Disciplinarum Scientia. Série: Naturais e Tecnológicas, Santa Maria, v. 20, n. 3, p. 313-323, 2019.
Recebido em: 09.09.2019. Aprovado em: 04.11.2019.

ISSN 2176-462X

THE INTERACTION BETWEEN PHYSICAL EXERCISE AND NANOSCIENCE: A SYSTEMATIC REVIEW[1]

A INTERAÇÃO ENTRE EXERCÍCIO FÍSICO E NANOCIÊNCIA: UMA REVISÃO SISTEMÁTICA

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ABSTRACT

While the potential of nanoparticles in medicine has been widely explored, what do we know about their association with physical exercises? The aim of this study is to conduct a systematic review assessing the potential interaction between physical exercise and nanoparticles. This review was done in June 2019 on the Scielo, Medline, Pubmed, and Scopus databases, using the descriptors "exercise" and "nanoparticles." No articles were found on the Scielo database. The search on Medline, Pubmed and Scopus returned 38, 98 and 168 references, respectively. After assessing the title, abstract and descriptors, duplicate references were excluded as well as studies that did not have the exercise or nanoparticles as variables. After screening, 28 studies were included in this review. Our results show that there is a positive correlation between nanoparticles, specially those with antioxidant properties, and physical exercise, in different studies conducted around the world. However, there is little bibliography on the subject to affirm that a nanostructure is more efficient than the other. In addition, further studies should be conducted on physical exercise and nanoparticles.

Keywords: Nanoparticles, Physical Activity, Health.

RESUMO

Embora o potencial das nanopartículas na medicina tenha sido amplamente explorado, o que sabemos sobre sua associação com exercícios físicos? O objetivo deste estudo é realizar uma revisão sistemática, avaliando a potencial interação entre exercício físico e as nanopartículas. Esta revisão foi realizada em junho de 2019 nas bases de dados Scielo, Medline, Pubmed e Scopus, utilizando os descritores "exercício" e "nanopartículas". Nenhum artigo foi encontrado na base de dados Scielo. Na pesquisa no Medline, Pubmed e Scopus retornaram 38, 98 e 168 referências, respectivamente. Após avaliação do título, resumo e descritores, foram excluídas referências duplicadas e estudos que não apresentavam o exercício ou nanopartículas como variáveis estudadas. Após a triagem, 28 estudos foram incluídos nesta revisão. Nossos resultados mostram que existe uma correlação positiva entre nanopartículas, especialmente aquelas com propriedades antioxidants, e exercício físico, em diferentes estudos realizados em todo o mundo. No entanto, há pouca bibliografia sobre o assunto para afirmar que uma nanoestrutura é mais eficiente que a outra. Além disso, novos estudos devem ser realizados relacionados ao exercício físico e nanopartículas.

Palavras-chave: *Nanopartículas, Atividade Física, Saúde.*

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INTRODUTION

It is already established that the practice of physical activity is an ally for improving health and quality of life. The benefits of exercise come from different factors, which can be physical, social and mental (MATSUDO, 1999; MACEDO, 2003). These benefits are the result of a series of reactions. To perform physical exercises, the body needs energy, and in order to get this energy, metabolism causes different physiological adaptations. Physical exercises have two sides (positive and negative) for the human body. Low intense physical exercises generate a small amount of oxygen-reactive species, but, intense physical exercise can generate a large amount of reactive oxygen species that can cause muscle damage induced by mechanical stress resulting in an increase in the circulation of free radicals (HALLIWEL; GUTTERIDGE, 1989; HALLIWEL, 2001). Different studies are being conducted to try to minimize these deleterious effects of exercise (MATSUDO, 1999; MACEDO, 2003).

One way to minimize the deleterious effects of physical exercise is with antioxidant supplementation. Antioxidants are substances capable of minimizing, inhibiting or delaying the oxidation of a substrate (HALLIWEL, 1990). Bioactive with antioxidant properties can prevent or minimize the damage caused by intense physical exercise, improving recovery after exercise, thus reducing the circulation of oxygen-reactive species (HALLIWEL; GUTTERIDGE, 1989; HALLIWEL, 2001).

In this sense, studies have shown that the use of compounds with antioxidant activity can minimize the negative effects of physical exercise (BLOOMER, GOLDFARB, 2004; RISTOW, 2009; DE SOUSA, 2017). However, many of these compounds have low bioavailability and low water solubility, which makes their applications in clinical trials difficult. Therefore, a way to cope with these challenges is to incorporate the assets into nanoparticles (MUSSOI *et al.*, 2017; NISHIHIRA *et al.*, 2019).

