

Review

Fructose Consumption in the Development of Obesity and the Effects of Different Protocols of Physical Exercise on the Hepatic Metabolism

Rodrigo M. Pereira¹, José Diego Botezelli¹, Kellen Cristina da C. Rodrigues¹, Dennys Esper Cintra¹, José Rodrigo Pauli¹, Adelino Sanchez Ramos da Silva², Eduardo Rochette Ropelle¹ and Leandro P. de Moura^{1,*}

¹ Laboratory of Molecular Biology of Exercise (LaBMEx), School of Applied Science, University of Campinas, ZIP code 13484-350 Limeira, Sao Paulo State, Brazil.

² School of Physical Education and Sports, São Paulo University, Ribeirão Preto, Brazil.

rodrigo_mpereira@hotmail.com (R.M.P.); jdbotezelli@yahoo.com.br (J.D.B); kellen.rodrigues.nut@gmail.com (K.C.C.R.); dennys.cintra@fca.unicamp.br (D.E.C); jose.pauli@fca.unicamp.br (J.R.P); adelinosanchez@usp.br (A.S.R.S); eduardo.ropelle@fca.unicamp.br (E.R.R); leandropereiram@hotmail.com (L.P.M)

* Correspondence: leandropereiram@hotmail.com; Tel.: +55-19-3701-6706

Abstract: Fructose consumption has been growing exponentially and, concomitant with this, the increase in the incidence of obesity and associated complications has followed the same behavior. Studies indicate that fructose may be a carbohydrate with greater obesogenic potential than other sugars. In this context, the liver seems to be a key organ for understanding the deleterious health effects promoted by fructose consumption. Fructose promotes complications in glucose metabolism, accumulation of triacylglycerol in the hepatocytes and alterations in the lipid profile, which, associated with an inflammatory response and alterations in the redox state, will imply a systemic picture of insulin resistance. However, physical exercise has been indicated for the treatment of several chronic diseases. In this review, we show how each exercise protocol (aerobic, strength or a combination of both) promote improvements in the obesogenic state created by fructose consumption as an improvement in the serum and liver lipid profile (HDL increase and decrease TG and LDL levels) and a reduction of markers of inflammation caused by an excess of fructose. Therefore, it is concluded that the practice of aerobic physical exercise, strength or a combination of both is essential for attenuating the complications developed by the consumption of fructose.

Keywords: fructose; obesity; liver, aerobic exercise, strength exercise, combined exercise.

1. New story/old enemy

The high consumption of sugary beverages rich in fructose, is directly related to the development of obesity and its consequences, such as metabolic syndrome [1–3]. Concomitant with the increased incidence and prevalence of obesity and metabolic syndrome, the consumption of fructose has increased around 30% in the last 40 years [4]. More specifically, because fructose is less able to promote satiety and is more palatable, it will stimulate a higher consumption of food [4], and alter the metabolism of lipids and carbohydrates, thereby favouring the synthesis and accumulation of fat [5]. The accumulation of adipose tissue has come to be considered a global public health problem. The hypertrophy of this tissue generates harmful effects on the organism through the secretion of various types of adipokines, and for this reason obesity happens to be considered one of the major risk factors for the development of metabolic syndrome and, consequently, is listed as one of the most serious problems in relation to quality of life [6]. According to epidemiological data, it is expected that by 2025, approximately 18% of men and 21% of women worldwide will be considered obese [7]. With that in mind, since fructose consumption is strongly associated with the development of obesity, studies aimed at evaluating its role in the development of obesity are of paramount importance for a better understanding of the development process of obesity.

A recent meta-analysis found that consumption of fructose-rich beverages leads to increased body weight gain, elevated systolic blood pressure, hyperglycaemia, hyperinsulinaemia, and serum triglyceride concentration [8]. On the other hand, it was demonstrated that the replacement of fructose by glucose in beverages for 4 weeks resulted in an improvement in insulin sensitivity in adipose tissue in young subjects diagnosed with non-alcoholic fatty liver disease (NAFLD) [9]. The harmful effects of fructose can also be found from the first months of life. Newborn babies, who were breastfed by mothers who had ingested this sugar during pregnancy or lactation, presented metabolic alterations that can last throughout life. Zheng and collaborators [10] showed that children of mothers who consumed fructose had increased body weight, food intake and circulating levels of leptin, and decreased insulin sensitivity. Later Hu and collaborators [11] demonstrated that each glass or can of fructose-enriched beverage ingested daily by a child increases by up to six times the probability of that child becoming obese during adulthood [12], thereby listing fructose as an important sugar in the genesis of obesity.

2. The history of fructose consumption

Sucrose has been widely used since the Middle Ages as a dietary component. It was originally derived from sugar cane in countries such as New Guinea and the Indian subcontinent, from where it was transported to Europe where it was consumed only by royalty and the most fortunate. In the fifteenth century the countries of the Iberian Peninsula began to increase the planting of sugar cane and sugar production. However, only after the 1500s, with the discovery of the Americas and the use of slave labour, did cane planting and sugar export begin to expand. Consequently, with the increase in its production, sugar began to be consumed by the whole population, becoming widely used for the production of sweets during the eighteenth century, so that the average consumption per capita of sugar in England jumped from 1.8 kilograms in the year 1700 to 8.1 in 1800 [4]. Finally, it was only in the 1960s that fructose was included as a sweetener in the diet with the production of “sweet corn-based syrups” known as “high-fructose corn syrups” (HFCSs) [13].

