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Onde está a abordagem farmacológica no tratamento da obesidade infantil? Uma breve revisão

Where are the pharmacological approach withexercise-training in childhood obesity? A brief review

¿Dónde está el enfoque farmacológico eneltratamiento de laobesidad infantil? Una breve revisión

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Resumo

O treinamento físico emergiu como uma ferramenta não farmacológica promissora para a melhoria da composição corporal de uma grande variedade de populações clínicas, incluindo idosos, pacientes com doenças crônicas e crianças com obesidade. É importante destacar a obesidade infantil (CO) como uma preocupação de saúde pública que deve ser atenuada para um melhor crescimento e desenvolvimento da criança. Embora existam vários modelos de treinamento, o ganho particular entre todos é a melhora metabólica que contribui para o aumento da massa muscular e a perda de gordura. Por outro lado, existem vários medicamentos envolvidos no tratamento da obesidade, atuando em caminhos semelhantes relacionados ao treinamento físico para o tratamento da CO. Isso provoca uma questão crucial: considerando o exercício que apenas o exercício e os medicamentos poderiam tratar CO, devemos avaliar a segurança e / ou os efeitos da abordagem farmacológica com o exercício para potencializar o tratamento de CO? Sob essa perspectiva, o objetivo deste estudo foi revisar os efeitos da interação entre medicamentos e treinamento com exercícios no CO e fornecer informações importantes para a adesão dos medicamentos ao exercício nessa população. Trata-se de uma revisão narrativa de caráter descritivo acerca do efeito do exercício e medicamentos na CO. Com base na literatura atual, sugere-se que os medicamentos para exercícios e obesidade apresentem caminhos semelhantes no tratamento de CO. Além disso, recomenda-se que futuros ensaios clínicos randomizados relatem e discutam o efeito do exercício mais medicamentos para obesidade no tratamento ou redução de CO.

Palavras-chave: Infância; Obesidade; Farmacologia; Exercício físico.

Abstract

Exercise-training has emerged as a promising non-pharmacological tool for the improvement of body composition for a plethora range of clinical populations including old people, patients

with chronic diseases and child with obesity. There is an importance to highlight childhood obesity (CO) as a public health concern that must be attenuated for a better growth and development of the child. Although there are a number of training models, the particular gain among all of them is the metabolic improvement which contribute for muscle mass increase and fat loss. On the other hand, there are a number of medications which are involved in the treatment of obesity, acting in similar pathways related to exercise-training used to treat CO. This provoke a crucial question: given the regard that exercise and medications alone could treat CO, should we evaluate safety and / or the effects of pharmacological approach with exercise to potentiate the treatment of CO? From this perspective, the aim of this study was to review the effects of the interaction between medications and exercise-training in CO, and to provide important insights for the compliance of medications with exercise in this population. It is a narrative review carried out according with a descriptive character about the studies that verified the relation and influence of exercise and / or medications in the treatment of obesity. Based on the current literature, it is suggested that both exercise and obesity medications presented similar pathways in the treatment of CO. In addition, it is recommended that future randomized controlled trials report and discuss the effect of exercise plus obesity medication to treat or reduce CO.

Keywords: Childhood; Obesity; Pharmacology; Physical exercise.

Resumen

El entrenamiento físico se ha convertido en una herramienta prometedora no farmacológica para mejorar la composición corporal de una amplia variedad de poblaciones clínicas, incluidos los ancianos, pacientes con enfermedades crónicas y niños con obesidad. Es importante destacar la obesidad infantil (OC) como un problema de salud pública que debe mitigarse para el mejor crecimiento y desarrollo del niño. Aunque existen varios modelos de entrenamiento, la ganancia particular entre todos es la mejora metabólica que contribuye al aumento de la masa muscular y la pérdida de grasa. Por otro lado, hay varios medicamentos involucrados en el tratamiento de la obesidad, que actúan de manera similar en relación con el entrenamiento físico para el tratamiento de la OC. Esto plantea una pregunta crucial: considerando el ejercicio que solo el ejercicio y las drogas podrían tratar la OC, ¿deberíamos evaluar la seguridad y / o los efectos del enfoque farmacológico con el ejercicio para mejorar el tratamiento de la OC? Desde esta perspectiva, el objetivo de este estudio fue revisar los efectos de la interacción entre los medicamentos y el entrenamiento físico en OC y proporcionar información importante para la adherencia de los medicamentos al ejercicio en

esta población. Es una revisión narrativa de carácter descriptivo sobre el efecto del ejercicio y la medicación en el CO. Con base en la literatura actual, se sugiere que los medicamentos para el ejercicio y la obesidad tengan caminos similares en el tratamiento del CO. Además, se recomienda que los ensayos controlados aleatorios futuros informen y discutan el efecto del ejercicio más los medicamentos para la obesidad en el tratamiento o la reducción del CO.