With these evidences in mind, the association between nanoparticles and exercise is a promising field to be explored by researchers. Among the challenges to assess this association are: i) choosing the most appropriate antioxidant, ii) choosing the nanostructure that best delivers bioactive compounds to target cells, iii) choosing the best techniques to evaluate the effect of nanoparticle on exercise compared to sedentary lifestyle, and finally, iv) it is a large area of research to be explored. Thus, the aim of this systematic review was to verify on the databases what is the current evidence regarding the interaction between physical activity and nanoparticles, and which are the main nanostructures used.

MATERIAL AND METHODS

To carry out this study, different databases such as Medline, Scielo, Pubmed and Scopus were acessed. The authors understand that these are the main health-related databases. The descriptors “exercise” and “nanoparticles” were used regardless of the time of publication. Articles in Portuguese, English, and Spanish were included. Articles that did not present physical activity as a study variable

or that did not present the interaction of physical exercise with any nanoparticles, as well as duplicate references were excluded from this review.

RESULTS AND DISCUSION

Articles with the most varied nanoparticles interactions were found, however, physical activity was always present as the main study variable. On the Medline database 38 references were found and after applying the inclusion and exclusion criteria, only 08 articles were included. No relevant references were found on the Scielo database. On the Pubmed database 98 articles were initially found and after applying the inclusion and exclusion criteria, only 07 references were included in this review. We found the largest number as references on the Scopus database, with 168 initial references, from which after applying the inclusion and exclusion criteria 14 references were included in this review. Thus, overall 304 articles were initially found and after applying the inclusion and exclusion criteria, 28 references were included in this review.

Of these 28 included references, the first publication is from 2007, with peak production in the subject in the years 2017 and 2018 (according to table 01). The included references were conducted in different countries such as Brazil, China, Iran, Japan and the United States, demonstrating a diversity of laboratories working on the subject.

Table 01 - Statement of publications extracted by year

Year of publication	Number of study
2007	01
2009	01
2010	03
2011	01
2013	03
2014	02
2016	02
2017	07
2018	07
2019	01

Font: Author creation

The included references were divided into categories following the type of nanoparticles or nanostructures presented in each study.

ACETONE

Only one study addressed this nanoparticle, due to the lack of appropriate biomedical sensors to monitor the rates of corporal fat burning and to guide physical activities or dietary interventions for

efficient weight loss, this study developed a sensor based on acetone nanoparticles. During exercise, the sensor revealed the progression of acetone levels that indicate an increase in corporal fat oxidation. This process was pronounced during the fasting period of 3h after exercise. This acetone sensor facilitates the monitoring of body fat burning as it is portable and provides immediate and personalized feedback on treatment effectiveness (GÜNTNER *et al.*, 2017).

POLYLACTIDE

Nanoparticles provide a promising perspective for tumor therapy, and the practice of physical activity is also becoming accepted as a beneficial adjunct therapy for maintaining or improving the quality of life in cancer patients. The study investigated the antitumor efficacy of paclitaxel-loaded polylactide/poly (ethylene glycol) in physically active subjects. All the phagocytosis rates of macrophages were significantly decreased and there was an increase of paclitaxel. The results indicated a significant antitumor effect in the nanoparticles and the exercise group. Physical activities can further increase their therapeutic efficiency (ZHANG *et al.*, 2013).

SELENIUM

Among all researched articles, there was a small predominance of selenium nanoparticles correlated with physical activity, there were 5 articles addressing this relationship. One study investigated the effects of interval aerobic training and the antioxidant effect with selenium nanoparticle (Se-n) supplementation on interleukins and inflammatory cytokines in mice with breast cancer. Interval aerobic training increased anti-inflammatory (TNfα) and interleukin levels (IL10 and IL15). The combination of physical training and supplementation prevented cachexia, loss of muscle mass, and it decreased the volume of the tumors. These findings suggest that combining physical training and supplementation with antioxidants may be a strategy for tumor volume control and cachexia prevention (MOLANOURI SHAMSI, M. *et al.*, 2017). Also, another study examined the effects of aerobic interval training and Se-n supplementation on protein expression of cytokines in liver tissue in mice with breast cancer. A simultaneous use of selenium nanoparticles and training may help reduce tumor volume and modulate cytokine levels in the liver. This study findings suggests that the combination of exercise and selenium affects the antitumor immune response in splenocytes and it induces antitumor cytokines such as oncostatin (OSM) and TNF-α in tumor tissue (MOLANOURI SHAMSI, MAHDIEH *et al.*, 2019).

