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REVIEW ARTICLE

Exercise to reduce leptin on obesity: A review

Putu Adi Suputra . *Faculty of Medicine. Ganesha University of Education. Bali, Indonesia.*
Student of Doctoral Program Faculty of Medicine. Udayana University. Bali, Indonesia.

ABSTRACT

Obesity is a worldwide health problem associated with hypertension, diabetes, and cancer. An unhealthy and excessive diet, low physical activity, and a sedentary lifestyle are risk factors for obesity. Obesity causes adipokine dysfunction, one of which is leptin. Leptin is known to play a role in the regulation of metabolic homeostasis, especially in obesity. Hyperleptinemia in obesity is caused by leptin resistance, the result of excess energy intake and lack of physical activity or exercise, causing high levels of leptin in circulation. Regular physical exercise improves leptin signalling by regulating several proteins involved in signal transduction pathways in the hypothalamus. Physical exercise also reduces inflammation in the hypothalamus or acts as an anti-inflammatory. Stress on the endoplasmic reticulum is associated with hypothalamic inflammation and failure of insulin and leptin signalling. Improvement of leptin resistance is more effective in moderate and high-intensity aerobic exercise as well as resistance training carried out for >12 weeks with a frequency of exercise 3-4 times a week. Acute exercise and <12 weeks of exercise are not very effective in reducing leptin levels in obesity.

Keywords: Obesity; Leptin; Hypertension; Diabetes; Cancer; Diet; Physical activity; Sedentary lifestyle.

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Corresponding author. *Jl Ida Made Rai, Kecamatan Banjar, Buleleng, Bali 81152, Indonesia.*
E-mail: dr.adisuputra@gmail.com
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INTRODUCTION

Obesity is a worldwide health problem associated with hypertension, diabetes, and cancer. Over the last two decades the incidence of obesity has increased worldwide (Arroyo-Johnson & Mincey, 2016) According to the Endocrine Society, obesity also increases the incidence of death from cardiovascular disease, myocardial infarction, sleep apnoea, hepatobiliary disease, gout, and osteoarthritis (Cinteza & Cinteza, 2018; Jensen et al., 2014). According to the Global Burden of Disease Group, reported in 2017, states that since 1980 the prevalence of obesity has doubled in more than 70 countries and is also possible in other countries (Caballero, 2019) Every year, 2.8 million adults die due to overweight, and obesity. In 2016, 650 million adults aged over 18 years are obese. Of 13 percent of the world's adult population (11% of men and 15% of women) were obese in 2016 (WHO, 2021). According to the 2020 National Health and Nutrition National Survey (NHANES), the prevalence of obesity among American adults is 42.4% in the 2017-2018 year. At the age of 20-39, it was 40%, aged 40-59 it was 44.8%, aged more than 60 years it was 42.8% (Hales et al., 2017). According to the 2018 Riskesdas data, the prevalence of obesity in Indonesia was 21.8%, when compared to the year 2013 data the prevalence of obesity was 14.8%, while the 2007 data was 10.5% (Kemenkes RI, 2018). Unhealthy and excessive diet, low physical activity and a sedentary lifestyle are risk factors for obesity (Igel et al., 2017; Kim et al., 2019). Treatment of obesity requires multidisciplinary treatment, so dietary adjustments, exercise, and lifestyle changes are important components in the treatment of obesity (Igel et al., 2017). Moderate-intensity activity of 150 minutes per week is more beneficial in reducing abdominal obesity than 149 minutes per week or less (Kim et al., 2019).

