Impact of physical exercise on metabolic dysfunction-associated fatty liver disease (MAFLD)

Impacto do exercício físico na doença hepática gordurosa associada à disfunção metabólica (DHGAM)

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ABSTRACT
Obesity is a chronic multifactorial disease characterized by excess adiposity. Adipose tissue hypertrophy favors lipid deposition in ectopic tissues, such as the liver, which favors the development of the metabolic dysfunction-associated fatty liver disease (MAFLD), characterized by excessive accumulation of lipids in the cytoplasm of hepatocytes (fatty liver). Triglyceride overload in hepatocytes observed in obesity is associated with inflammation and insulin resistance status. Non-pharmacological strategies, such as the practice of physical exercise, seem to be an effective in reducing inflammatory markers and improving insulin sensitivity in obese individuals with MAFLD attenuating hepatocellular steatosis. Thus, this review aims to demonstrate the factors involved in the development of hepatic steatosis, as well as investigate the impact of physical exercise on insulin sensitivity and inflammatory markers in the condition of obesity-associated MAFLD.

Keywords: obesity, fatty liver, inflammation, insulin resistance, exercise.

RESUMO
A obesidade é uma doença crônica multifatorial caracterizada pelo excesso de adiposidade. A hipertrofia do tecido adiposo favorece a deposição de lipídios em tecidos ectópicos, como o fígado, o que favorece o desenvolvimento da doença hepática gordurosa associada à disfunção metabólica (DHGAM), caracterizada pelo acúmulo excessivo de lipídios no citoplasma dos hepatócitos (fígado gorduroso). A sobrecarga de triglicerídeos nos hepatócitos observada na obesidade está associada à inflamação e ao estado de resistência à insulina. Estratégias não farmacológicas, como a prática de exercício físico, parecem ser eficazes na redução de marcadores inflamatórios e na melhora da sensibilidade à insulina em obesos com DHGAM, atenuando a esteatose hepatocelular. Assim, esta revisão tem como objetivo demonstrar os fatores envolvidos no desenvolvimento da esteatose hepática, bem como investigar o impacto do exercício físico na sensibilidade à insulina e nos marcadores inflamatórios na condição de DHGAM associada à obesidade.

Palavras-chave: obesidade, fígado gorduroso, inflamação, resistência à insulina, exercício.

1 INTRODUCTION

Obesity is a chronic multifactorial disease characterized by excess adiposity. It is explained by hypercaloric food intake and physical inactivity, which negatively affects health[1]. According to the World Health Organization, the incidence of obesity increases every year. Currently, its prevalence represents almost three times the number of cases

since 1975. In 2016, obesity among adults over 18 years of age accounted for 13% of the world's population, corresponding to 650 million individuals inserted in 1.9 billion overweight adults in the same age group[2]. Obesity is characterized mainly by cellular hypertrophy, which favors lipid deposition in non-adipose or ectopic tissues, a result of limited capacity of subcutaneous lipid storage adipose tissue[3]. Ectopic adiposity is related to lipotoxicity in muscle, pancreatic, and hepatic tissue[4], favoring chronic metabolic diseases, such as metabolic dysfunction-associated fatty liver disease (MAFLD)[5], also known as non-alcoholic fatty liver disease (NAFLD)[6].

Responsible for the prevalence of cases of chronic liver disease[7], MAFLD is characterized by morphophysiological alteration in the liver, resulting from excessive accumulation of lipids in the cytoplasm of hepatocytes (fatty liver)[8]. Liver disease affects a quarter of the world's adult population[6] and is strongly associated with obesity. Authors point out that MAFLD is present in approximately 70% of overweight individuals and between 90 and 95% of those with morbid obesity[9].