The inclusion of HFCS as a sweetener brought benefits such as longer shelf life and lower cost [4]. Thus, the creation of HFCS-42 in 1967 and HFCS-55 in 1977 (HFCS-42 consisted of 42% and HFCS-55 consisted of 55% fructose, respectively) promoted new opportunities for the sweetener and beverage industries. Since then, consumption of sucrose and HFCS has grown exponentially. In the 1970s, syrup accounted for less than 1 per cent of the calories ingested through caloric sweeteners in the United States, reaching a rate of 42 per cent in the 2000s and it is currently found in most foods containing caloric sweeteners [14]. While efforts to combat the development and treatment of obesity are rising, food production containing fructose, sucrose or HCFs is increasing quickly. Currently, an American individual consumes on average 72 g/day of sugar, corresponding to approximately 275 kcal/day [15]. Over the years, syrups rich in fructose have been produced from a variety of other raw materials, such as sugar cane, tapioca, rice, wheat, manioc and beet [13]. This led several research groups to identify the intake of this nutrient as the main engine of the current obesity pandemic [16,17].

3. Sweet poison

Found in several processed foods, fructose is usually either bonded to glucose molecules (sucrose) or not (HFCS). After ingestion, the fructose molecules pass through the digestive tract and reach the small intestine where they are rapidly absorbed by the intestinal epithelium through the glucose transporters (GLUT5) [18] and then released into the bloodstream. In the bloodstream, this nutrient is absorbed by different tissues but mainly by the liver, which has high amounts of glucose transporter 2 (GLUT2) [18]. On the other hand, virtually no fructose is absorbed by pancreatic beta cells because they lack expressive amounts of GLUT2 and GLUT5 transporters [19]. This characteristic is extremely important for understanding the pathogenesis of obesity. While glucose triggers the release of insulin by pancreatic beta cells, fructose is not able to do so [15]. In addition, this nutrient also appears to not stimulate leptin release and does not suppress the release of ghrelin in starvation [15,20]. These three peptide hormones play a fundamental role in the control of food intake and basal energy expenditure, acting both in the central nervous system and peripheral tissues [21,22]. While ghrelin increases the forkhead box protein 01 (FoxO1) binding to DNA, both insulin and leptin phosphorylate FoxO1, releasing it from DNA, thereby reducing the hunger signal and hepatic gluconeogenesis and contributing to increased energy expenditure [23,24]. Animal studies have shown that following the administration of fructose directly into the hypothalamus, rodents showed increased food intake while glucose injection had the opposite effect [25]. These findings explain in part the increased prevalence of obesity in individuals who consume this nutrient in the form of sugary drinks or industrialized foods [11]. Although the lack of effects on satiety, energy expenditure, and glucose uptake in itself is extremely damaging, fructose also activates extremely harmful signalling pathways in liver tissue cells.

Most cells have reduced GLUT2 content, which leads to a marked transport of this nutrient to the hepatocytes where the presence of these transporters is abundant [18]. Inside the cytoplasm, fructose may provide an energetic substrate for hepatic glucose production (gluconeogenesis) or be rapidly phosphorylated and converted to fructose 1-phosphate (fructose 1-P) by the action of the enzyme fructokinase, which uses the energy of an ATP molecule. This conversion decreases energetic availability in the hepatocyte and increases the contents of intracellular ADP and AMP. Elevated levels of ADP and AMP activate mitochondrial energetic pathways, increasing the NAD

$^{+}/\text{NADH}$ ratio. An increased $\text{NAD}^{+}/\text{NADH}$ ratio leads to increased activity of Sirtuin-1 (SIRT-1) and phosphoenolpyruvate carboxykinase (PEPCK) [26]. Finally, the strong deacetylation activity of SIRT-1 [25] deacetylates the already known FoxO1 protein, increasing its binding to nuclear DNA and triggering the expression of the protein kinase C (PKC) and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 α) genes [27,28]. All this fine mechanism triggered by the simple elevation of fructose in the intracellular environment results in increased rates of hepatic gluconeogenesis and hyperglycaemia. In addition to the effects on the control of glycaemic homeostasis, increased AMP concentration triggered by fructose activates the AMP deaminase enzyme, starting the hypoxanthine pathways, which increases the inflammatory process and produces uric acid. Uric acid is a potent inhibitor of the nitric oxide synthase enzyme that acts on the production of nitric oxide by the conversion of arginine to citrulline [29]. Nitric oxide plays a key role in endothelial relaxation leading to vasodilation through increased lumen diameter of arteries. As a result, fructose, through increased levels of uric acid, may prevent the proper functioning of blood vessel gauge control pathways and contribute to elevated systemic blood pressure [30]. All these mechanisms initially triggered by the transport of fructose into the hepatocyte are extremely relevant and contribute to the development of diseases such as hyperglycaemia, gout, endothelial inflammation and arterial hypertension [2,31].