Palabras clave: Infancia; Obesidad; Farmacología; Ejercicio físico.

1. Introduction

Nowadays, the obesity is significantly increasing among subjects at different ages (Anatoliotakis et al., 2013; Loeffler & Wolf, 2014; Nakayama, Nishida, & Otsu, 2016; Ogden, Flegal, Carroll, & Johnson, 2002; Raj, Pecoits-Filho, & Kimmel, 2020; Romano, Serviddio, De Matthaeis, Bellanti, & Vendemiale, 2010; Zhao et al., 2011; Zieliński, Slominska, Król-Zielińska, Krasiński, & Kusy, 2019). However, childhood and adolescence are critical periods for prevention and intervention efforts (McManus & Mellecker, 2012). Childhood obesity (CO) is increasing exponentially in the past decades (Jack A Yanovski, 2015; Jack Adam Yanovski, 2001), and is related to a set of clinical-physiological, psychological, and neurocognitive abnormalities that can affect the growth and development process of children and adolescents (Gurnani, Birken, & Hamilton, 2015). Therefore, physicians and the scientific community are looking for strategies to reduce CO and change habits and behaviors related to it(Chao, Wadden, & Berkowitz, 2018; Dietz & Robinson, 2005; Gurnani et al., 2015; Hutchinson, Emerick, & Saxena, 2016; Ip et al., 2017; Kelsey, Zaepfel, Bjornstad, & Nadeau, 2014).

The practice of regular exercise is seen as a fundamental instrument in the process of the prevention and treatment of obesity(Mogul, Irby, & Skelton, 2014), and childhood obesity (McCambridge et al., 2006; McManus & Mellecker, 2012), since it is associated with greater recruitment of muscle mass along with an increased local hyperemia, inducing improvement in lipid profile, glucose uptake and blood pressure control(Molina-Garcia et al., 2019; Monteiro et al., 2015; Mortensen & Saltin, 2014; Noland, 2015). A meta-analysis demonstrated that exercise is associated with a significant increase in adiponectin and maintenance of leptin and resistin levels(García-Hermoso et al., 2017). All of these conditions will improve the comorbidities associated to CO.

It is known that exercise-training increases the humoral mediating parameters related to mitochondrial biogenesis (Wright et al., 2007), insulin sensitivity (Borghouts & Keizer,

2000) and vasodilatation(Gilligan et al., 1994) that are important for improving the comorbidities associated with childhood obesity, allowing new knowledge about the best types and forms of exercise prescriptions on different molecular anti-obesity pathways, as well as better understanding on drug interaction and its impact on exercise responses.

On the other hand, there are a plethora of medications that could treat obesity (Khera et al., 2016)and CO (Boland, Harris, & Harris, 2015; Danielsson, Janson, Norgren, & Marcus, 2007). Chao et al.(Chao et al., 2018)have shown that orlistat results in modest weight losses and may be beneficial for some patients with CO. Furthermore, Danielsson et al.(Danielsson et al., 2007) demonstrated a significant weight reduction caused by sibutramine of hypothalamic and syndromal CO. Although the pharmacological approach seems safe for child and adolescents with obesity (Boland et al., 2015), the impact of exercise-training in together with medications still largely unknow. From this perspective, the aim of this study was to review the effects of the interaction between medications and exercise-training in CO, and to provide important insights for the compliance of medications with exercise in this population.

2. Methodology

It is a narrative review carried out (Pereira et al., 2018), with a descriptive character about the studies that verified the relation and influence of exercise and / or medications in the treatment of obesity. It was considered eligible, a study that carried out in children from 7 to 10 years old that related exercise and / or medications to obesity. It was searched in the MEDLINE, Embase and Web of Science databases without restricting the publication date. The reference lists of the studies found were also checked to identify potentially eligible studies.

