RESPONSES OF PLASMA ADIPOKINES TO HIGH INTENSITY INTERVAL TRAINING: SYSTEMATIC REVIEW

INTRODUCTION

Obesity is one of the major diseases of modern times. However, the explanation for its pathophysiology is recent and has not yet been fully elucidated. White adipose tissue synthesizes and secretes adipokines that affect several pathologies related to obesity. Excessive growth of this tissue results in increased levels of pro-inflammatory adipokines and a consequent decrease in anti-inflammatory adipokines. Nevertheless, most studies use moderate intensity training, limiting the understanding of high intensity interval training in these proteins. Objective: To verify the latest information on the effects of HIIT in improving the profile of circulating adipokines. Methods: A search was performed on the databases PUBMED, Lilacs, HighWire, BVS and the Cochrane Database of Systematic Reviews, with the following keywords: HIIT adipokines, HIIT leptin, HIIT adiponectin. Eleven studies were selected, published in English and Portuguese between 2013 and 2017. Results: HIIT proved to be effective in increasing adiponectin in the adolescent population and in Olympic athletes, but this depended on a good prescription parameter and exercise intensity. However, maximum or supramaximal intensities were superior to low and moderate intensities. In turn, leptin presented a significant decrease in response to HIIT due to the reduction of adipose tissue, demonstrating a directly proportional relation. Other adipokines, such as omentin-1 and interleukin-10, also responded positively to HIIT, resulting in improved anti-inflammatory status. Conclusion: HIIT proved to be an efficient method to reduce inflammation due to obesity, as well as inducing an improvement in sports performance. However, the effects depend on training volume, intensity and prescription method. Level of evidence I; Therapeutic study–Investigating the results of treatment.

Keywords: Adipokines; Leptin; Adiponectin.

RESUMO

Introdução: A obesidade é uma das principais doenças dos tempos modernos. Entretanto, a explicação da sua fisiopatologia é recente e ainda não foi totalmente esclarecida. O tecido adiposo branco sintetiza e secreta adipocinas que acometem diversas patologias relacionadas à obesidade. O aumento excessivo desse tecido resulta no aumento dos níveis de adipocinas pró-inflamatórias e na consequente diminuição de adipocinas anti-inflamatórias. Entretanto, a maioria dos estudos utiliza o treinamento de intensidade moderada, limitando o entendimento do treinamento intervalado de alta intensidade nessas proteínas. Objetivo: Verificar as mais recentes informações sobre os efeitos do HIIT na melhoria do perfil das adipocinas circulantes. Métodos: Foi realizada uma pesquisa nos bancos de dados PUBMED, Scielo, Lilacs, HighWire, BVS e Cochrane Database of Systematic Reviews, com as seguintes palavras chaves: HIIT adipocinas, HIIT leptin, HIIT adiponectin. Onze estudos foram selecionados, publicados em inglês e em português, entre os anos de 2013 e 2017. Resultados: O HIIT mostrou-se eficiente para aumentar a adiponectina na população adolescente e em atletas olímpicos, mas isso depende de um bom parâmetro de prescrição e da intensidade do exercício. Entretanto, as intensidades máximas ou supramáximas se mostraram superiores às intensidades baixas e moderadas. Por sua vez, a leptina apresentou significativa diminuição em resposta ao HIIT devido à redução do tecido adiposo, demonstrando uma relação diretamente proporcional. Outras adipocinas, como a omentina-1 e a interleucina-10, também responderam de forma positiva ao HIIT, resultando em um melhor estado anti-inflamatório. Conclusão: O HIIT demonstrou ser um método eficiente para diminuir a inflamação decorrente da obesidade, assim como induzir uma melhora no rendimento esportivo. Entretanto, os efeitos dependem do volume de treino, intensidade e método de prescrição. Nível de evidência I; Estudo terapêutico–Investigação dos resultados do tratamento.

Descritores: Adipocinas; Leptina; Adiponectina.