Raising the levels of fructose-1P inside cells activates other important energy pathways. The 1P form of this nutrient activates peroxisome proliferator-activated receptor-gamma coactivator 1 beta (PGC1- β) protein, which in turn increases the expression of the sterol regulatory element-binding protein 1c (SREBP1c). SREBP1c initiates the transcription of fatty acyl-coA synthase (FAS) and acetyl-CoA carboxylase (ACC) proteins [32]. All these mechanisms prepare the cell for an increase in fatty acid synthesis using the carbon chains supplied by intracellular fructose. The fructose-1P is converted into glyceraldehyde and dihydroxyetonephosphate, two intermediates of glycolysis. This process, called "fructolysis", requires the activity of the enzyme fructose-1P aldolase [33]. Glyceraldehyde provides carbon chains for the production of pyruvate, which goes to the mitochondria where it is reduced to Acetyl-CoA. In the mitochondrial matrix, Acetyl-CoA is converted to citrate through the Krebs cycle and then migrates from the mitochondria to cytoplasm where it will be converted into malonyl-CoA by the enzyme ACC. The excess of malonyl-coA in cytoplasm inhibits the activity of the protein carnitine palmitoyl transferase 1 (CPT-1), thereby blocking the transport of lipids to the mitochondria, and stopping the β -oxidation [34]. Malonyl-coA will be converted to acyl-coA by the enzyme FAS (transcribed by increased activity of SREBP1c). This fatty acid now has three different targets in the cell. Part of the acyl-coA produces triglyceride molecules that accumulate in the hepatocyte, leading to non-alcoholic fatty liver disease. Another amount binds to apolipoprotein (ApoB) to produce very low density lipoprotein (VLDL), or simply diffuses in the form of free fatty acids into the bloodstream, triggering hypercholesterolaemia and dyslipidaemia [1,33]. The excessive influx of lipids can now reach the white adipose tissue, generating WAT hypertrophy of it; the skeletal muscle, where it triggers insulin resistance [35]; or the pancreas, inhibiting the production and secretion of insulin. Finally, high levels of acyl-coA can be converted to diacylglycerol (DAG) by diacylglycerol acyltransferase [36]. DAG activates the protein PKC ϵ , which, in turn, activates the protein c-jun-N terminal kinase-1 (JNK1) [37]. This protein leads to hepatic insulin resistance through the phosphorylation of IRS-1 on Serine307 residue (IRS-1Ser307). This mechanism of hepatic insulin resistance perpetuates the sign of hepatic

gluconeogenesis, leading to a marked increase in blood glucose and contributing to weight gain [14,38]. In 2000, Ueno and collaborators (2000) observed that insulin signalling was reduced by nearly 72% in the hepatic tissue of rodents exposed to a fructose-rich diet for 28 days [39]. In addition to inducing hepatic insulin resistance, activation of JNK-1 activates transcription factor 1 (AP-1). AP-1 transcribes inflammatory genes and activates the synthesis of inflammatory cytokines by the hepatocyte. Once released into the extracellular environment, these cytokines will bind to cytokine receptors in Kupffer cells. These cells perpetuate the inflammatory signal and can further overwhelm the hepatocyte through the release of reactive oxygen species and cytokines [40]. Both alcohol consumption and fructose consumption activate the formation of reactive oxygen species and increase the expression of inflammatory proteins in the hepatocyte, contributing to tissue damage and inflammation through this tricky process [16,41]. In addition, fructose can exist in two different stereoisomeric forms, one linear (ketone form) and the other in the form of a furanosidic ring (fructofuranose). The ratio of both forms depends on the pH and temperature of the medium. In the bloodstream most of the fructose is in the linear form with the ketone group exposed and susceptible to fructosylation reactions. In fact, fructose fructosylation releases large amounts of superoxide anion, leading to the disproportionate formation of reactive oxygen species [42]. The expressive increases of reactive oxygen species (ROS) leads the system to increase the antioxidant response by abruptly raising the expression of reducing proteins [43]. This response may be compromised in children and adults with micronutrient deficiency leading to cellular and tissue damage [44]. Even under ideal micronutritional conditions, long-term administration of fructose can result in the failure of the antioxidant system [45,46]. In addition, this imbalance in the redox state and increased cell damage also lead to increases in JNK phosphorylation and activation of the AP-1 transcription factor. This pro-inflammatory additive perpetuates the insulin resistance and hepatic lipogenesis [47]. Finally, the excessive consumption of fructose produces a link between white adipose tissue and the liver [48]. Hypertrophy of white adipose tissue triggers an increased release of inflammatory cytokines by the adipocyte. Among these cytokines is the tumour necrosis factor family. In a study published by our group in 2016, we showed that levels of circulating tumour necrosis factor alpha (TNF- α) in animals fed a high fructose diet were practically doubled [49]. These cytokines bind to specific cellular receptors and activate the cascade to perpetuate the inflammatory signal and insulin resistance. In the liver, these cytokines may increase the expression of another family of inflammatory receptors, the toll-like receptors (TLRs) [50], leading to overlapping systems repeating an already deregulated process of inflammatory feedback. In skeletal muscle, the presence of these cytokines can trigger insulin resistance [49]. In the central nervous system, the presence of inflammatory cytokines prevents efficient signalling of leptin and insulin by inhibiting the effect of these peptides on food consumption, energy expenditure and central control of hepatic gluconeogenesis through reduced FoxO1 phosphorylation [24].