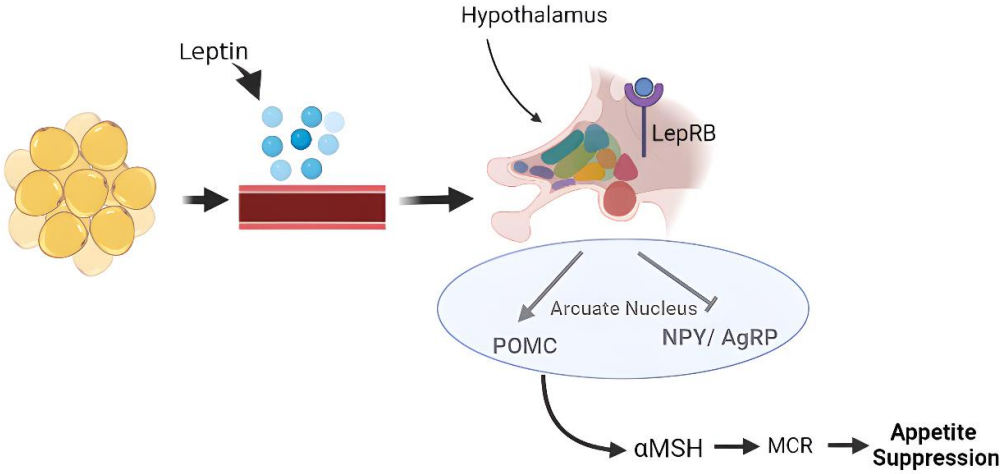
In obesity, there is an accumulation of fat mass in the body. These fats secrete adipokines which play an important role in the process of food intake, insulin action, lipids, glucose metabolism, and energy balance. Dysfunction of these adipokines will lead to obesity. Leptin and adiponectin are adipokines that are known to play a role in the regulation of metabolic homeostasis, especially in obesity (Jafari-Sfidvajani et al., 2020). Leptin, which is a product of the obesity gene, plays a role in weight control by regulating food intake and energy expenditure. Leptin acts as a hormone in energy homeostasis and also regulates neuroendocrine functions, including reproduction (Landecho et al., 2019) Increased leptin in obesity or hyperleptinemia is an etiological factor in cardiometabolic syndrome, inflammation, and malignancy. Thus obesity associated with hyperleptinemia is not only an indicator of metabolic abnormalities but plays an important role in the pathogenesis of its complications. So interventions aimed at reducing hyperleptinemia can reduce morbidity (Rostás et al., 2017).

Hyperleptinemia in obesity is caused by leptin resistance, the result of excess energy intake and lack of physical activity or exercise, causing high levels of leptin in the circulation (Fedewa et al., 2018) Increased physical activity and exercise have beneficial effects on health and are one of the therapeutics in controlling obesity, hypertension, and dyslipidaemia (Gondim et al., 2015). A meta-analysis found that resistance training can reduce hyperleptinemia without diet adjustment and significant weight loss (Rostás et al., 2017). Aerobic exercise for more than two weeks can reduce leptin, but most leptin reduction is directly proportional to weight loss (Fedewa et al., 2018) Exercise 5 weeks of high-intensity interval training (HIIT) and moderate intensity continuous training (MICT) only improves cardiorespiratory function but does not reduce leptin and body composition in obese subjects (Kong et al., 2016) Combination of aerobic exercise and resistance training for 12 weeks as a therapeutic method to improve metabolic risk by reducing leptin in obesity (Bharath et al., 2018) However, the combination of aerobic exercise and resistance training for 10 weeks with a duration of 150 minutes per week and 270 minutes per week did not significantly reduce leptin, only 450 minutes per week of exercise significantly reduced leptin in obesity (S. Li et al., 2020).

From the above background, the authors want to compile this paper to provide an overview and explain the effect of physical exercise on reducing leptin in obesity. In this paper, the authors also want to explain the intensity and frequency of exercise that can reduce leptin in obesity. The search method in this mini-review was carried out on PubMed, Science Direct, and Google Scholar search engines with the keywords "Obesity" OR "*Obese*", "*Obese*" OR "*Obesity*" AND "*Exercise*" OR "*Aerobic*", "*Aerobic*" OR "*Exercise*" AND "*Leptin*", "*Aerobic*" OR "*Exercise*" AND "*Leptin*" AND "*Obesity*" OR "*Obesity*". Obesity prevalence data was taken from the WHO website and the Indonesian Ministry of Health.