Obesity associated with MAFLD has the potential to stimulate inflammatory pathways and oxidative stress. Hypertrophy of adipose tissue promotes the release of pro-inflammatory cytokines, which act on liver cells, limiting their regeneration capacity, which is hampered by cell damage resulting from the steatosis[10]. Insulin resistance (IR) is also linked to the pathogenesis of steatosis, since it predisposes the release of free fatty acids (FFA), followed by hyperinsulinemia resulting from this and the consumption of high energy diets, promoting the accumulation of lipids in the liver tissue[10,11]. Sedentary lifestyle and hypercaloric diet intake are linked to increased adiposity and IR[12].

Non-pharmacological strategies, such as the practice of physical exercise, have been used to improve IR[13] and inflammatory markers[14]. Authors relate the potential of physical exercise to the property of reducing ectopic fat deposition in liver tissue[15–18]. Cotrim et al.[19] (2016) suggest that physical exercise contributes to reduction of intrahepatic fat and points out that aerobic or resistance training can be effective; however, there is little evidence about the impact of exercise on inflammation and insulin sensitivity to confirm the absence or effectiveness of benefits for the condition of obesity-associated MAFLD. Thus, the current study aims to identify the factors involved in this process, as well as investigate the impact of exercise training on insulin sensitivity and inflammatory markers in the condition of obesity-associated MAFLD.

2 METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Fatty liver can be classified by excessive and chronic consumption of alcoholic beverages or arising from other risk factors. Until recently, the diagnosis of NAFLD should cover hepatocellular steatosis greater than 5% of the hepatic parenchyma[20] and express disconnection with alcoholism or secondary causes[21], such as medication and some syndromes[22]. Presently new criteria for the diagnostic of MAFLD include evidence of fat accumulation in the liver, which may be by biopsy, imaging or blood biomarker and present one of the three requirements, namely overweight/obesity, presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation[6].

Liver disease integrates isolated steatosis, nonalcoholic steatohepatitis (NASH), and its progressions[20] (Figure 1). In isolated steatosis, there is lipid accumulation that extends through the tissue[23], its progression to NASH represents about 20% of patients. In NASH, there is the presence of steatosis, lobular inflammation, and lesions in hepatocytes (ballooning) and may also present fibrosis and evolve to cirrhosis and hepatocellular carcinoma. It is estimated that NASH may progress to fibrosis and cirrhosis in approximately 40% and 20% of affected patients, respectively[24,25]. In addition, individuals with NASH have a 12-fold annual rate of hepatocellular carcinoma than patients with isolated steatosis[24]. Hepatocellular carcinoma is a malignant tumor[26] that can progress from both cirrhotic and non-cirrhotic NASH[27]. However, little is known about the mechanisms that lead to progression[26]; it is believed that pro-inflammatory status, IR, and lipotoxicity may be associated[27].

Figure 1. Progression of MAFLD. In MAFLD, hepatic steatosis may progress to the condition of NASH, a condition related to inflammatory process and fibrosis, which has a high predisposition to more degenerative conditions, such as cirrhosis and HCC. NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma

Source: Author

3 METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE AND OBESITY

The pathogenesis of obesity is complex, and there are several conditions involved in its causality and persistence, such as genetic and epigenetic factors, hypercaloric food intake, and low energy expenditure, among others[28]. The increased availability and

accessibility to hypercaloric foods, added to the decrease in the practice of physical exercises, are factors of potential increase for the gain of adiposity[1], since they are important determinants of the energy balance[29].

In obesity, there is a marked increase in this tissue of adipocytes hypertrophy and hyperplasia[30], which are structural constituents of adipose tissue (AT) responsible for fat storage in the form of triglycerides. In this context, it is known that adipocytes have an expansive limit, which favors the fat deposition in ectopic tissues[31], contributing to the onset of MAFLD[32].

