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ANIMAL MODELS IN THE EVALUATION OF INFLAMMATION CAUSED BY CARBOHYDRATE-RICH DIETS: BRIEF SCIENTIFIC LITERATURE REVIEW

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ABSTRACT

The quality of diet influences in development of chronic diseases as obesity and metabolic syndrome that trigger low-grade inflammatory process. With the objective of analyzing the reflexes of obesity and metabolic inflammation animal models of diseases have been proposed to induce inflammatory processes through different types of diets, such as high-carbohydrate (HCD) and high-fat diets (HFD), both of them producing deleterious effects on the body. Studies show that the model of obesity induced by diets with high energy density, specifically HCD, is a relevant model for inflammatory processes linked to obesity. This study proposes to do an integrative review on dietary obesity and inflammatory animal models, especially using HCD within the last ten years, using the description words obesity, animal model and inflammation. 1,126 papers were published on these characteristics, with publication peaking in 2015. HCD diets were related to inflammation, important deleterious effects to the metabolism, generating systemic and tissue damages mainly at adipose, cardiac and hepatic levels, higher expression of proinflammatory cytokines along with greater visceral adiposity.

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INTRODUCTION

According to the World Health Organization (WHO, 2004), consumption of inadequate diets and physical inactivity are among the main risk factors for morbidity and mortality. Several studies have addressed the influence of diet on chronic diseases such as cardiovascular, obesity, diabetes (Gadenz and Benvegnú, 2013; Misirli *et al*., 2012; Mente *et al*., 2009), genetic disorders and cancer (Mourouti *et al*., 2015; Kaczmarczyk *et al*., 2012).

Those searches show how foods can change the body's inflammatory parameters (Casal and Garcia, 2014; Ma *et al*., 2008; *Ma et al*., 2006). In fact, obesity is responsible for triggering low-grade inflammatory processes due to changes in adipose tissue function, which produces adipokines, cytokines, and inflammatory factors that are related to the onset of other metabolic disorders. (Sanyal *et al*., 2017; Gomes *et al*., 2016; Uusitupa and Schwab, 2013; Vellosa *et al*., 2013). Inflammation presents a possible bidirectional connection with

the metabolic syndrome through insulin resistance, in which any chronic inflammatory process leads to insulin resistance, which in turn influences the inflammatory process in the body. (Dandona *et al*., 2007). Scientific studies have shown that qualitative and quantitative changes in diet composition play a protective role for obesity and are responsible for the improvement of levels of inflammatory markers(Gomes *et al*., 2016; Bourassae *et al*, 2016; Uusitupa and Schwab, 2013).Thus, it is important to analyze studies that use different experimental diets to understand the changes induced by increased adiposity (Oliveira *et al*., 2013) seeking besides the treatment of obesity the prevention of comorbidities. Considering that diverse diets can influence the metabolic state and inflammation in different ways, along with the gradative risen ingestion of carbohydrates, characterized by refined sugar on western diets and mainly in development countries and the difficulty to assess in humans the effects this diet model, animal models has been used to evaluate the inflammatory effects caused by different types of diet.

MATERIALS AND METHODS

The present review wasbased on published results ofanimal models of dietary inflammation and obesity related with diets, especially those related to high-carbohydrate diet. It was included studies within the last 10 years of 2007 – 2016 period frames in the PubMed, using the joint descriptors: animal models; inflammation and obesity. The selection of studies for full reading and inclusion in the review was made through the reading of the abstracts, including studies based on dietary animal models of disease that analysis of at least one inflammatory parameter.Were excluded studies that assessed the effects only of HFD, or the inflammation was not key component. Some studies that did not fit the search criteria, but that are relevant in the theme were included. In total, 45 papers were selected to this review.