All cascades exposed so far perpetuate the harmful signal of fructose metabolism in the hepatocyte by activating a vicious cycle that can only be stopped by replacing this nutrient with another in the diet [51–53], and they are shown in Figure 1.

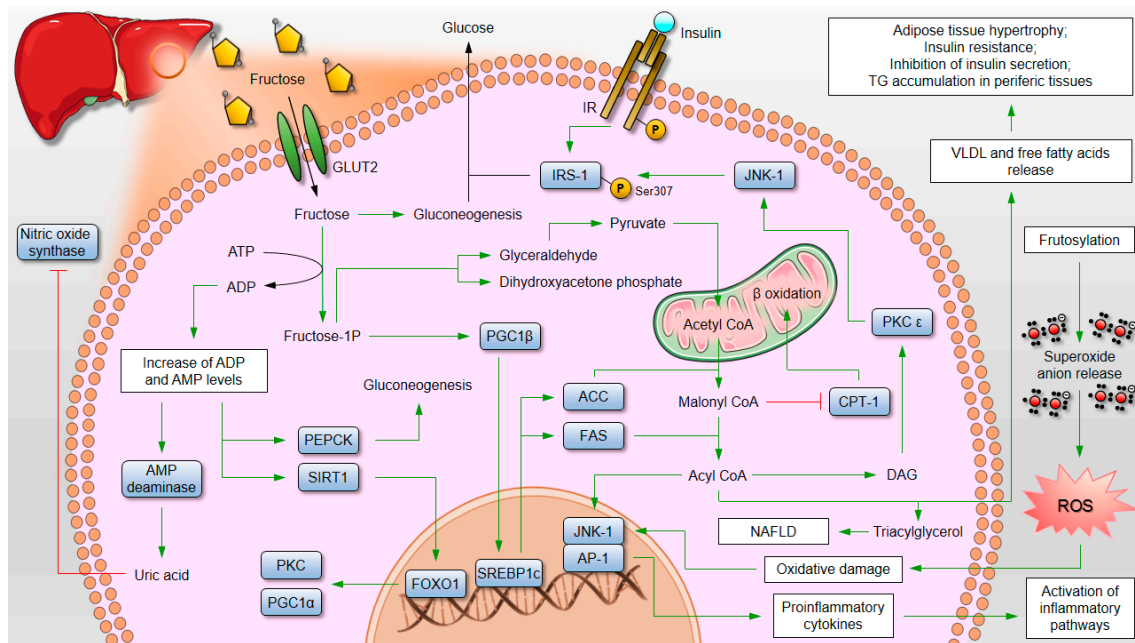


Figure 1 - Role of fructose on metabolic diseases. Fructose reduces the phosphate biodisponibility leading to acid uric production and nitric oxide synthase inhibition contributing to hypertension. Reduced phosphate biodisponibility also activate SIRT-Dependent deacetylase of FoxO1 contributing to gluconeogenesis and hyperglycemia. Fructose-1P upregulates PGC-1 β expression promoting lipogenesis through SREBP1c activation. The same nutrient provides carbon chains for the synthesis of triglycerides, diacylglycerides and VLDL cholesterol contributing to hypertriglyceridemia, hepatic insulin resistance and dyslipidemia. Sub products of fructose target another tissues leading to systemic insulin resistance and inflammation. Finally, ROS generating by fructolysation increases oxidative damage and stress response in the inner of cell leading to DNA damage proinflammatory cytokines production. GLUT2: glucose transporter-2; SIRT-1: Sirtuin-1; PEPCCK: Phosphoenolpiruvate carboxylase. PGC-1 β : peroxissome proliferator-activated receptor gamma coactivator 1-beta. FoxO1: forkhead box protein 1; SREBP1c: Sterol regulatory element-binding protein; ACC: acetyl-coA carboxylase; FAS: fatty acil-coA synthase; JNK-1: c-jun N-terminal kinase 1; AP-1: activator protein 1; CPT-1: carnitine palmytoil transferase -1; DAG: diacylglycerol; VLD: very-low density cholesterol; TG: triglycerides; IRS-1: insulin receptor substrate-; PKC: protein kinase C; ROS: reactive oxygen species; NAFLD: non-alcoholic fatty liver disease.

4. How to deal with the enemy

Thus, several studies have demonstrated evidence that fructose is a nutrient with great obesogenic potential, associated with several metabolic complications and the promotion of *de novo* lipogenesis [1,54].

Together with obesogenic stimuli from nutritional factors, epidemiological studies also show that the genesis of obesity in contemporary society is also linked to the progressive decrease in the time available for the practice of physical activities by the global population [55]. Thus, it is strongly proposed that exercise is an important tool for combating weight gain and its associated complications, acting in the prevention and treatment of the deleterious changes promoted by high consumption of fructose. However, different models of exercise have been proposed for an

improvement in metabolic health, such as aerobic exercise, strength and the combination of both. Therefore, we will discuss the different models separately.