RESUMEN

Introducción: La obesidad es uno de las principales enfermedades de los tiempos modernos. Entretanto, la explicación de su fisiopatología es reciente y aún no se ha dilucidado completamente. El tejido adiposo blanco sintetiza y secreta adipocinas que afectan diversas patologías relacionadas a la obesidad. El aumento excesivo de este tejido resulta en el aumento de los niveles de adipocinas proinflamatorias y la consiguiente disminución de las adipocinas proinflamatorias. El objetivo de este estudio es revisar los últimos informes sobre el efecto del entrenamiento a intervalos de alta intensidad (HIIT) en la mejora del perfil de adipocinas circulantes. Métodos: Se realizó una búsqueda en los bancos de datos PUBMED, Scielo, Lilacs, HighWire, BVS y Cochrane Database of Systematic Reviews con las siguientes palabras clave: HIIT adipocinas, HIIT leptina, HIIT adiponectina. Once estudios fueron seleccionados, publicados en inglés y en portugués, entre los años de 2013 y 2017. Resultados: El HIIT demostró ser un método eficiente para aumentar la adiponectina en la población adolescente y en atletas olímpicos, aunque esto depende de un buen parámetro de prescripción y de la intensidad del ejercicio. Además, las intensidades máximas o supramáximas se mostraron superiores a las intensidades bajas y moderadas. Por su vez, la leptina presentó una significativa disminución en respuesta al HIIT debido a la reducción del tejido adiposo, demostrando una relación directamente proporcional. Otras adipocinas, como la omentina-1 y la interleucina-10, también respondieron de forma positiva al HIIT, resultando en un mejor estado anti-inflamatorio. Conclusion: El HIIT demostró ser un método eficiente para disminuir la inflamación decorrente de la obesidad, así como inducir una mejora en el rendimiento deportivo. Entretanto, los efectos dependen del volumen de entrenamiento, intensidad y método de prescripción. Nivel de evidencia I; Estudio terapéutico–Investigación de los resultados de tratamiento.
Adipokines are bioactive substances expressed and secreted by adipocytes. Once considered only as a passive tissue that stored excess energy in the form of triacylglycerols, adipose tissue produces endocrine signaling through these substances.

Adipokines play a crucial role in the pathophysiology of multifactorial metabolic diseases. Some of these proteins are involved in lipid metabolism, insulin sensitivity, complement system, vascular hemostasis, blood pressure regulation and angiogenesis, as well as energy balance. However, there is a growing list of classical adipokines (TNF-alpha, IL-1b, IL-6, IL-8, IL-10), growth factors (transforming growth factor beta, nerve growth factor) involved in inflammatory processes, as well as deregulation of the acute phase proteins (inhibitor of plasminogen activator-1, haptoglobin and serum amyloid A), all caused by excess adipose tissue.

Leptin and adiponectin are the most abundant adipokines in adipose tissue and perform different functions. Leptin was the first adipocyte-specific hormone to be identified and among its main activities are the control of energy expenditure and the regulation of appetite. Adiponectin has shown effects on the regulation of energy metabolism and insulin sensitivity, as well as the stimulation of AMP-activated protein kinase (AMPK) in skeletal muscle, which has been shown to increase the number and mitochondria oxidative capacity.

However, the increase in body adiposity causes a deregulation in the gene expression and secretion of the adipokines, resulting in metabolic dysfunctions. A positive energy balance and sedentary lifestyle lead to the visceral fat accumulation, infiltration of macrophages and pro-inflammatory T cells. The proinflammatory phenotype of M1 macrophage predominates and inflames adipose tissue, which in turn releases proinflammatory adipokines, such as tumor necrosis factor (TNF), causing a mild but significant systemic inflammation.

In obese individuals, resistance to leptin is observed, resulting in an increase in circulating leptin. Hyperleptinemia can be attributed to decreased transport of leptin to the brain or decreased hypothalamus leptin signaling. The relationship between leptin and female sexuality seems to be well defined in the literature, the concentration of leptin is directly related to maturational stages and an inverse relationship with age of menarche, because the increase in plasma leptin is one of the first signs of initiation and activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in increased estrogen and progesterone concentration.

Studies have suggested an important role of physical exercise in the regulation of. Among the different modalities, high intensity interval training (HIIT) has been used as a strategy to prevent metabolic syndrome. HIIT can be characterized by short duration sessions composed of high intensity repetitions, interspersed with active or passive rest. There is evidence that HIIT is able to induce lipolytic hormone secretion, probably by the action of IGF-1 on protein kinase B stimulation and by the signaling of testosterone in the androgen receptor, in addition to increasing oxidative capacity, being directly related to the reduction of metabolic disturbances.

Studies involving the practice of HIIT on the secretion of adipokines have been developed in different populations, especially obese and athletes. Thus, the present work aims to gather the latest information about the effects of different protocols of HIIT on adipokine plasma concentrations.