Obesity and Diet-Induced Metabolic Inflammation

In the case of obesity, visceral fat deposits are subject to adipocyte hypertrophy (Gustafson *et al*., 2015), which may lead to the activation of inflammation through the release of inflammatory cytokines or increased expression of genes involved in the inflammatory process, with consequent recruitment of macrophages into adipose tissue (Francisqueti *et al*, 2015). Increased infiltration of pro-inflammatory immune cells in adipose tissue, such as monocytes, macrophages, natural killer cells and lymphocytes, provides a pro-inflammatory microenvironment, with an imbalance in the secretion of adipokines and increase in the release of pro-inflammatory cytokines, , interleukin-6 (IL-6) and -1β (IL-1β), tumor necrosis factor-α (TNF-α). On the other hand, there are decreased anti-inflammatory such as adiponectin and interleukin-10 (IL-10) (Ferrante, 2013; Osborn and Olefesky, 2012; Sánchez *et al*., 2011). Adipose tissue cells and other immunity-related cell types such as adipose tissue cells and macrophages have similar roles in metabolic pathways such as activation of the complement cascade and production of inflammatory cytokines (Wellen and HotamisligiL, 2003). Experimental studies with lean and obese animals have demonstrated a large amount of inflammatory genes in adipose tissue (Soukas *et al*., 2000), as well as identified that infiltration of macrophages in this tissue may be key to these inflammatory changes (Xu *et al*., 2003; Weisberg *et al*., 2003).

The infiltration of macrophages in the adipose tissue has a primordial role in the perpetuation of obesity and insulin resistance. In fact, the development of metabolic diseases is associated with the number and phenotype of these macrophages. In the obese individual, classically activated macrophages (M1) infiltrate adipose tissue and form crown-like structures around adipocytes, releasing proinflammatory cytokines, which will contribute to the development of insulin resistance and Type 2 Diabetes Mellitus (DM2). However, in normal individuals prevail macrophages of phenotype M2 with anti-inflammatory character (Appariet *et al.,* 2017). In research conducted with mice, Shao *et al*. (2012) found macrophage infiltration in the adipose tissue of animals using a high fat diet (45% fat) and absence of this characteristic in animals on a hypolipid diet (10% fat). Results similar were also found by Van Der Heijdene *et al*. (2015).This inflammation profile also can be observed systemically in other specific organs such as liver, skeletal muscle, pancreas, brain and intestinal microbiota. In this case, inflammation contributes to the development of cardiovascular diseases and pathogenesis in patients with obesity and insulin resistance/DM2 (Appari *et al*., 2017; Pirola and Ferraz, 2017). In addition to the macrophages present in adipose tissue, Th17 cells are responsible for producing some specific cytokines such as IL-17, which were related to insulin resistance (Caër *et al*., 2017). Adipose tissue from dietary-induced obesity models also expresses higher levels of adipogenic genes such as PPARc, c/EBPa, FAS and aFABP (Kim *et al*., 2001).

According to Volp *et al* (2008), the main inflammatory markers used for the study are: Proinflammatory cytokines: interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), Interleukin-1β IL-1β), interleukin-18 (IL-18) and CD40 and CD40L; Inflammatory markers synthesized by hepatocytes: C-reactive protein (CRP), fibrinogen, serum amyloid A protein (SAA); Inhibitors of inflammation: urinary microalbumin; Enzymes: COX-2 and phospholipase-A2-associated lipoprotein; Anti-inflammatory cytokines: interleukin-10 (IL-10); Adipokines: adiponectin, Chemocins: MCP-1 (monocyte chemoattractant protein-1). As pro-inflammatory biomarkers have been widely used in animal models to monitor and evaluate the inflammation status, a review is necessary highlighting the animal models in the evaluation of inflammation caused by diets, especially in high carbohydrate diets due to high consumption of this macronutrient.