4.1. Fructose consumption and its complications: the role of aerobic exercise

The knowledge that aerobic exercise is capable of promoting improvement in metabolic health is not recent. Studies performed at the beginning of the 20th century already provided information that physical exercise could potentiate the action of insulin, and thus increases the uptake and utilization of glucose [56]. Recently, studies using immunofluorescence staining technique demonstrated that the glucose transporters 4 (GLUT4) are stored in vesicles in the intracellular environment during rest. However, shortly after an exercise session, the GLUT4 are homogeneously redistributed by the plasma membrane, as well as when there is insulin stimulation [57]. One of the main mechanisms proposed for this phenomenon involves the activation of the protein sensitive to AMP intracellular levels, the AMP-activated protein kinase (AMPK), which is considered essential for the control of energy balance [58]. When activated, AMPK promotes the phosphorylation and activation of Akt substrate that weight 160 kDa, the AS160. This protein, will promote the release of GLUT4, allowing the transporter going to the cell membrane by independent mechanisms of insulin action [59,60].

Furthermore, Matos and colleagues [61] demonstrated that, when stimulated by insulin, obese animals that were submitted to an aerobic exercise session showed insulin signaling pathway activation similar to the control group, while the sedentary obese animals showed a consistent reduction in this activation. It is suggested that this effect may be caused due to the fact that aerobic exercise reduces the levels and activity of pro-inflammatory proteins [62,63], and protein-tyrosine phosphatase 1B (PTP-1B), thereby reducing the insulin resistance state [62]. Therefore, aerobic exercise increases both insulin action in skeletal muscle and glucose uptake by mechanisms that are independent of the action of this hormone. Thus, we can infer that aerobic exercise provides an agonist action of insulin in skeletal muscle. However, the improvement of metabolic process promoted by this type of exercise is not limited to skeletal muscle [61,62], It also extends to other key tissues such as liver [64,65], hypothalamus [66,67] and adipose tissue [65].

In hepatic tissue, our group demonstrated that with only one exercise session it is possible to reduce the levels of PTP-1B [64], a protein which is able to down-regulate insulin signal transduction [68]. The same study also found decreased levels of proteins involved in gluconeogenesis, such as PEPCK and glucose-6-phosphatase (G6Pase). Aerobic exercise also proved to be able to reduce the phosphorylation of proteins kinase RNA-like endoplasmic reticulum kinase (PERK) and eukaryotic initiation factor 2- α (eIF2 α) [65], which are regarded as the greatest stress markers of endoplasmic reticulum [69]. Thus, the phosphorylation of insulin receptor tyrosine and their substrates and activation of protein kinase B (Akt) increased as well as decreased inflammation in this tissue.

In the central nervous system, specifically in the hypothalamus, aerobic exercise seems to influence the control of hunger and satiety. Ropelle et al. [66] Observed that the energy intake of animals treated with a hyperlipid diet is higher than that of animals treated with commercial feed. The authors also showed that when these same animals were submitted to aerobic exercise session, both on a treadmill as swimming, the energy intake of obese group was equal to the control group within 12 hours following the completion of the exercise. In addition, even though there was no reduction in body weight and adipose tissue, mRNA levels of pro-opiomelanocortin (POMC) were

increased and the levels of neuropeptide-Y (NPY) were decreased in the hypothalamus of these animals. Rodrigues and co-authors [67], Demonstrated that aerobic exercise reduced the phosphorylation and translocation of FoxO1 into the nucleus, thus inhibiting the transcription of orexigenic neuropeptides. Moreover, the protein content and activity of a mammalian homolog of *Drosophila* tribbles 3 (TRB3) - which may be associated with AKT and down-regulate insulin signaling in hypothalamus - was decreased.

Adipose tissue is also the target of molecular changes promoted by aerobic exercise. Besides reducing the amount of fat in different regions [70,71], aerobic training is also able to reduce hypertrophy of adipocytes in obese animals [71], which is essential to improve the systemic inflammatory status promoted by obesity, since, when hypertrophied adipose tissue is responsible for the secretion of a series of proteins with pro-inflammatory activity [6]. Consequently, pro-inflammatory pathways such as JNK and I-kappa-B-alpha ($I\kappa B\alpha$) are less activated [65].

Once enhanced insulin activity in several tissues that are responsible for the metabolic control, the serum levels of pro-inflammatory proteins [65,67], and fasting glucose [61,72] are reduced. After 8 weeks of endurance training, da Luz et al. [65] observed a decrease in serum levels of TNF- α , demonstrating that there was a systemic decrease in the inflammation of obese animals. Likewise, aerobic exercise also reduces oxidative stress and increases the antioxidant capacity.

Aerobic exercise is also proposed as a strong strategy for the prevention and treatment of NAFLD. Gauthier et al. [73] found that sedentary obese animals had a 72% increase in fat accumulation in the liver, with vacuoles lipid 48% higher compared to animals treated with standard diet. However, animals that performed aerobic exercise during obesity induction period, the development of NAFLD has been completely reduced. Similar results were found by Shen and colleagues [71], in which the amount of fat observed in the liver of obese and exercised animals was similar to that observed in the control animals. These results were still accompanied by a reduction in the gene expression of stearoyl-CoA desaturase-1 (SCD-1), described as key regulator of lipid metabolism, so that this deletion provides an improvement in the oxidation of fatty acids machinery in the liver [74]. Charbonneau et al. [70] also observed that after training the obese animals equated the liver TG levels to the control group.