WHAT IS LEPTIN

Adipocytes are the main source of circulating leptin. The level of leptin concentration is closely related to fat cells in both humans and mice (Zhang & Chua, 2018). Leptin is a peptide hormone that plays a role in food intake, body mass, reproductive function, pro-inflammatory response in the immune system, angiogenesis, and lipolysis. Leptin is produced in white adipose tissue (WAT), and only small amounts are found in brown adipose tissue (BAT), foetal tissue, placenta, stomach, bone marrow, teeth, and brain (Obradovic et al., 2021). Apart from being a hormone, leptin also acts as a cytokine. As a hormone, leptin affects endocrine functions for energy homeostasis, while as a cytokine leptin enhances the inflammatory response. So that the increase in leptin levels in obesity contributes to the occurrence of low-grade inflammation which is a risk factor for cardiovascular disease, type 2 diabetes, and degenerative diseases (La Cava, 2017).



Note. LepRB: Leptin receptors binding; POMC: Pro-opiomelanocortin; NPY: Neuropeptide Y; AgRP: Agouti-related peptide; aMSH: alpha melanocyte stimulating hormone; MCR: Melanocortin receptors. Created in https://www.biorender.com/

Figure 1. Leptin Regulation: Adipocyte release leptin to circulation and bind leptin receptors in the hypothalamus. After binding with leptin receptors. Leptin act in arcuate nucleus to activate POMC neuropeptides (anorexigenic) and deactivate NPY/AgRP neuropeptides (orexigenic). Stimulate the release of aMSH molecules to synapse and binding with MCR to suppress appetite.

Adipocytes release leptin into circulation, then bind to leptin receptors in the hypothalamus and provide information on the amount of energy stored in the body. After binding to the leptin receptor (LepR) it regulates the activity of hypothalamic neurons also orexigenic and anorexigenic neuropeptides (Ghadge & Khaire, 2019). In preclinical trials, leptin acts in the arcuate nucleus of the hypothalamus to activate pro-opiomelanocortin (POMC) which produces anorexigenic molecules such as αMSH (a-melanocyte stimulating hormone) and deactivates orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) (Perakakis

et al., 2021). αMSH is released into the synapse to activate neurons through binding to the melanocortin receptor (MCR) and causes appetite suppression (Obradovic et al., 2021).

Leptin binding to its receptors activates the Janus Kinase 2 (JAK2)/Signal Transducer And Activator Of Transcription 3 (STAT3), Insulin Receptor Substrate (IRS-1), Phosphoinositide 3-kinases (PI3K), mitogen-activated protein kinase (MAPK) signalling pathway. Activation of JAK2/STAT3 signalling is involved in the modulatory effect of leptin on changes in gene expression. The PI3K pathway provides more rapid signalling via the phosphorylation of a cytoplasmic protein that plays an important role in regulating food intake and arterial hypertension. However, all of these pathways play an important role in the regulation of energy homeostasis (Babaei & Hoseini, 2022; Igel et al., 2017).

Leptin binds to the Leptin receptor B (LepRb) and then activates Janus Kinase 2 (JAK2). JAK2 will undergo autophosphorylation and tyrosine phosphorylation of Tyr985, Tyr1077, and Tyr1138 in the receptor. Phosphorylation of JAK2 and Tyr985 causes phosphorylation of SH2-containing protein tyrosine phosphatase 2 (SHP2) thereby activating the MAPK/ERK pathway and causing energy homeostasis. Phosphorylation of the Signal transducer and activator of transcription 5 (STAT5) is caused by phosphorylation of JAK2 and Tyr 1077 which play a role in the reproducing effect of leptin. Phosphorylation of JAK2 and Tyr1138 activates STAT3. Tyr 1138 and STAT3 signalling binding then enter the cell nucleus, undergoing transcription of target genes, including genes from the suppressors of the cytokine signalling (SOCS3) family which are inhibitors of leptin signalling. The SOCS3 protein binds to Tyr985 at the leptin receptor and causes negative feedback on the leptin signal transduction system. SHP-2 overexpression will reduce the work of SOCS3 in inhibiting the leptin pathway through a competitive mechanism to bind to Tyr985 (Peng et al., 2021).