Several factors may be involved in the pathophysiology of MAFLD. Obesity is presented as an independent risk factor for triglyceride deposition in hepatocytes[33]. The underlying constraints are not yet fully understood[34], but it is believed the deposition of triglycerides in liver tissue may come from diet fat derived from intestinal kilomicrons, circulating FFA from the lipolysis of AT, *de novo* hepatic lipogenesis, from the reduction of lipid oxidation, and by secretion of triglycerides by the liver[35]. The mechanisms involved in the association between obesity and MAFLD are specific[33], since the MAFLD pathophysiology also involves a complex interaction between its determinants[36]. The triglyceride overload in hepatocytes observed in obesity conditions favor the state of lipotoxicity[37]. Lipotoxicity is due to the imbalance between the content and hepatic degradation of triglycerides; this process promotes an influx of FFA into hepatocytes[38].

In addition, the pathophysiology of MAFLD may be associated with IR and the action of pro-inflammatory mediators[39,40].

4 OBESITY, INFLAMMATION, AND METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

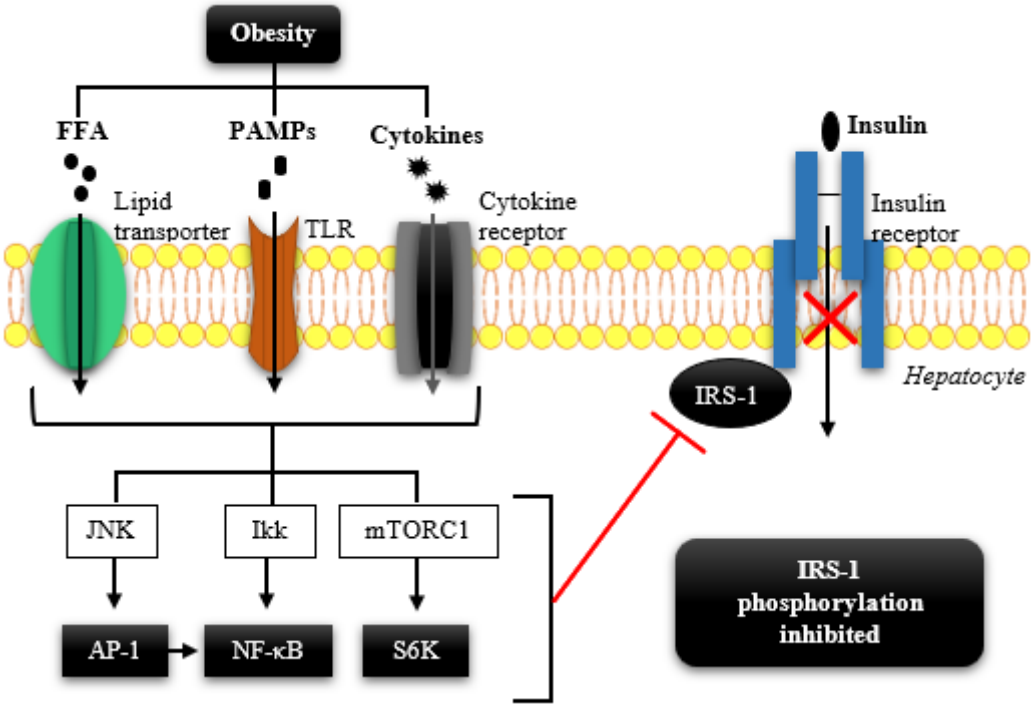
The expansiveness of AT promotes infiltration of immune cells and secretion of cytokines that are associated with reduced insulin sensitivity[41]. Thus, individuals less sensitive to the action of insulin are characterized by presenting lower functionality and greater size of adipocytes, lower subcutaneous AT, and greater accumulation of visceral fat in skeletal muscle and liver, with a consequent increase in inflammatory potential[42]. Under the action of immune cells, the inflammation is characterized as a physiological response to pathological aggressors and cellular damage[43]; thus, the balance of the immune response is related to functional regulation of AT. AT is associated with activation of macrophages that act on cytokine production and secretion[30]. Chronic

inflammation promotes increased signaling and release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (1L-6), and interleukin-8 (IL-8)[44], associated with decreased insulin sensitivity and adiponectin levels[30,44].