Animal Models of Dietary Obesity and Inflammation

In the last 10 years, number of published animal model studies related to obesity and inflammation has increased. This increase in scientific manuscripts involving animal models can be seen in Figure 1 below. Although for the year 2016 the numbers of studies are lower than those of 2015, both have higher values than 2007. In Figure 1, the number of published articles with animal model involves obesity and inflammation caused by different types of diet. The major animal models of disease for dietary obesity and inflammation are carried out using rodents, especially rats and mice of various strains. Such animal models involve of diet variations in the macronutrient proportions, the principal's models are the High Fat Diet (HFD) that contains a high fat and High Carb Diet (HCD) with high carbohydrate content like the cafeteria diet that simulates the western ultra-processed diet pattern. Studies have shown that consumption of diets rich in fats or refined carbohydrates can lead to comorbidities such as insulin resistance and

glucose intolerance (Oliveira *et al*., 2014). High calories diets, with the principal source been lipids, have been related to an increase in size and quantity of adipocytes, and hence, larger inflammatory cytokine release.

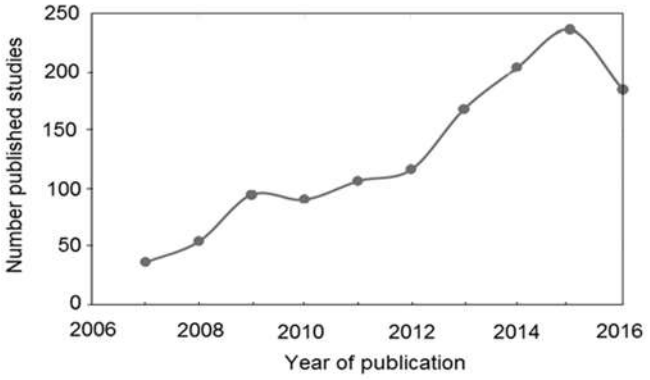

Figure 1. Temporal evolution of published studies related to obesity and inflammation involving animal models of disease in the last 10 years (from 2007 to 2016, n = 1,126 studies). *Source: PubMed, descriptors: obesity, animal models, inflammation

Fatty acids can be classified as unsaturated and saturated, the latter type being related to their obesogenic role and may trigger the metabolic syndrome (Dispirito and Mathis, 2015). According to Cortez *et al*. (2013), the prolonged consumption of a diet rich in lipids stimulates an inflammatory state. Adipose tissue macrophages release cytokines (IL-1, IL-6 and TNF-α) and pro-inflammatory chemokines by propagating this state and further increasing insulin resistance (Van DerHeijden *et al*., 2015). Studies have shown that HFD in rats induces chronic low-grade inflammation and, at the same time, impairments in the insulin signaling pathway in skeletal muscle (Todd *et al*., 2007; Yaspelkis *et al*., 2007). The insulin receptor-1 substrate (IRS-1) is an important target in the inflammatory process as well as other proteins involved in the normal insulin signaling process and activation of proinflammatory cytokines such as TNF-α, IL- 6 and IL-1β (Muurling *et al*., 2003; Karin *et al*., 2000; Zandi *et al*., 1997).

Kim *et al*. (2001) used mice fed a low fat diet (10% fat) and compared them with high fat diet (60% fat) and found higher amounts of IL-1, IL-6 and TNF-α in plasma and colon of animals fed high fat. Van Der Heijden *et al*. (2015) obtained higher TNF values using mice fed a high fat diet (45% of total calories from lard) when compared to mice fed a low fat diet (10% of total calories from lard).Similarly, Cortez *et al*. (2013), found higher amounts of IL-1, IL-6 and TNF-α in Wistar rats fed a diet containing 60.9% fat compared to animals using AIN-93 diet. In addition to the exacerbated consumption of saturated fats, a typically Western diet is also characterized by high intake of energy-dense foods from refined carbohydrates, such as high-fructose corn syrup (Myers and Allen, 2012; Jurdak *et al.*, 2008) which are considered sources of carbohydrates used in animal models for induction of obesity and associated factors, as well as the addition of sucrose (Martin*et al*., 2011; Jurdak *et al*., 2008). According to Casal and Garcia (2014), glycemic and insulin peaks related to carbohydrate-rich dietary intake can cause inflammatory effects in the body. Aliment studies using animal models also seek to better elucidate the consequences of consuming a high carbohydrate diet, especially in the associated inflammatory process in order to reproduce changes in the western diet (Woodie and Blythe, 2017). Masi *et al*. (2017) compared HCD and HFD in order to determine if both diets had The animals were fed for eight weeks with an HCD (79% carbohydrate, maize starch being the main source) or with an HDF diet (59% fat, with lard being the main source).However, half of these animals were separated and received a bowl of condensed milk (68% carbohydrates). As a result, it was observed that all diets were responsible for causing an increase in adipocyte size, but only animals fed HFD + HCD diet showed a pro-inflammatory increase in IL-16 and IL-1β, showing that the high consumption of carbohydrates may promote an increase in lipogenesis and thus causing storage of the triglycerides that will influence the inflammatory process. Other study conducted by Li *et al*. (2015) found that rats that consumed liquid HCD for 16 weeks (70% carbohydrates) had an 83% increase in inflammatory response when compared to the HFD group (60% fat), which presented only 25%. Among the inflammatory markers found in the HCD group were increased IL-1β, TNF-α while IL-6 and IL-18 were decreased.