3. Results and Discussion

3.1. A Brief Epidemiology and Pathophysiology of Obesity

The prevalence of obesity in adults and children reached 56.9 and 20.8% in 2013, respectively (Dias, Henriques, Anjos, & Burlandy, 2017). In the United States of America, estimates are that 16.9% are obese, and 31.8% are overweight (Mogul et al., 2014). However, the increase in obesity is not only occurring in adults. Hutchinson et al. (2015) showed an increase in the incidence of the worldwide CO from 1988 to 2012, which explains the

increase in the incidence of obesity in adulthood today (Hutchinson et al., 2016).

Thus, the increase in the occurrence of childhood obesity can also be considered as a futureworryingpublic health problem, implicating in an economic burden condition having a total economic cost estimated to be $US68.8 billion in 1990(Wolf & Colditz, 1994). Also, psychological issues are prevalent in people with obesity (Friedman, Reichmann, Costanzo, & Musante, 2002), incurring body image disorders, suicides and decrease the action of neurotransmitters in the brain, increasing depression and anxiety, weak cognitive development due to low neuroplasticity in limbic and other regions, as obese children use less muscle and produce less brain-derived neurotrophic factor (Gray et al., 2006). This might culminate in social problems, as these conditions at population levels could profoundly affect social organization, tolerance and other functions related to rational human behavior, since a low brain development can mean a more primitive mentality (Nicolaidis, 2019).

The obesogenic behavior in childhood could alter market, industrial and agricultural production patterns, since increased consumption, especially of industrialized products with flavorings, could force the production of more food than necessary and in a more industrialized way to cope, which could affect the sustainability of the planet(Skouteris et al., 2014). These consumptions can increase the infertility related to obesity, such as the epigenetic reprogramming altering human reproduction and bringing possible consequences to the process of evolution, even because the human being has evolved amid scarcity and as the abundance of calories is something recent, the perpetuation of the condition of obesity, before the reproductive period could be catastrophic (Pasquali, Patton, & Gambineri, 2007).

It is relevant to elucidate its pathophysiology and possible treatments, contributing with information for its treatment and improving the quality of life of those who have this pathology. There is still no consensus on the pathophysiology of obesity (Gurnani et al., 2015). However, several pathways have been elucidating the process of this disease, which is a disorder of energy metabolism, which causes an excessive storage of triglycerides in adipose tissue (Molina-Garcia et al., 2019). However, it can be said that obesity is mainly due to the excessive intake of foods rich in lipids and high glycemic index(K. Steinbeck, 2001; Jack A Yanovski, 2015; Jack Adam Yanovski, 2001). This increase in adipose tissue can lead to an increase of blood lipids (Fisher-Wellman & Bloomer, 2010; Gurnani et al., 2015), increasing lipotoxicity in the endoplasmic reticulum and mitochondria of the liver and the pancreas, contributing to insulin resistance, hypertension, dyslipidemia and inflammation(Donatsky, 1976; Escrivão, Oliveira, Taddei, & Lopez, 2000; Fisher-Wellman & Bloomer, 2010).

It is relevant to note that obesity is increasing significantly thought the past years. Therefore, considering the comorbidities associated to it, the non-pharmacological and pharmacological treatments are becoming fundamental to improve the understanding of how to revert or treat the condition of obesity. Also, this could bring insights about the magnitude of obesity, such as what it could be affecting on daily life.

3.2. Treatments

Some precautions need to be taken before applying a pharmacological treatment, since it should be prescribed only considering the severity of obesity, previous changes in habits and behaviors as well as possible side effects and risks(Boland et al., 2015).In addition, physical training also requires caution when applied to obese children, as it is necessary to perform a complete physical evaluation to check for possible heart disease or other obesity associated diseases(Fang et al., 2019).However, to the best of our knowledge, no studies compiled exercise-training with obesity drugs. In this sense, it is crucial that further studies on this subject are carried out to improve the treatment of childhood obesity.

The uptake of medications that accelerate sympathetic activity and decrease hunger, seems to go against anti-anxiety and depression drugs, with a clash of goals, since obese child and adolescents could use a weight loss drug that accentuates the anxiety problem or depression(Srivastava & Apovian, 2018). However, antidepressants and anxiolytics have the effect to increase body weight which could impair in exercise dynamics.

Some drugs that decrease appetite may act on anorectic neurotransmitters, such as the transcribed by amphetamine, this effect could cause sleep disorders, which can attenuate the effect of exercise-training (Srivastava & Apovian, 2018). Also, there are some medications that inhibit fat acid absorption, which could decrease the levels of essential fat acids in the organism(Srivastava & Apovian, 2018). Thus, exercise might be affected negatively by that kind of medications.