**METHODS**

In order to organize this systematic review, a search was made in the databases PubMed, Lilacs, HighWire, BVS and Cochrane Database of Systematic Reviews with the following keywords: HIIT adipokines, HIIT leptin, HIIT adiponectin.

We found 13 articles, published in English and Portuguese between 2013 and 2017. Of these, 11 were selected after a selective reading to assess whether the topic of the article was pertinent to the present review, followed by an exploratory reading, where we sought to read and interpret the data present in the studies (Figure 1). Quality assessment was conducted using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale awards a score out of 10 based on criteria described elsewhere. For a better understanding of the data, classic studies were used in the discussion.

**RESULTS AND DISCUSSIONS**

Studies that sought to assess the effects of HIIT on plasma adipokine levels are shown in Table 1. There are few jobs in this area, in addition, the various ways of using the method (eg ergometer rowing, cycle ergometer, outdoor all-out shots) make it difficult to analyze on a training basis. However, all studies reported here have demonstrated the effectiveness of HIIT as a method for the prevention or treatment of metabolic disorders caused by sedentary lifestyle and obesity or improvement of adipokines related to sports performance, such as adiponectin.
Effects of HIIT on adipokine plasma concentrations

Adiponectin

Adiponectin has shown an inverse relationship with visceral fat, this can be explained by tumor necrosis factor (TNF-α) has been reported as a strong inhibitor of the action promoted by adiponectin. Other proinflammatory cytokines regulate the anti-inflammatory activity of adiponectin, specifically interleukin-6 (IL-6) and C-reactive protein (CRP); TNF-alpha and adiponectin are mutually inhibited; the expression of PCR is down-regulated by adiponectin; the expression of adiponectin is suppressed by IL-6. Low levels of plasma adiponectin have been found in type 2 diabetics, suggesting that adiponectin is an important hormonal factor in the control of insulin sensitivity. Most of the interventions occurred with female adolescents, where adiponectin changed positively at that age when HIIT occurred three times a week for 12 weeks, but did not change when the frequency was twice a week for six months. The difference in the result may also have occurred due to a singularity in the training performed by Racil et al. because his protocol had increases in speed every four weeks, which was not specified by Blüher et al. where the intensity increase depended on the improvement in heart rate.

The combination of HIIT with plyometric training also seems to result in positive effects on leptin and adiponectin. Racil et al. distributed 68 obese adolescents in 3 groups: HIIT, plyometry + HIIT and control, all trained three times a week for twelve weeks (with the exception of the control). The group that used plyometric exercise in conjunction with HIIT had superior effects to the group that only did HIIT in the percentage of fat-free mass, in the plasma concentration of leptin, glucose and adiponectin, leptin-adiponectin ratio, HOMAR-IR and Squat Jump. Thus, the author concluded the efficacy of HIIT in obese female adolescents, but recommends the use of plyometric exercises to improve the adaptations.

It is interesting to note that adiponectin appears to respond positively to HIIT when it is prescribed from maximal aerobic velocity, but not when maximal heart rate (HRmax) is used. Another interesting observation is that the first two studies used maximum or “supramaximal” intensities, the latter two using submaximal intensities. In addition, there was monitoring of the respiratory exchange rate (RER) during the pre-training tests when adiponectin responded positively, but not when it did not change or responded negatively. This fact can be explained by the training intensity is more accurately monitored when the intensity related to the anaerobic threshold (Lan) is known, which can be estimated by the RER, but the HRmax is not a strong predictor of the Lan at all intensities.

Meyer, Gabriel, Kindermann et al. have shown that the prescription from the HRmax can vary depending on the individual. The individual anaerobic threshold (IAT) ranged from 53 to 85% when the heart rate was at 70% of the HRmax and ranged from 87 to 116% of the IAT when the heart rate was at 85% of the HRmax. These data show that HRmax-only prescription can cause high or supramaximal intensities in different individuals, even if they are in the same percentage of HRmax.