In addition to increased pro-inflammatory adipokines, studies have shown that adiponectin reduction occurs in the presence of hypertrophic adipocytes[30,45]. Under normal conditions, it is associated with reduced lipogenesis, which stimulates the oxidation of fatty acids, inhibiting its deposition in liver tissue[46]. In the liver, adiponectin receptor 1 (AdipoR1) stimulates the activity of the adenosine monophosphate-activated protein kinase (AMPK)[47], a protein associated with hepatic autophagy activation[48], where lipids accumulated in hepatocytes are degraded[49]. However, obesity and IR models presented lower liver autophagy and with this, reduction of lipid oxidation[50].

In obesity, FFA released by AT, pro-inflammatory cytokines, and pathogen-associated molecular patterns (PAMPs) act in a cascade of inflammatory signaling, which begins with binding to their respective membrane receptors. These bonds allow the activation of inflammatory pathways, such as the enzymes c-jun N-terminal kinase (JNK) and IkB kinase (IkK) and the mammalian target of rapamycin complex 1 (mTORC1), to which they recruit the following molecules, activating protein 1 (AP-1), nuclear factor kappa B (NF-κB), and S6 kinase (S6K), respectively[51]. Thus, the respective molecules act in inhibiting phosphorylation of the insulin receptor 1 (IRS-1), contributing to non-glucose uptake and the state of hepatic IR[51,52], which is associated with fat deposition in hepatocytes[53] (Figure 2). In addition, a JNK activation can also activate NF-κB[54], which acts on pancreatic islet dysfunction, while also being related to greater macrophage expression by AT and new production of pro-inflammatory cytokines[55].

Figure 2. Potential inflammatory mechanisms involved in insulin resistance condition. FFA: free fatty acids; PAMPs: pathogen-associated molecular patterns; TLR4: toll-like receptor 4; JNK: c-jun N-terminal kinase; IkK: IkB kinase; mTORC1: mammalian target of rapamycin complex 1; AP-1: activator protein 1; NF-kB: nuclear factor kappa B; S6K: kinase S6; IRS-1: insulin receptor 1.



Source: Adapted from Asrih & Jornayvaz, 2015[51].
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Although it is well known that inflammatory cytokines originate mainly in AT, other tissues, such as the liver and pancreas, are target organs of the inflammatory process[56]. Thus, chronic inflammation in obesity promotes various comorbidities, including MAFLD[10].

5 OBESITY, INSULIN RESISTANCE, AND METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Insulin is an anabolic hormone secreted by pancreatic β cells, which among its functions responds to glucose, protein, and lipid metabolism[57]. The insulin signaling pathway involves a series of phosphorylations, which begin with extracellular signaling of insulin to its membrane receptor, IRS-1[58]. Therefore, phosphorylation of phosphatidylinositol 3-kinase protein (PI3K) occurs, followed by phosphorylation of phosphatidylinositol 4,5-biphosphate (PIP_2) in phosphatidylinositol 3,4,5-triphosphate (PIP_3), leading to the recruitment of phosphoinositide-dependent kinase 1 (PDK1) and protein kinase B (Akt), which act directly on glucose uptake by translocating the glucose transporter to the plasma membrane[59].

