalcin, C-terminal telopeptides of type I collagen, tartrate-resistant acid phosphatase, and amino-terminal propeptides of type I procollagen.

In the study by Huang *et al.* (2008)[28], bone remodeling activity was also measured through the serum carboxy-terminal propeptide of type I procollagen (PICP) and the carboxy-terminal cross-linked telopeptide of type I collagen (ICTP). The ratio between PICP and ICTP (PICP / ICTP ratio) served as an index of bone ratio in training activity and was numerically higher in the running and intermittent resistance group ($P = 0.078$) in the study by Huang[28] . Since type I collagen is a constituent of the bone matrix, both its degradation products and its precursors, such as type I procollagen, can be sensitive markers to changes in bone metabolism[30].

Finally, in the study by Iwamoto *et al.* (2004)[15], the authors measured bone markers and calciotropic hormones in the urine and blood of Wistar rats after completing an exercise regimen. Following seven weeks of physical exercise, there was a decrease in urinary deoxypyridinoline levels, and after eleven weeks, an increase in serum alkaline phosphatase levels was observed, with a reduction in serum tartrate-resistant acid phosphatase. Deoxyridinoline is a constituent of collagen that acts in intermolecular cross-links and joining collagen chains that form bone tissue[31]. After seven and eleven weeks of physical exercise, an increase in serum levels of osteocalcin and 1,25-dihydroxyvitamin D3 was observed, with a decrease in PTH. It is well-known that exercise promotes a positive calcium balance and increases skeletal mass, largely due to increased 1,25-dihydroxyvitamin D3 levels and intestinal calcium absorption in rats[15]. In the study by Nebot *et al.* (2017)[14], there was an increment in serum corticosteroid levels and a decrease in testosterone. Since glucocorticoids induce a sex hormone deficiency and alter vitamin D metabolism, this may explain the influence on bone modeling, affecting growth and skeletal integrity[27].

CONCLUSION

In this literature review, it was possible to verify that the analyzed studies used distinct training protocols and different types of physical exercise. Bone and muscle analyses did not always occur simultaneously in the selected articles. Therefore, it was impossible to conduct a meta-analysis. The main results found included an increase in bone mineral density in the cancellous bone of long bones and higher serum levels of 1,25-dihydroxyvitamin D3 in the groups of trained animals as compared to the sedentary ones.

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