Both studies addressed mice with breast cancer, unlike the studies by Kojouri (2013) and Kojouri and Sharifi (2013) which deal with donkeys and the correlation of selenium and physical activity. The results showed that the HSP90 gene expression and blood selenium concentration increased significantly. This finding may explain the beneficial role of short-term oral supplementation

with donkeys in cell stability under stressful conditions such as intense exercise (KOJOURI *et al.*, 2013). Another study determined the effects of oral administration of Se-n on blood urea nitrogen (BUN), creatinine and total protein concentrations during intense donkey physical activity. These findings may explain the positive effects of Se-n supplementation on serum BUN and creatinine changes in response to intense exercise physical (KOJOURI; SHARIFI, 2013).

IRON OXIDE

The search regarding the iron oxide nanoparticle and iron resulted in two references. The aim of the included studies was to investigate the effect of concurrent aerobic exercise and iron oxide nanoparticles on liver enzymes and liver histological appearance. Histological examination of the liver showed that in the nanoparticle only and nanoparticle and exercise groups, liver cells were damaged and congestion, inflammation, mononuclear cell infiltration, and balloon degeneration occurred. Tissue injuries in the nanoparticle and exercise group were minor. These findings indicate that hepatotoxicity was caused by iron oxide nanoparticles. However, low-intensity aerobic exercise can decrease the damage (VASILI *et al.*, 2016). Results from another study demonstrated that humans have different responses when exposed to nanoparticles forming unique biomolecule coatings and that exercise influences biomolecule interactions (KOBOS *et al.*, 2018)introduced into a biological environment, accumulate a coating of biomolecules or biocorona (BC.

LIPIDS

The aim of this study was to evaluate the effects of resistance training on the metabolism of a low density lipoprotein (LDL) nanoemulsion and on lipid transfer to HDL, an important step in HDL metabolism. This study was conducted in human subjects, under a regular resistance training for a minimum period of 1 year and maximum of 4 years. The training program consisted of 3-4 sets of 8-12 repetitions maximum with 3-4 exercises for each muscle group. Exercise accelerated the clearance of LDL-type nanoemulsion and reduced oxidized LDL levels and changed the balance of free and esterified cholesterol. However, exercise had no effect on parameters related to HDL metabolism (DA SILVA *et al.*, 2011).

In another study, training increases plasma LDL clearance, as tested by an artificial LDL-like nanoemulsion method, presumably increasing the LDL receptor activity. The study, investigated whether training could also improve LDL clearance in hypercholesterolemic individuals who are exposed to increased risk of cardiovascular events. Physical training increased LDL removal, as tested by nanoemulsion, and this probably represented a decreased LDL cholesterol and a decreased LDL susceptibility to oxidation (FICKER *et al.*, 2010).

Another study related to lipids aimed to evaluate the effects of physical training on plasma removal of a cholesterol-rich nanoemulsion (LDE) that mimics the lipid structure of LDL and binds to LDL receptors. These results show that physical training increases LDE plasma removal, which in turn suggests that it also increases LDL receptors or LDL receptor activity (VINAGRE *et al.*, 2007).

MITOXANTRONE

The first study investigated the effect of exercise on breast cancer inhibition. Significantly longer tumor growth retardation was seen in the exercise+DHAQ groups (WEN *et al.,* 2017). Another research regarding the synthesis of modification of the Arginine-Glycine-Asparti (RGD) peptide copolymer: poly (lactic-co-L-lysine) (PLA-PLL-RGD) and the preparation of mitoxantrone-loaded PLA-PLL (DHAQ). -RGD nanoparticles (DHAQ-NP), and the evaluation of the antitumor efficacy of exercise and DHAQ-NP in hepatoma and breast carcinoma suggests that the same intensity of exercise may cause different antitumor efficiencies for different tumors undergoing targeted therapies (LIU *et al.*, 2009).

Another study by the same author describes the synthesis of modification of Arginine-Glycine-Aspartic (RGD) peptide modification of copolymer: poly (lactic-co-L-lysine) (PLA-PLL-RGD) and preparation of PLA-PLL with mitoxantrone (DHAQ) -RGD nanoparticles (DHAQ-NP) and addressed the effects of exercise on the antitumor efficacy of DHAQ-NP in hepatocellular carcinoma suggesting that exercise cannot significantly influence the antitumor efficacy of DHAQ-NP (LIU *et al.,* 2008).