Furthermore, Masi *et al*. (2017) analyzed the use of HFD, HCD, HFD + HCD and diet control, observed a greater inflammatory effect in the use of the diet combining lipids and carbohydrates. However, HCD has been shown to be more proinflammatory than HFD, with higher IL-6 values. Male rats (Sprague-Dawley) with six weeks of age were submitted to three types of diets: HFD - with 60% of the total caloric value (VET) derived from lipids; HCD - with 55% of the VET represented by carbohydrates, in this case fructose; and control group following a standard diet for rodents with 5.8% of calories from lipids and 44.3% of carbohydrates. At the end of nine weeks with the three groups following the proposed diets, two serum inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured. However, the results obtained showed metabolic differences only in the animals that consumed HFC-based fructose diet, such as increased insulin and triglyceride values, but without statistical difference regarding the inflammatory process between the three groups (Woodie and BlythE, 2017).

Cafeteria diet-induced inflammation

Highly palatable and energetic diets similar to human consumption of foods of very low nutritional content are examples of HCDs, associated or not with HFD, also known as cafeteria diets and are used in rodent disease models (Johnson *et al*., 2016). The cafeteria diet easily induces animal models of the metabolic syndrome by voluntarily promoting hyperphagia and increased body mass and visceral fat deposits, as well as changes in glycemic and insulin levels with induction of inflammation in the adipose tissue and liver (Zeeni *et al*., 2015; Lalanza *et al*., 2014; Brandt *et al*., 2010; Shafat *et al*., 2009). Smith *et al* (2016) conducted a study with three different diets: cafeteria diet with 3 of 16 pre-established industrialized items commonly consumed in western diet with access to a bottle of water and a bottle containing 12% sucrose w/v; a standard group with access to regular chow and water and a switch group, who was in cafeteria dietfor three months and then switched to regular chow and water. The cafeteria diet group supplemented with sacarose suggested that a diet high in carbohydrates, especially sugar, can be key to induction of metabolic syndrome, through neuroinflammation. The switch group reverted in one month the neuroinflammation caused by three months of feeding with cafeteria diet, inferring that standard diet has limited this cellular proliferation.

Cigarroa *et al*. (2016) used Sprague-Dawley females in their studies and allied the dietary intervention to the practice of exercises, dividing them into groups with cafeteria diet and standard diet in the presence or absence of exercises in the treadmill at different intensities.The groups that received cafeteria diet presented a series of altered obesogenic parameters, such as body weight gain, greater weight of retroperitoneal adipose tissue, as well as higher circulating levels of glucose, insulin, triglycerides and leptin. Thus, those parameters represent a combination that tends to predispose to the inflammatory process characteristic of obesity. Other inflammatory markers would be MAC1 macrophage markers, as well as CD68 and the inflammatory marker MMP3 in white adipose tissue, which consequently increase resistin levels, as occurred in C57BL/6 mice fed a high-sucrose sucrose diet (34%) (Yang *et al*., 2012). In a study conducted with cafeteria diet-fed Wistar rats, there were metabolic changes since the results demonstrated increased expression of fatty acid binding proteins, Elv ol6, fatty acid binding protein 3 and fatty acid binding protein 5, as well as a reduction in the major anti-inflammatory genes, specifically IL-33 and cd22 cytokines after gene analysis of white-type adipose tissue (Johnson *et al*., 2016).