| Authors          | Design and Quality             | Sample                        | HIIT                          | Prescribing criteria | Sessions per week | Total duration | Adiponectin | Leptin | Other adipokines |
|------------------|--------------------------------|-------------------------------|-------------------------------|----------------------|-------------------|----------------|-------------|--------|-----------------|
|Blüher et al. 2016 | Randomized Controlled Trial, quality = 5/10 | 20 obese adolescents | Not specified | HRmax: 80-95% / 50-60% | 2                 | 6 months      | NC          | NC     | AFABP not changed |
| Kong et al. 2016  | Randomized Controlled Trial, quality = 4/10 | 10 people, overweight or obese | Increase based on body weight | 4                   | 5 weeks          | NM            | NC          | NM     | NM              |
| Gerosa-Neto et al. 2016 | Randomized Controlled Trial, quality = 5/10 | 32 men and women overweight or obese | 4x 4’/3’ | HRmax: 90% / 70% | 3                 | 16 weeks       | ↓           | NM     | ↑ TNF-alpha ↑↓ IL-6 ↓ IL-10 not changed |
| Ouerghi et al. 2017 | Nonrandomized Controlled Trial, quality = 5/10 | 9 obese men and 9 men in the ideal weight | 2x 8x30’/30’ | MAS: 100-110% / 50% | 3                 | 8 weeks        | NM          | NM     | Omentin-1 ↑↑↑↑ in the trained group; PCR not altered |
| Racil et al. 2016 | Randomized Controlled Trial, quality = 6/10 | 47 obese adolescents | 3x 4-8x15’/15’ | MAS: 100% / 50% | 3                 | 12 weeks       | NM          | ↓      | NM              |
| Shing et al. 2013  | Randomized Controlled Trial, quality = 9/10 | 7 state and national level rowers | Incremental test: 90% / 40% | 2                   | 4 weeks          | ↑ (acute)      | NM          | NM     | NM              |
| Sim et al. 2015  | Randomized Controlled Trial, quality = 5/10 | 10 overweight men | Repetitive shots 15’/ 60’ | Peak VO2: 170% / 32% | 3                 | 12 weeks       | NM          | ↓      | NM              |
| Vardar et al. 2018  | Nonrandomized Controlled Trial, quality = 5/10 | 12 women, overweight or obese | 4-6x wingate test (30s maximum effort) / 4-5’ | Wingate test: 0.065 kg / body weight / passive rest | 2                 | 19 days        | ↑ (acute)  | ↓ (acute) | NM              |
| Racil et al. 2015 | Randomized Controlled Trial, quality = 5/10 | 68 obese adolescents | 2x 6-8x30’/30’ or 2x 6-8x30’/30’ + plyometrics | Peak VO2: 100-110% / 50% | 3                 | 12 weeks       | ↑           | ↓      | NM              |
| Sim et al. 2015  | Randomized Controlled Trial, quality = 5/10 | 10 overweight men | Repetitive shots 15’/ 60’ | Peak VO2: 170% / 32% | 3                 | 12 weeks       | NM          | ↓      | NM              |
| Racil et al. 2015 | Randomized Controlled Trial, quality = 5/10 | 54 obese adolescents | 2x 8x30’/30’ | MAS: 100-110% / 50% | 3                 | 12 weeks       | ↑           | NM     | NM              |
Adiponectin has also been studied as a performance marker. Juramae et al. reported that rowers selected to represent the Olympic team had increases in circulating adiponectin after a maximum of 2000 meters, since the unselected rowers had a decrease in circulating adiponectin. This is possibly due to the effect of adiponectin on bioenergetic function, such as AMPK activity and increase of PGC1-alpha, leading to consequent mitochondrial biogenesis. Shing et al. tested the effect of HIIT on state and national level rowers for four weeks, training consisted of 90% of the effort measured through an incremental test (Ti) for two minutes and thirty seconds, intercalated by recovery to 40% of the effort reached in Ti until the heart rate returned to 70% of maximum or reached a maximum of 5 minutes of active recovery. The training was performed in a rowing ergometer to facilitate the adaptation of the athletes. At the end of the intervention the adiponectin improved in acute response to exercise and a broad but non-statistically improvement in adiponectin at rest was observed. The study also included a group with a traditional training ranging from 35 to 40 minutes, corresponding to the intensity reached at a lactate concentration of 2 to 3 mmol / L. But this group did not experience any significant difference in post-exercise adiponectin or adiponectin at rest. These data can be interpreted in two ways, HIIT may have been superior to traditional training in improving the concentration of adiponectin, because it had a much greater intensity per unit of time or the athletes responded better due change in their exercise routine mediated by HIIT. The authors also recommended that further studies be conducted to clarify the relationship of the increase of adiponectin with various physiological adaptations observed, such as decreased fat mass and increased Vo2max in the HIIT group, but not in the traditional training group.29

Leptin

The effect of HIIT on the plasma concentration of leptin is not yet fully elucidated because the findings are controversial, with a decrease in plasma concentration in some studies. While it doesn’t present modifications in others.29,30