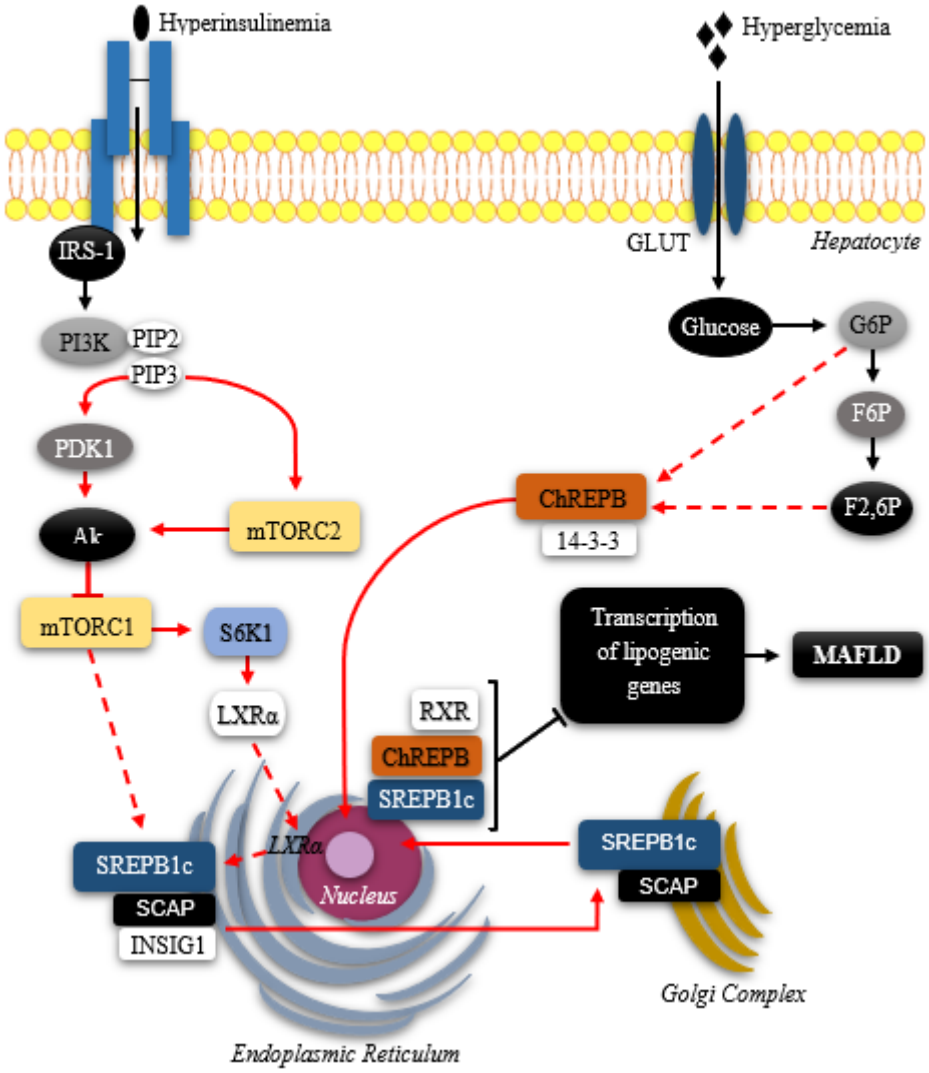
Physiologically, insulin production occurs according to food intake or by hormonal, neural, and humoral stimulus[57]. Under IR conditions, the β cells are stimulated to produce a greater amount of the hormone in order to compensate for the defect in glucose uptake[60]. In lipid metabolism, IR promotes increased AT lipolysis[61] and synthesis of new fatty acids. FFA, if not oxidized, can cause cellular damage and lipotoxicity when absorbed by ectopic tissues[62]. The IR condition acts on the activity of AT lipases, responsible for the breakdown of triglycerides. Overactivation of the hormone-sensitive lipase (HSL) occurs, favoring greater release of FFA, which can later be reabsorbed by the liver[63]. The state of hyperinsulinemia present in IR acts on that of *de novo* hepatic lipogenesis[53], a pathway that synthesizes fatty acids from the catabolism of ingested carbohydrates in excess[64].