As discussed previously, the lipogenic properties of fructose are associated with large increases in triglyceride levels [75–77]. In this context, the practice of exercise, especially aerobic exercise, is shown to promote important and consistent effects related to the pathogenesis of dyslipidaemias [72,78]. In an important meta-analysis involving 51 studies, Leon and Sanchez [79] found that after 12 weeks or more of aerobic exercise intervention, the subjects had a mean reduction of 3.7% in triglyceride levels, while HDL levels were elevated by 4.6% and LDL reduced by 5% on average.

Finally, there is evidence that aerobic exercise is an important tool to combat various metabolic complications induced by high fructose consumption [49,80]. In a study conducted by Stanišić et al. [81], Wistar rats received a 10% glucose solution for 8 weeks, and thereafter a significant increase in insulin levels and severe insulin resistance were observed. However, animals that underwent running exercise on a treadmill during the experiment had such attenuated complications. In addition, another study involving healthy humans revealed that even after adding 75g daily of fructose in their diet, physical activity was able to reduce insulin levels and keeping unchanged the triglyceride levels of active volunteers, while, on the other hand, the inactive people showed an increase in this parameter [82]. Egli et al. [83] observed that aerobic exercise (moderate intensity)

completely eliminated the deleterious effects promoted by 4 days of diet consumption composed by 30% of fructose. Our research group [49] Aerobic exercise, in addition to reducing the activity of inflammatory proteins in the skeletal muscle of animals fed a high fructose diet, also increased levels of interleukin 10, described as a protein with a potent anti-inflammatory potential [84]. Exercised rodents treated with fructose also decreased in oxidative stress markers [85] and NAFLD [80], and lower TG accumulation in liver tissue [49].

4.2. Fructose consumption and its complications: the role of strength exercise

Although we are reaching a century of publications on metabolic syndrome related to aerobic exercise, the same does not apply to the strength exercise. In 1984, Miller and colleagues [86], in a longitudinal study of healthy subjects, observed the effects of the completion of 10 weeks of isotonic exercise with weights. After the training protocol, participants showed no differences in fasting glucose, but the plasma insulin levels were significantly reduced, from $10.85 \pm 1.55 \mu\text{U/mL}$ to $6.79 \pm 1.19 \mu\text{U/mL}$. During the glucose tolerance test, the area under the insulinemic curve of subjects submitted to resistance training was also lower than that of those who remained sedentary during the same period, thus bringing the first evidence that strength exercise also has the capacity to improve the insulin sensitivity. Finally, the authors also observed an increase in the amount of muscle mass in the trained group, and that these gains had a strong negative correlation with insulin levels during glucose tolerance test. A decade later, Treuth et al. [87] showed evidence on the relationship of strength training with adiposity control and, consequently, obesity. After 16 weeks of exercise performed 3 times per week, the authors observed that although the body weight of participants was not changed, the amount of intra-abdominal adipose tissue was significantly reduced [88].

Recent studies have provided us with a better understanding of how strength exercise is able to improve for glycemic control. A performed study which used obese animals and submitted them to strength exercise on staircase [89], besides confirming reductions in serum insulin levels showed that after 8 weeks of training some proteins from insulin pathway had increased their action, such as phosphatidylinositol 3-kinase (PI3-K) and Akt. Furthermore, the GLUT4 gene expression was also increased in these animals. Another study published by the same group of researchers [90] showed that serum levels of TNF- α and interleukin 6 are reduced with training, accompanied by increase of adiponectin [91]. However, obese subjects undergoing strength training showed improvement in insulin sensitivity even without changes in serum levels of proinflammatory cytokines [92].

Several studies have begun to suggest the strength exercise as an important strategy for the prevention and treatment of obesity [93–95] and in one of these Schmitz and colleagues [94] found positive results in body composition of women who performed strength exercise. In the fifteenth week of intervention, there was a reduction of body fat and muscle mass gains. In another state, after one year of intervention, reduction in the amount of intra-abdominal fat were also observed [95].

After a strength exercise session, positive changes on the lipid profile were observed by Lira et al [96]. However, interestingly, different responses were observed according to the intensity of the effort. After 72 hours of the end of the session, the plasma TG levels were reduced only in subjects who trained in the intensities of 50% and 75% of 1RM, while those trained at 90% and 100% showed no differences. Also, after an exercise session, the sensitivity to insulin in the hepatic tissue was improved at $8\% \pm 1\%$ reductions in glucose production rate and $12\% \pm 5\%$ glycogenolysis [97].

In summary, the strength exercise promoted consistent improvements in the metabolism of rodents fed a high fructose diet [49]. As aerobic exercise, resistance exercise provided lower levels of glucose and insulin during glucose tolerance test. Moreover, strength exercise decreases IL-6 and TNF- α levels. Regarding liver tissue, strength exercise decreases fat accumulation and greater reduction in the levels of nuclear factor-kappa B (NF- κ B) and I κ B- α , demonstrating that the strength exercise can be promising for the reduction of inflammation promoted by diet rich in fructose.