COPPER

The research sees low dimensions of copper nanoparticles and physical training prevent myocardial infarction through preconditioning GSK-3β phosphorylation. The ability to increase no level, lipid profile and reduced oxidative stress improve the potency of the combined strategy (SHARMA; KUMAR; SAHU *et al.*, 2018). Another study by the same authors focused on the therapeutic potential of copper nanoparticle (CuNP) and physical training through its molecular interaction with GSK-3β, an inflammatory cytokine, oxidative stress, and necrosis. A significant reduction in oxidative stress and inflammatory mediators was observed in the CuNP and training group in addition to bioavailability. CuNP treatment and physical training alone or in combination favorably phosphorylate the GSK-3β kinase pathways and further decrease oxidative stress, inflammatory cytokines, apoptosis, and increase bioavailability which tends to protect myocardial damage (SHARMA; KUMAR; TANEJA *et al.*, 2018).

CURCUMIN

Three included studies used this particular delivery method. One study found significant cardiac modulation, metabolic damage, cardiac injury, and bioenergetics in rats receiving both nanocurcumin supplementation and treadmill pre-conditioning compared to rats receiving only one of the treatments. This strategy showed an improvement in cardiac acclimatization compared to exercise preconditioning or nanocurcumin supplementation, which was evident from the effective modulation in homeostasis, metabolic, contractile and bioenergetic (NEHRA *et al.*, 2017).

A different study aimed to investigate the effect of six-week aerobic exercise with moderate intensity and nanocurcumin consumption on TNF-α and memory in women aged 60 to 65 years with metabolic syndrome. After eight-week interventions, TNF-α significantly decreased and memory recall significantly increased in all treated groups. These changes were significantly greater in the Exercise + Curcumin group (OSALI, 2018).

Another study aimed to investigate the interactive effects of two forced treadmill running and voluntary running techniques and the supplementation of nanocurcumin in liver damage. The findings suggest that the implementation of these training methods supplemented with nanocurcumin partially mitigates the side effects of doxorubicin, but this level of intervention is not sufficient to protect against doxorubicin-induced hepatotoxicity in older model rats (SADAT-HOSEINI, 2017).

VENLAFAXIN

The aim of the study was to investigate the potential of venlafaxine-loaded alginate nanoparticles for the treatment of intranasal depression. The treatment significantly improved the behavioral analysis parameters (swimming, climbing, and immobility) compared to the non-nanoparticle and non-exercise group. In addition, this study also demonstrated the higher transmission capacity of nanoparticles compared to free (HAQUE *et al.,* 2014).

RNA

One included study aimed to evaluate the levels of circulating extracellular vesicles (EVs) and the selected micro RNA (miR) content within them in response to exercise. The study concluded that mild to moderate exercise-induced muscle injury altered the miR-31 profile of circulating EVs in the first 24 hours after exercise. These data demonstrate that EVs carry selectively packaged loads that may be affected by exercise (LOVETT; DURCAN; MYBURGH, 2018).

Another included study investigated whether exercise could increase the levels of circulating endothelial progenitor cell-derived exosomes and their miR-126 load, and why they promote protective

function. The conclusion of the study was that exercise can increase the release of exosomes and thus promote protection from injuries (MA *et al.*, 2018).

OXIDE CERIUM

A synthetic, inorganic, antioxidant nanomaterial, 'Cerium oxide nanozyme' (CON) was used. Higher physiological resistance was observed in the exercised muscle supplemented with CON. Increased muscle mass, glycogen, and ATP content, the ratio of type I fibers were found, resulting in significantly higher muscle endurance and an increase in the number and size of mitochondria, higher levels of oxidative phosphorylation and glycolysis (ARYA *et al.,* 2017).

MAGNESIUM OXIDE

There were no significant differences between the analgesic effect of exercise alone and Magnesium Oxide (MgO) or nanopartículas de magnesium oxide (MgONPs) with exercise. The analgesic effects of physical activity and MgO supplements are probably induced by common mechanisms in the central nervous system (ZAMANEH, *et al.,* 2017).

HYDROXYAPATITE

Hydroxyapatite (HAp) is an alkaline inorganic material with good biocompatibility. Slowly degrades in vivo and releases traces of calcium ions. It reduces cell damage by reacting with polylactic acid and neutralizes acid medium. It can significantly prolong swimming time and improve serum LDH activity, but it does not affect latic acid concentration. In conclusion, intravenous injection of hydroxyapatite nanoparticles can significantly improve the exhaustive swimming capacity of mice, mainly because of the high HAp-induced blood LDH activity (HU; HU; ZHANG, 2014).

CONCLUSION

Thus, it is concluded that there is a variety of studies on nanoparticles with the exercise variable, which proves it to be a growing area. However, many studies deal with nanoparticles, not showing a nanoparticle of greater interest, but the nanostructures with antioxidant properties of interest to this research do stand out. Therefore, further studies involving nanoparticles and exercise to prove the positive interaction between these variables are of fundamental importance.

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