In obese patients with MAFLD and hyperinsulinemia, 26% of hepatic lipid accumulation comes from *de novo* lipogenesis[11]. The *de novo* hepatic lipogenesis is regulated by transcriptional factors; thus, the most important factor for lipid synthesis is the sterol regulatory element binding protein 1c (SREBP-1c), regulated by insulin[63]. In the insulin signaling pathway, the mammalian target of rapamycin complex 2 (mTORC2) phosphorylates the Akt then there is activation of the mTORC1; this protein activates the ribosomal protein S6 kinase beta-1 (S6K1), promoting nuclear location of the liver X receptor-α (LXRα), heterodimerization with retinoid X receptor (RXR), and transcription of SREBP-1c. After synthesizing in the endoplasmic reticulum, the factor SREBP-1c is associated with SREBP cleavage activated protein (SCAP) and the insulin-induced gene 1 (INSIG1). When phosphorylated, INSIG1 dissociation occurs, and the SREBP-1c-SCAP complex is transported to the Golgi complex, the site in which the dissociation of the SCAP and removal of transmembrane domain occurs, enabling the input of the factor to the cell nucleus. In the nucleus, mature SREBP-1c promotes transcription of lipogenic genes, including fatty acid synthase (FAS), stearoyl-CoA desaturase 1 (SCD1), elongation of long-chain fatty acids family member 6 (ELOVL6), and acetyl coenzyme A carboxylase (ACC)[63,64] (Figure 3).

In addition to transcription factor SREBP-1c, the regulation *de novo* lipogenesis may occur by the action of the carbohydrate response element binding protein (ChREBP), stimulated by hepatic glucose. It is suggested that, when entering the hepatocytes through glucose transporter 2 (GLUT-2) and starting their degradation process, the products of their phosphorylation, glucose 6-phosphate, fructose 6-phosphate, and fructose-2,6-

biphosphate, lead to ChREBP dephosphorylation and dissociation from the cytosolic protein 14-3-3 thus facilitating the localization of the factor in the cell nucleus and enabling the transcription of the lipogenic genes mentioned above[64] (Figure 3).

Figure 3. Signaling pathways for activation of hepatic lipogenic genes in the state of hyperinsulinemia and hyperglycemia. IRS-1: insulin receptor 1; PI3K: phosphoinositide 3-kinase; PIP2: phosphatidylinositol (4,5)-bisphosphate; PIP3: phosphatidylinositol (3,4,5)-trisphosphate; PDK1: phosphoinositide-dependent kinase 1; Akt: protein kinase B; mTORC1: mammalian target of rapamycin complex 1; mTORC2: mammalian target of rapamycin complex 2; S6K1: ribosomal protein S6 kinase beta-1; LXR: liver X receptor α; RXR: retinoid X receptor; SREBP-1c: sterol regulatory element binding protein 1c; SCAP: SREBP cleavage activated protein; INSIG1: insulin-induced gene 1; GLUT2: glucose transporter 2. G6P: glucose 6-phosphate; F6P: fructose 6-phosphate; F2,6P: fructose-2,6-bisphosphate; ChREBP: carbohydrate response element binding protein; 14-3-3: cytosolic protein 14-3-3.



Source: Adapted from Sanders & Griffin, 2016)[64].