4.3. Fructose consumption and its complications: the role of combined Exercise

In the last decades the effects of combined physical exercise have been gaining prominence in the scientific community. This exercise protocol consists of endurance and strength exercises performed in the same training session or alternate days. Initially, the practice of combined exercise did not seem to be an interesting strategy for metabolic health, since in the 1980s, a classic study revealed that when subjects performed strength exercises and subsequently practiced cycling and running, the strength gains, muscle mass and consequent increase in body weight were compromised [98]. However, the gains in aerobic performance were not different between individuals who performed aerobic training and those who underwent the combined training. A few years later, the results found by Kraemer et al [99] corroborated the above article, where the authors found that subjects underwent combined exercise showed smaller area in the muscle fibers compared to those performed only strength exercise. Thus, it was also shown that combined exercise not only compromised the strength gains, promoted by strength exercise, but also hypertrophy of different muscle fibers.

However, subsequent studies began to demonstrate evidence that challenged the negative influence of combined exercise on strength gain and cross-sectional area on muscle fibers. In their study, McCarthy et al. [100] showed that the combined exercise, performed 3 times a week, for 10 weeks, promoted the same increase in flexor and knee extensor muscle area than strength exercise alone, with no difference also in neural activation. De Souza et al. [101], Although they did not find hypertrophy after the combined training protocol, did not find differences in the expression of genes related to the control of protein synthesis, Suggesting that the control of other training variables such as session volume may be related to these different responses found in the different protocols. Finally, it has also been demonstrated in humans that the activation of proteins involved with protein synthesis such as the mechanistic target of rapamycin (mTOR) and ribosomal protein S6 kinase beta-1 (S6K1) are not compromised because AMPK activation [102], protein strongly described with increased activity by the increase in AMP levels provided by aerobic exercise [63,103], that in rodents was shown to be able to negatively influence the stimulation of protein synthesis by inhibiting the mTOR pathway [104]. From this, many other studies have been conducted to better understand the changes promoted by this new and promising exercise protocol, in many different contexts, since it is believed that this type of exercise can activate different pathways and promote several improvements. For these reasons, currently, the combined exercise is widely recommended by the American College of Sports and Medicine [105].

Monteiro and colleagues [106] observed positive effects on body composition in obese adolescents after 20 weeks of combined exercise. At the end of the experiment, the participants presented reduction of body weight and body mass index (BMI). Interestingly, the magnitude in reducing body fat was very close between the groups who underwent the combined exercise and

aerobic exercise only, and this reduction was 3.5% and 3.9% respectively. Moreover, consistent results were also found in the lipid profile, with reduction in circulating levels of TG and VLDL and increase in HDL levels. On the other hand, the waist circumference of these participants was not different.

Medeiros et al. [107] also found positive results of combined exercise on body composition in obese subjects, reflecting an improvement in insulin resistance and oxidative stress markers. Interestingly, the authors used two groups with similar exercise protocols, but one group exercised 3 days a week, while the other exercised 5. Both groups showed a reduction in body weight and BMI. The group that exercised 5 days per week reduced the amount of fat mass and increased the amount of muscle mass. The group that performed the training protocol 3 days per week presented reductions in fasting blood glucose levels and the HOMA-IR index. Reductions in protein carbonylation levels were observed in the group that performed 3 weekly sessions, indicating an improvement in the antioxidant machinery, since this is a process triggered by ROS [108]. The activity of glutathione peroxidase was decreased and lipid peroxidation increased in both groups. It is known that exercise can moderately increase ROS production, and thus provide positive adaptations for the entire antioxidant system [109]. Thus, these results suggest that combined exercise may be an important strategy for combating insulin resistance and oxidative stress associated with obesity, but more studies are needed to fully understand controls of exercise variables, such as exercise intensity and frequency.

Finally, the combined exercise was also able to present improvements in several deleterious contexts promoted by the high consumption of fructose [49]. Our research group revealed that combined exercise when performed on alternate days (aerobic and strength on separate days), despite not promoting reduction in body weight, was able to provide an increase in glucose tolerance and insulin sensitivity compared to aerobic protocol. The circulating levels of HDL were increased, and the reduction of hepatic TG accumulation was strongly visible in histological sections, when compared to the sedentary animals that received high doses of fructose. Finally, exercise also provided a lower activation of NF- κ B, thus presenting a decrease in systemic inflammation.

5. Conclusion

The consumption of fructose has been increasing and with it grows the harmful effects of this sugar on the organism. Fructose may trigger changes in the circulating and hepatic lipid profile, favouring the installation of chronic and subclinical inflammation. The regular practice of aerobic physical exercise, strength or a combination of both, in turn, has the ability to reverse these parameters, mainly by improving the circulating and tissue lipid profile and reducing inflammation (Figure 2). Therefore, the regular practice of physical exercise is an essential tool for attenuating the obesogenic disorders caused by the consumption of fructose.