Cardoso *et al*. (2017) evaluated the inflammatory process from intestinal inflammatory mediators in Wistar rats and Zucker rats (fa/fa). As results it was observed in Wistar rats only an increase in the production of reactive oxygen species (ROS) in the intestine and myeloperoxidase activity in the gastrointestinal tracts of rats fed with a cafeteria diet, without alterations in the genetically modified animals. The cafeteria diet used hyperlipidic and rich in refined carbohydrates, presented responses to chronic energy overload, with a stimulus of intestinal inflammation, a sustained inflammatory state and an increase in oxidative stress. Within this context both being linked to the development of pathologies associated with obesity. In addition to inflammatory bowel alterations, BALB/c mice presented damage in cardiac, renal and hepatic tissue, with increased levels of IL-6 after cafeteria diet, representing a model of obesity with important physiological alterations (Zeeni *et al*., 2015). These results corroborate observations of increased oxidative stress in obese humans, demonstrating that the obesity model induced by highly energetic diets is a relevant model of human disease (Johnson *et al.,* 2016). The number of studies involving the effects of cafeteria dieton rats is superior when compared with mice models. However, mice are important animal models since, in the context of obesity, they develop important endocrine and physiological disorders and, in addition, they are relevant in the study of the role of genes involved in obesity, using knockout animals, with the purpose of genetic issues that relate to human physiology (Zeeni *et al*., 2015). On the other hand, there have been studies demonstrating the involvement of cafeteria dietin rats, resulting in deleterious metabolic effects similar to those of the cafeteria diet in mice (Cardoso *et al*., 2017; Johnson *et al*., 2016; Zeeni *et al*., 2015; Castro *et al*., 2014; Brandt *et al*., 2010).

In mice, 15 weeks of cafeteria dietresulted in excess abdominal fat with worsening of glucose tolerance and increased levels of total cholesterol and LDL. In addition, the animals presented damage to the organs, such as heart, kidney and liver, these factors being inflammatory, with an increase in IL-6 serum levels and a decrease in adiponectin when compared to HCD and HFD (Zeeni *et al*., 2015). Sampey *et al* (2011) reported that cafeteria dietin rats for 15 weeks resulted in hyperphagia, increased body mass, hyperinsulinemia, hyperglycemia and glucose intolerance when compared to HFD. In addition, increased inflammation was observed in target tissues such as white, brown adipose tissueand liver, with an increase in non-esterified fatty acids associated with the elevation of inflammatory markers such as TNF-α with intense infiltration of macrophages, forming the so-called "crown-like structures", concluding that cafeteria dietis an important model of metabolic syndrome that leads to greater metabolic and inflammatory damage than HFD. On the other hand, Brandt *et al* demonstrated that cafeteria dietin rats for 12 weeks did not exhibit the same molecular mechanisms of impairment of insulin signaling and no increase in inflammation in skeletal muscle (Brandt *et al*., 2010). However, the specific metabolic tissue in the study should be taken into account, since in the cafeteria dietwere observed deleterious effects on glycemic metabolism and presence of inflammation in the white and brown adipose tissue, as well as in the liver (Sampey *et al*., 2011). Such deleterious metabolic effects present in animals submitted to cafeteria dietare results of oxidative damages in the white adipose tissue that, consequently, can affect the homeostasis of this tissue. Oxidative stress can lead to the activation of inflammatory pathways and result in impairment in insulin signaling with major risks in the development of glucose intolerance and diabetes (Johnson *et al*., 2016).