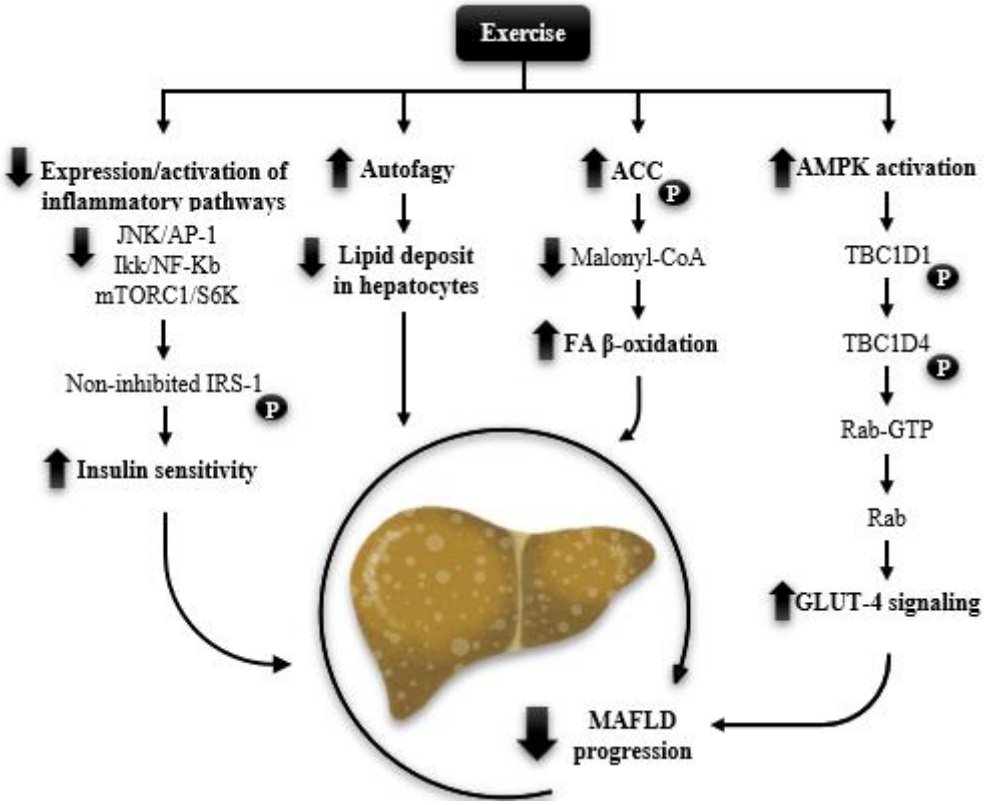
The state of IR associated with the condition of obesity contributes to increase lipogenesis and lipotoxicity of the liver, leading to excessive accumulation of lipids in hepatocytes[62,63].

6 EFFECT OF EXERCISE ON METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

6.1 EFFECTS ON INFLAMMATION

Exercise training plays an important role in regulating inflammation. It is associated with reduced expression/activation of JNK/AP-1 and Ikk/NF-κB inflammatory pathways[65], which are significant contributors to the condition of IR[66,67] (Figure 4). In addition, physical exercise is also associated with negative regulation of mTORC1/S6K pathway signaling (Figure 4), under the action of AMPK, a physiological inhibitor of mammalian target of rapamycin (mTOR)[68]. AMPK, the signaling molecule, is activated during exercise in metabolic response to muscle stress[69]. It is believed that AMPK's action occurs in response to energy consumption during the exercise, inducing signaling cascades, as it is mediated by the increase of the endothelial nitric oxide synthase (eNOS) enzyme, activation of the mitogen activated protein kinases (MAPK), activation of calcium-dependent protein kinase (CaMK), activation of protein kinase C (PKC) or hypoxia. AMPK acts on the phosphorylation of TBC1 domain family member 1 (TBC1D1) and in the subsequent phosphorylation of TBC1D4, which favors the dissociation of rab protein and the signaling of glucose transporter 4 (GLUT-4) translocation to the membrane[70] (Figure 4). During exercise, increased glucose uptake may occur through an insulin-independent route[71].

Figure 4. Possible effects of exercise on MAFLD attenuation. JNK: c-jun N-terminal kinase; AP-1: activator protein 1; IkK: IkB kinase; NF-kB: nuclear factor kappa B; mTORC1: mammalian target of rapamycin complex 1; S6K: kinase S6; IRS-1: insulin receptor 1; ACC: acetyl coenzyme A carboxylase; Malonyl CoA: malonyl coenzyme A; FA: fatty acid; AMPK: adenosine monophosphate-activated protein kinase; TBC1D1: TBC1 domain family member 1; TBC1D4: TBC1 domain family member 4; Rab-GTP: rab-GTP protein; GLUT-4: glucose transporter 4; MAFLD: metabolic dysfunction-associated fatty liver disease.