LEPTIN IN OBESITY

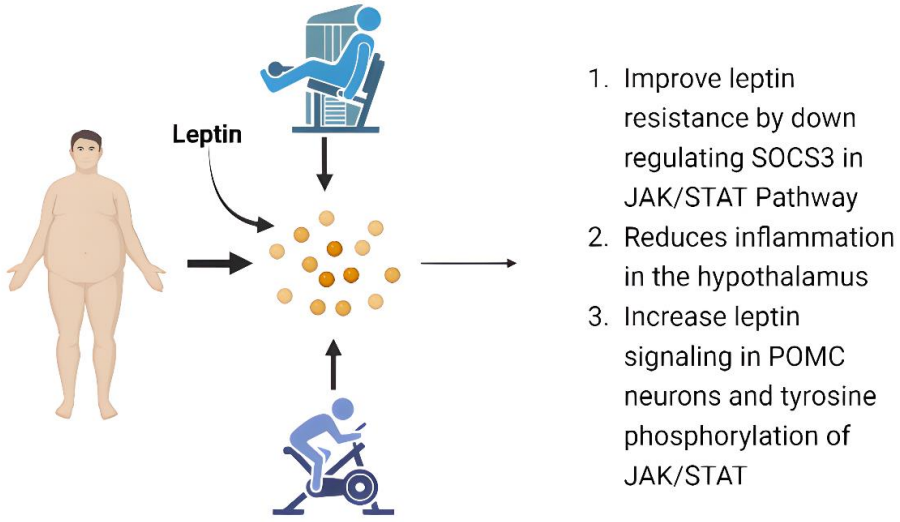
Increased levels of leptin are associated with obesity. In human subjects, obesity is associated with hyperleptinemia and leptin resistance (Ghadge & Khaire, 2019) Under normal physiological conditions, circulating leptin levels are proportional to adipose tissue mass. Elevated leptin levels or hyperleptinemia in obesity are associated with several metabolic disorders such as insulin resistance, and renal and cardiovascular disease (Zhao et al., 2020) In a state of endogenous hyperleptinemia, leptin dysfunction occurs which causes increased food intake, impaired nutrient absorption, and inhibition of lipid and glucose metabolism. This situation causes leptin resistance, the mechanism of which is divided into three, namely gene mutations, blood-brain barrier permeability, and disruption of leptin receptor signalling (Hwang et al., 2021). Leptin resistance occurs due to mutations in the OB and DBU genes which cause an increase in appetite, which is called hyperphagia, which is very rare. The occurrence of gene mutations causes impaired secretion of the hormone thyrotropin and growth hormones. This indicates that gene mutations are not the only cause of leptin resistance (Gruzdeva et al., 2019). In obesity, pathological changes occur in the cellular resistance of the blood-brain barrier resulting in disruption of leptin transport from the circulation to the brain. Decreased permeability of the blood-brain barrier causes an increase in circulating leptin, resulting in leptin resistance (Gruzdeva et al., 2019; Izquierdo et al., 2019). Furthermore, disruption of leptin receptor signalling can lead to leptin resistance. Impaired leptin signalling caused by hypothalamic inflammation and stress on the endoplasmic reticulum causes leptin resistance (Hwang et al., 2021).

Increased leptin levels are associated with increased body mass index (BMI) in obese subjects. BMI > 25 kg/m^2 – 30 kg/m^2 have lower leptin levels than obese subjects with BMI > 30 kg/m^2 (Sinorita et al., 2009) Obese people have higher leptin levels compared to normal weight. This is due to an increase in free fatty

acids and excessive food intake causing lipotoxicity, stress on the endoplasmic reticulum, and inflammation which causes an increase in leptin levels (Bouillon-Minois et al., 2021) The increase in leptin levels was found to be higher in obese and pre-obese subjects compared to normal weight. In terms of gender, higher leptin levels were found in women than men in obese and pre-obese in Nigeria. Previous in vitro and in vivo studies concluded that there was an increase in inflammatory mediators such as tumour necrosis factor-alpha (TNF-α), c-reactive protein (CRP), interleukin-6 (IL-6), and leptin. Increased TNF-α increases circulating leptin in obesity (Sáinz et al., 2015). Increased leptin levels are in line with increases in body mass index, waist circumference, total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol in obese female subjects in Saudi Arabia (Al-Amodi et al., 2018). There is a relationship between leptin and insulin resistance in obese class III female subjects, but leptin is not a predictor of insulin resistance (Osegbe et al., 2016).