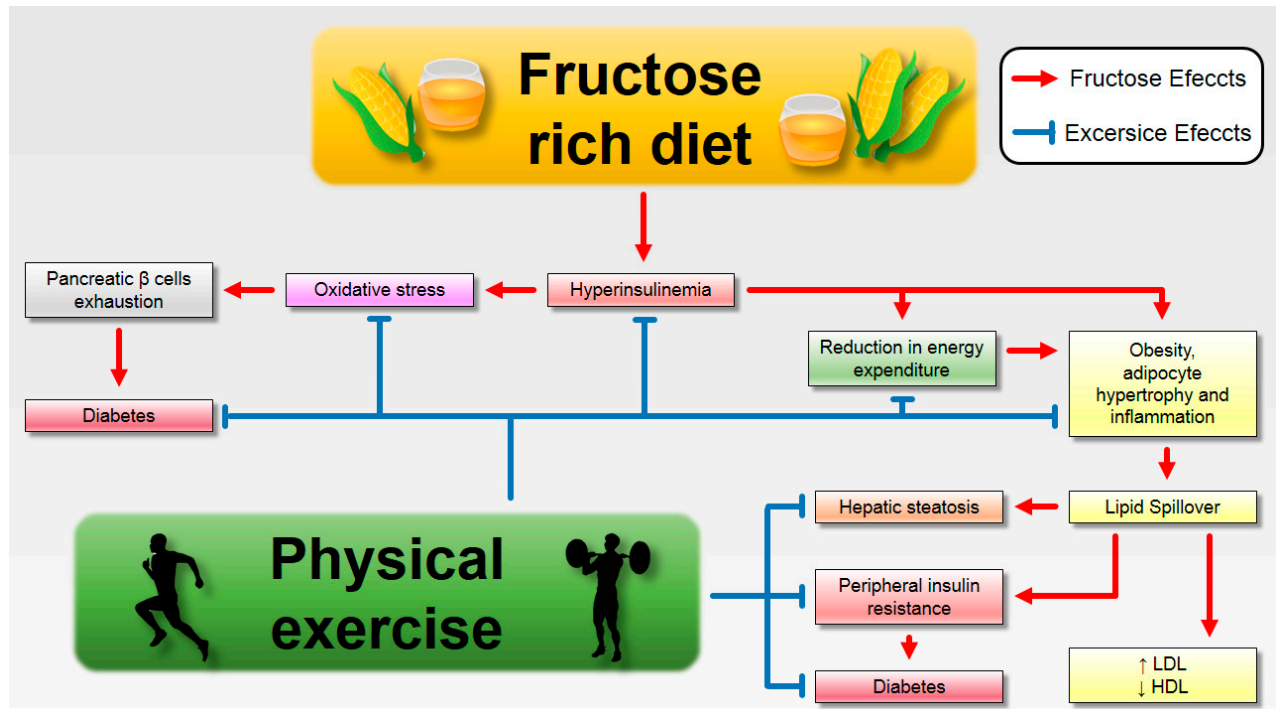


Figure 2 - Exercise prevents and treats the deleterious effects of high consumption of fructose. Besides to promote increase in the energy expenditure, physical exercise consistently attenuate inflammation and oxidative stress related to excessive consumption of fructose, reflecting in positive changes both in lipid profile and fat metabolism. In this way, insulin resistance and hyperinsulinaemia are diminished, collaborating with the prevention and treatment of diseases such as hepatic steatosis and type 2 diabetes.

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Abbreviations

The following abbreviations are used in this review:

ACC	Acetyl-CoA Carboxylase
ADP	Adenosine Diphosphate
Akt	Protein kinase B
AMP	Adenosine Monophosphate
AMPK	AMP-activated protein kinase
AP-1	Activator Protein - 1
ATP	Adenosine Triphosphate
BMI	Body mass index
CPT-1	Carnitine Palmitoyl Transferase 1
DAG	Diacylglycerol

DNA	Deoxyribonucleic Acid
eIF2 α	Eukaryotic initiation factor 2- α
FAS	Fatty Acyl - CoA Synthase
FoxO1	Forkhead box protein 01
Fructose 1-P	Fructose 1 - Phosphate
G6Pase	Glucose-6-phosphatase
GLUT2	Glucose Transporter 2
GLUT4	Glucose Transporter 4
GLUT5	Glucose Transporter 5
HDL	High-Density Lipoprotein
HFCS - 42	High-Fructose Corn Syrup with 42% of Fructose
HFCS - 55	High-Fructose Corn Syrup with 55% of Fructose
HFCS	High-Fructose Corn Syrup
I κ B α	I-kappa-B-alpha
IRS-1	Insulin Receptor Substrate 1
JNK 1	C-Jun-N terminal kinase - 1
LDL	Low-Density Lipoprotein
mTOR	Mechanistic target of rapamycin
NAD ⁺ /NADH	Nicotinamide Adenine Dinucleotide
NAFLD	Non-Alcoholic Fat Liver Disease
NF- κ B	Nuclear factor-kappa B
NPY	Neuropeptide-Y
PEPCK	Phosphoenolpyruvate Carboxykinase
PERK	Protein kinase RNA-like endoplasmic reticulum kinase
PGC-1 α	Peroxisome Proliferator-Activated Receptor - Gama Coativator 1 Alpha
PGC-1 β	Peroxisome Proliferator-Activated Receptor - Gama Coativator 1 Beta
PKC	Protein Kinase C
POMC	Proopiomelanocortin
PTP-1B	Protein-tyrosine phosphatase 1B
ROS	Reactive Oxygen Species
S6K1	Ribosomal protein S6 kinase beta-1
SCD-1	Stearoyl-CoA desaturase-1
SIRT-1	Sirtuin-1
SREBP1c	Sterol Regulatory Element-Binding Protein 1c
TG	Triglycerides
TNF- α	Tumour necrosis factor alpha
TRB3	Tribbles homolog 3
VLDL	Very Low Density Lipoprotein
WAT	White Adipose Tissue

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