Source: Author

6.2 EFFECTS ON INSULIN SENSITIVITY

The effect of exercise on the improvement of insulin sensitivity can be observed at its maximum, 3–4 h after the training session[71] and may still be evident up to 72 h and absent within 5 days[72,73]. In a review conducted by Bird and Hawley[73] (2017), a positive effect on the reduction of IR was observed in obese individuals who practiced moderate aerobic exercise for 30 min, 3 days a week, for 8 weeks[73]. On the other hand, exercises with high intensity, interspersed with periods of low intensity, were also positively associated[74]. Corroborating the results, a study conducted by Kraus et al.[75] (2001) showed that both moderate intensity exercise (40%–55% VO_2max) and high intensity (60%–75% VO_2max) exercise for 8 months had benefits in the condition of IR[75]. Although, a review study conducted in 2016 suggested that moderate intensity exercise appears to be more effective compared to high intensity exercise[76].

In addition, when assessing the effectiveness of exercise in improving insulin sensitivity, a review conducted in 2012, including a total of 42 studies, suggested that the reduction of IR occurred regardless of changes in body adiposity, especially when in high intensity exercises[77]. With regard to the type of exercise, both aerobic and strength training seem to be effective[74]. Moreover, in the condition of improvement of IR, the physical exercise is related to activation of the oxidation pathway and inhibition of *de novo* lipogenesis[69], regardless of the type of exercise[78].

6.3 EFFECTS ON REGULATION OF HEPATIC LIPID METABOLISM

In response to exercise, the regulation of hepatic lipid metabolism may occur by increased phosphorylation of ACC, promoting a reduction in the formation of malonyl coenzyme A (malonyl-CoA), increasing the β-oxidation of fatty acids in the tricarboxylic acid cycle (TCA)[18]. Considering the lipogenesis process, exercise may promote lower expression of FAS enzyme and ACC content[79]. In addition, there is an improvement in autophagy during exercise[80], where lipids accumulated in hepatocytes are absorbed by autophagosomes and degraded[49]. Obesity, accompanied by the condition of IR, was associated with decreased hepatic autophagy in models susceptible to liver disease. Impairments in autophagy promote decreased β-oxidation and increased lipid deposits in hepatocytes[50] (Figure 4).

6.4 EFFECTS ON ATTENUATION OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Studies point to the positive effect of exercise on attenuation of MAFLD[15–17]. Moderate-intensity aerobic exercise reduced intrahepatic fat[81–83] and reduced IR in subjects with suspected or confirmed diagnosis of MAFLD[82,83]. On the other hand, high-intensity aerobic exercise was also associated with reduced liver fat content in prediabetic individuals with MAFLD[84]. Study published in 2019 showed that high intensity interval aerobic exercise was able to reduce intrahepatic triglycerides, visceral lipids, and IR in obese diabetic individuals with liver disease[85]. Similarly, studies conducted in obese individuals with MAFLD have shown that both high-intensity aerobic exercise and moderate intensity exercise significantly reduced steatosis[15,86,87]; this reduction is not associated with changes in body mass and adiposity[15].

Regarding the type of exercise, both high-intensity strength and aerobic training were effective in reducing steatosis and IR, and these changes were also independent of weight loss[16]. Patients with NASH who underwent moderate to vigorous aerobic exercise, combined with strength training, presented reduction of intrahepatic and plasma triglycerides and visceral fat[88]. Similarly, high-intensity aerobic exercise and strength training, combined or isolated, were also effective in reducing steatosis and IR[17]. Although, a study conducted by Franco et al.[89] (2019) concluded that moderate aerobic exercise alone was more effective in reducing the grade of the liver disease when compared to aerobic combined with strength training in individuals with MAFLD.

There is evidence as to the positive relationship between exercise and MAFLD; however, there is no consensus as to the recommended duration, frequency, and type of exercise[19,20,90].

7 CONCLUSION

The findings show that exercise is an effective tool in reducing the inflammation and improving the insulin sensitivity in obese individuals with MAFLD. The main signaling pathways described involve the inhibition of JNK/AP-1, Ikk/NF-κB, and mTORC1/S6K, as well as AMPK activation. Although there is an effect, recommendations regarding the exercise protocol need to be elucidated.

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DECLARATIONS OF INTEREST

The authors declares that there is no conflict of interest regarding the publication of this paper.

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