EFFECT OF EXERCISE ON LEPTIN IN OBESITY

Leptin is the main adipokine in obesity which indicates that there is a lot of fat accumulation that is at risk for cardiometabolic disorders (Rostás et al., 2017). Consumption of a lot of fat and a sedentary lifestyle are risk factors for obesity (Kang et al., 2013). Studies in rats and humans show the effect of exercise or exercise on reducing leptin and improving insulin resistance (Peng et al., 2021). Aerobic exercise can improve leptin resistance and reduce serum leptin levels in rats obese by downregulating suppressors of cytokine signalling 3 (SOCS3) in the JAK/STAT pathway(Babaei & Hoseini, 2022). Studies in rats that were given a high-fat diet, then given aerobic exercise for 12 weeks, significantly reduced serum leptin (Gopalan et al., 2021). Regular physical exercise improves leptin signalling by regulating several proteins involved in signal transduction pathways in the hypothalamus. Physical exercise also reduces inflammation in the hypothalamus or acts as an anti-inflammatory. Stress on the endoplasmic reticulum is associated with hypothalamic inflammation and failure of insulin and leptin signalling. Physical exercise increases leptin signalling in POMC neurons, increases tyrosine phosphorylation of JAK2 and STAT3, then migrates to the nucleus and transcribes anorexigenic neuropeptides (Rodrigues et al., 2018).



Note. SOCS3: Suppressors of cytokine signalling 3; JAK/STAT: Janus kinase/signal transducer and activator of transcription; POMC: Pro-opiomelanocortin. Created in https://www.biorender.com/

Figure 2. Effect of Exercise on leptin: exercise improve leptin resistance by down regulating SOCS3 in JAK/STAT pathway, reduce inflammation in the hypothalamus, increase leptin signalling in POMC neurons and tyrosine phosphorylation of JAK/STAT to suppress appetite.

A meta-analysis study found that resistance training was more effective in reducing leptin levels in obese elderly subjects than aerobic exercise (Rostás et al., 2017). However, according to other studies, it was concluded that moderate-intensity training reduced leptin and IL-6 in adolescent obese subjects (Many et al., 2013). Systematic review and meta-analysis concluded that aerobic exercise significantly reduced serum leptin compared to resistance training and combination exercise (Yu et al., 2017). A 12-week aerobic exercise program with a frequency of 5 times a week in obese subjects significantly reduced serum leptin (Martins et al., 2013). Moderate-intensity exercise reduced IL-6 and leptin in obese and overweight subjects who carried out an exercise program for 12 months (Gondim et al., 2015). Both aerobic and resistance exercise for 12 weeks reduced TNF-α and leptin in diabetic and non-diabetic rats (Dinari Ghozhdi et al., 2021). A systematic review and meta-analysis in obese subjects concluded that exercise for more than 2 weeks reduced serum leptin along with a decrease in body fat (Fedewa et al., 2018).

INTENSITY AND FREQUENCY OF EXERCISE ON LEPTIN IN OBESITY

Leptin is an adipokine that plays a role in the regulation of food intake and body weight. The level of circulating leptin levels is proportional to body fat mass so that obese individuals have more leptin levels than individuals with normal weight. Obese subjects experience resistance to inhibitory activity to control food and energy intake (Iikuni et al., 2008) Increased physical activity is used for the management of obesity, because of its effect on increasing energy expenditure. High-intensity exercise results in more energy expenditure compared to low- and moderate-intensity exercise (Tremblay et al., 2011) Resistance training for 12 weeks can significantly reduce leptin in obesity, but the decrease occurs most in interval resistance training compared to traditional resistance training and circular resistance training. Interval resistance training is done with 2 sets of 14 repetitions of 50% 1RM (Alizadeh et al., 2021) Interval resistance training and circular resistance training for 12 weeks, with a frequency of 3 times a week and 50 minutes each exercise is significant in reducing leptin (Ataeinosrat et al., 2022). Combination of aerobic exercise and resistance training for 12 weeks with a frequency of 5 times a week as a therapeutic method to improve metabolic risk by reducing leptin in obesity (Bharath et al., 2018) The effect of acute exercise with high-intensity interval training and moderate-intensity continuous training significantly reduced leptin both immediately after exercise and 1 hour after exercise, but both exercises increased interleukin-6 immediately after exercise (de Souza et al., 2018).