In studies where leptin declined there was a decrease in fat mass, which did not occur when it remained unchanged. This suggests that the decay of resting leptin is closely linked to the reduction of fat mass. However, Blüher et al. demonstrated that leptin remained unchanged even with fat mass reduction, this may have occurred because the fat mass percentage was too high before training and even with the post training decrease, was not enough to produce significant improvements in leptin concentration. Despite the previously mentioned effect of leptin, such as regulating appetite and increasing fatty acid oxidation, obese people do not seem to respond in a manner analogous to eutrophic persons. High plasma concentrations of leptin are associated with the same resistance, this can be caused by problems in the transport through the blood-brain barrier and impaired leptin neural signaling in the target neurons. Considine et al. reported that although the leptin concentration increases directly proportional to the percentage of fat mass, obese individuals have insensitivity to the endogenous production of the same. This fact corroborates the indications of failure of the leptin mechanism of action when its plasma concentration rises.30

Thus, it is interesting that leptin concentrations decrease in response to training, since this may be indicative of an improvement in energy metabolism or reduction of fat mass. In addition, it seems to be related to the improvement of peripheral insulin sensitivity (skeletal muscle) and modulation of pancreatic β-cell function, thus avoiding the development of type 2 diabetes.

Other adipokines

Some studies have found other adipokines such as TNF-alpha, IL-6, IL-10, omentin-1 and C-reactive protein (CRP) adipocyte fat (aFABP). The first study showed that pro-inflammatory markers, such as TNF-alpha and IL-6, increased and decreased, respectively. However, anti-inflammatory markers, such as IL-10 and adiponectin, did not change or decrease, respectively. However Gerosa-Neto et al. used as a predictive factor of training, which facilitates symptoms of nonfunctional overreaching and may lead to an inflammatory status.

Omentin-1 is a recently discovered adipokine, secreted primarily by visceral adipose tissue and has high expression in the adipose tissue of the stroma of vascular cells. It has been shown to improve insulin-mediated glucose transport and also to stimulate Akt phosphorylation in adipocytes, leading to the belief that it improves insulin sensitivity. On the other hand, CRP is a marker for the risk of cardiovascular diseases, also showing a strong predictor of future acute myocardial infarction.

Ouerghi et al. showed that HIIT training increased omentin-1 concentrations in obese individuals higher than those in the normal weight, but did not change the concentration of plasma PCR. The most pronounced improvement in obese individuals may be related to the decrease in body mass index (BMI) and fat mass in these individuals, which did not occur in people with normal weight. The authors also observed a positive relationship of omentin-1 with BMI, total cholesterol and Vo2max, but negatively with LDL-cholesterol and fat mass. However, it did not show any relation with HOMAR-IR, although this index has decreased in obese people.

aFABP is the main protein in the cytoplasm of mature adipocytes and macrophages, and is recognized as a key protein that binds factors such as obesity, diabetes and atherosclerosis. This adipokine is also related to the regulation of intracellular transport of fatty acids and in the pathogenesis of the metabolic syndrome. High production rates of aFABP are related to increased cholesterol and accumulation of triacylglycerols, as well as increased expression of pro-inflammatory markers. It has been shown that aFABP acts as a negative predictor of future acute myocardial infarction. Blüher et al. showed that aFABP did not change in response to HIIT, for a better understanding of the relationship of this adipocin with exercise, further research is needed.

In summary, due to the different methodological designs of HIIT and different samples, the data vary greatly (Figure 2). Obesity leads to deregulation of serum concentrations of various adipokines that will act on various organs.
organisms causing detrimental effects on morphology and function. HIIT acts as a noninvasive therapeutic agent that improves the concentration of adipokines in the blood, which can prevent such tissue damage.

**CONCLUSION**

The present review found that HIIT is an interesting methodology to be recommended in the treatment or prevention of the metabolic syndrome, because it acts directly on the physiological factors that lead to this condition. However, HIIT demonstrated only significant effects on adipokine plasma concentrations when it was prescribed at near-maximal, maximal or supramaximal intensity, so the intensity needs to be controlled by precise techniques, such as lactate concentration or ratio of respiratory exchange.

In a practical approach, HIIT appears to be a viable choice for reducing inflammation due to obesity even if no fat loss occurs. However, more studies are needed to provide health professionals, especially Physical Education, with a better understanding of the processes that mediate these responses, thus helping to apply more efficient protocols.

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