3.3. Pathways of Main Medications for Obesity

Sibutramine works through its secondary (M1) and primary (M2) amino metabolites, which are inhibitors of noradrenaline reuptake, serotonin (5-hydroxytryptamine, 5-HT) and dopamine. What increases satiety and makes the person eat less (Hansen, Toubro, Stock, Macdonald, & Astrup, 1998). Orlistat, inhibits gastrointestinal lipases that hydrolyze

triglycerides to free fatty acids and glycerol promoting their excretion (Padwal & Majumdar, 2007). Liraglutide is a glucagon-like peptide receptor inhibitor. Stimulates insulin secretion, reduces inappropriately high secretion of glucagon and improves the function of beta cells in a way dependent on glucose, which results in reduced of fasting and postprandial blood glucose (A Christou, Katsiki, & N Kiortsis, 2016). Lorcasein hydrochloride Increases the effect of serotonin by increasing satiety(Shukla, Kumar, & Aronne, 2015).

Other medications used in CO are the anti-diabetic drugs as metformin and exenatide, although their pathway in obesity treatment still largely unknow, their efficacy on it might be to the capacity to control glucose homeostasis, increasing insulin sensitivity. Also those two medications seems safety for patients aged ≥10years (Boland et al., 2015).

Antiepileptic drugs as topiramate and zonisamide also seems safe for CO treatments due to the capacity to increase the production of adiponectin and reduction of leptin contributing to weight loss. However, those two medications are not recommended as a weight loss therapy in patients without underlying seizure disorders (Boland et al., 2015).

Although the pharmacological treatments of obesity are a fundamental tool to treat it, they often present collateral effects that may impair in some other pathways. However, even with those effects, it still the most appropriated treatments for obesity, once there are many studies demonstrating a significant improvement in obesity by the uptake of these medications.

3.4. Overall Pathways of Exercise to Treat Obesity

Exercise-training can act on glycemic control and lipid metabolism once muscle activation can increase glucose uptake through independent insulin pathways (Rybczyńska et al., 2017; Xia et al., 2015). In this sense, exercise can be a suitable method to improve glucose metabolism of both adults and children, reducing the incidence of metabolic issues and type 2 diabetes in related to obesity.

Due to energy expenditure and oxidation of triglycerides and glycogen during exercise(Noland, 2015; Potter, 1946), it is necessary to mobilize fatty acids from adipocytes for the cellular restructuring of tissues where oxidation occurred during exercise. (Fisher-Wellman & Bloomer, 2010). In this way, exercise-training will cause a decrease in lipids in the adipocytes, reducing fat mass concomitant to an improvement in the child's body composition(Molina-Garcia et al., 2019; K. Steinbeck, 2001; K. S. Steinbeck, 2001). Also, exercise seems to cause a state of transient anorexia in obese girls by the stimulations of

peptide YY(3-36) and maintenance of leptin (Prado et al., 2014).In this regard, it seems that exercise-training acts in similar pathways as some obesity medications, however, some medications seems to antagonize the effect of exercise training.

Bearing in mind that depending on the drugs used in obesity, its effect may be agonist or antagonistic to exercise, studies in this field should be carried out with caution, investigating in detail the pathway of the medication and how it can interfere or complement the exercise effect.

3.5. Future Perspectives

Those mechanistic effects of exercise-training are similar to the medications aforementioned. In this perspective, if we use exercise and medication together, we can potentialize the both effects. In view of that, our manuscript provides the insight of combining medications with exercise as a novel treatment of CO, opening perspectives for new studies to investigate the effect exercise and medications in CO.

Therefore, in this brief review, we are pointing to a research gap that has not yet been investigated by the scientific community. It is suggested that further studies on the topic of obesity in the pediatric population should be carried out, bringing the intercommunication between medication and exercise for CO treatment. Studies in this context would have the potential to include a drug-exercise interaction session in the package inserts, since exercise is an important adjunct in the treatment of obesity.

4. Final Considerations

This study can contribute for the increase in the researches in the field of exercise plus medications in the treatments of CO. Opening perspective to the promising effect of the compilation of those two treatments with the potential to improve the condition of CO. In this regard, our objective was completely achieved once we have outlined the promising effects of the interaction between medications and exercise-training in CO and provided important insights for the compliance of medications with exercise in this population.

Based on the current literature, it is suggested that both exercise and obesity medications presented similar pathways in the treatment of CO. In addition, it is recommended that future randomized controlled trials report and discuss the effect of exercise plus obesity medication to treat or reduce CO.

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