In obese rat subjects with diabetes given aerobic training and resistance training for 12 weeks, it can help significantly reduce fasting blood sugar triglycerides, LDL, TNF-α, and leptin, but after detraining for 4 weeks, there is another increase in body weight, triglycerides, TNF-α, and leptin (Dinari Ghozhdi et al., 2021). Exercise 5 weeks, with a frequency of 4 times a week with high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) only improves cardiorespiratory function but does not decrease leptin and body composition in obese subjects (Kong et al., 2016) However, a study that compared HIIT and MICT performed 3 times a week for 12 weeks concluded that both exercises were effective in reducing leptin, but there was a greater decrease in leptin in HIIT (-0.35pg/ml) than in MICT (-0.16 pg/mL) (Hooshmand Moghadam et al., 2021). The combination of aerobic exercise and resistance training for 10 weeks with a duration of 150 minutes per week and 270 minutes per week did not significantly reduce leptin, only 450 minutes per week of exercise significantly reduced leptin in obesity (S. Li et al., 2020) Aerobic exercises such as badminton, cycling, jogging, sports games for 16 weeks with a duration of 240 minutes per week in obese female subjects aged 7-22 years, can significantly reduce leptin levels. The decrease in leptin is probably caused by a decrease in fat mass, intensity, and time of exercise (C. Li et al., 2022) Exercise for 8 weeks, 2 times a week, both aerobic exercise and resistance training, combined with a low-calorie diet, cannot reduce leptin levels (Muhammad et al., 2021) The combination of Aerobic exercise and resistance training compared

to HIIT for 12 weeks with a frequency of 3 times a week are equally effective in reducing leptin levels in postmenopausal obese subjects, but HIIT is more effective in terms of exercise time (Nunes et al., 2019) HIIT in obese women with a frequency of 2 times a week for 3 weeks, not effective in reducing leptin levels. This conclusion can be seen from the results of the reduction with acute HIIT exercise on day 1 after exercise not much different from day 19 after exercise (Vardar et al., 2018). Exercise <12 weeks did not produce a significant effect on reducing leptin in obesity, compared to exercise >12 weeks both on aerobic exercise as well as resistance training (Yu et al., 2017) The combination of a low-carbohydrate diet and a low-fat diet with HIIT is more effective at reducing leptin than the HIIT intervention alone in obese type 2 diabetes subjects (Asle Mohammadi Zadeh et al., 2018).

CONCLUSION

Obesity is a worldwide health problem associated with hypertension, diabetes, and cancer. Over the last two decades, the incidence of obesity has increased worldwide. In obesity, there is an accumulation of fat mass in the body. These fats secrete adipokines which play an important role in the process of food intake, insulin action, lipids, glucose metabolism, and energy balance. Dysfunction of these adipokines will lead to obesity. Leptin and adiponectin are adipokines that are known to play a role in the regulation of metabolic homeostasis, especially in obesity. Increased leptin in obesity or hyperleptinemia is an etiological factor for the cardiometabolic syndrome, inflammation, and malignancy. Hyperleptinemia in obesity is caused by leptin resistance, the result of excess energy intake and lack of physical activity or exercise, causing high levels of leptin in circulation. Increased physical activity and exercise have beneficial effects on health, and become one of the therapeutics in controlling obesity, hypertension, and dyslipidaemia. Regular physical exercise improves leptin signalling by regulating several proteins involved in signal transduction pathways in the hypothalamus. Physical exercise also reduces inflammation in the hypothalamus or acts as an anti-inflammatory. Stress on the endoplasmic reticulum is associated with hypothalamic inflammation and failure of insulin and leptin signalling. Improvement of leptin resistance is more effective in moderate and high-intensity aerobic exercise as well as resistance training carried out for >12 weeks with a frequency of exercise 3-4 times a week. Acute exercise and <12 weeks of exercise are not very effective in reducing leptin levels in obesity.

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No potential conflict of interest was reported by the author.

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