According to the study by Lackey *et al*. (2016), cafeteria dietsignificantly reduced the expression of anti-inflammatory genes such as interleukin-33 (IL-33) which is an important cytokine in the induction of helper (Th2), mast cells, eosinophils and basophils. It has been reported that there has been a production of type 2 cytokines, which activate M2-type macrophages and secrete anti-inflammatory cytokines and therefore play a crucial role in maintaining insulin sensitivity.
In a research conducted with Wistar rats submitted to cafeteria dietwith composition of 62.2% of carbohydrates (prevalence of simple sugars), 23% of lipids and 12.85% of proteins, Cardoso *et al*. (2017) in a 17-week study identified that prolonged diet induces weight gain and abdominal fat, dyslipidemia, and hyperglycemia and other symptoms associated with metabolic syndrome.In your analyzes in the ileus of the animals, they found increased NOs activity, increased ROS, MPO and TNFα production, linking the hyperglycemic cafeteria diet with intestinal inflammation and increased intestinal permeability. Thus, these results associate the hyperglycemic diet with the prevalence of simple sugars continuously to weight gain with a marked prevalence of mesenteric fat, inflammatory bowel process with production of proinflammatory cytokines related to the low level of chronic systemic inflammation, as well as obesity and other metabolic diseases.

A short-term exposure study (12 days) to cafeteria dietusing rats during childhood evaluated molecular adaptation under feeding and fasting conditions in metabolic organs such as adipose tissue, hypothalamus and liver. From these studies, an increase in abdominal fat deposits was observed, however, with no change in body weight, with an increase in food consumption (Castro *et al*., 2014). Castro *et al*. (2014) affirmed that after the fasting state, pups from rats submitted to cafeteria dietpresented metabolic alterations such as hyperleptinemia and attenuation in the orexigenic pathway,

that is, the ratio of NPY and proopiomelanocortin (Pomc) (NPY/Pomc) in the hypothalamus. In fasting states the presence of decreased levels of insulin contributes to the inhibition of lipogenesis and increased lipolysis, so in the adipose tissue, the cafeteria dietwas not able to modify transcription factors related to lipogenesis as a receptor activated by peroxisome proliferators-γ (PPAR-γ) and sterol-1 regulatory element binding protein (Srebf-1). From these results the data indicated impairment of the adaptive response in fed/fasting conditions with notorious dysfunction in food intake and appetite control. The cafeteria dietin young rats were also able to decrease the expression of lipogenic genes, such as Srebf-1, sterol coenzyme A desaturase-1 (Scd1) and fatty acid synthase (Fasn), also exacerbated the expression of genes involved in lipid oxidation, PPAR-α, carnitinepalmitoyltransferase 1a (Cpt1a) and pyruvate dehydrogenase kinase 4 (Pdk4) in the liver under conditions of free access to cafeteria diet.

In addition, cafeteria dietwas able to increase the gene expression and protein content of the insulin receptor in the liver. Insulin directly regulates the expression of Srebp-1c, which is an important lipogenic transcription factor that activates genes involved in the synthesis of fatty acids and triglycerides (Castro *et al*., 2014). As a consequence, with the decrease in expression of these lipogenic genes, such as Srebf-1, Scd1 and Fasn, due to the consumption of cafeteria dietwith increased expression of the insulin receptor in the liver is suggestive of an impairment in insulin signaling. Although no changes were observed in insulin levels or expression of the hepatic Akt protein involved in insulin signaling in these animals, this results may conclude that a short period of cafeteria dietin young rats affects hepatic metabolism (Castro *et al*., 2014). There are other factors that may potentiate the deleterious action of cafeteria dietin energy metabolism. The term "social jet-lag" (Sj-1) is defined when individuals present differences in bedtime and sleep duration during weekdays and weekends. These factors create discrepancies between working hours and free days, probably influenced by social conditions and biological time, ie groups exposed to interruption of the circadian cycle (Wittmann *et al*., 2006). Bautista *et al*. (2017) demonstrated that in rats exposed to Sj-1 associated with cafeteria dietpresented 5 parameters of metabolic syndrome, among these hyperinsulinemia, high levels of total cholesterol and triglycerides, as well as increased abdominal fat and body mass.

On the other hand, physical exercise may contribute to the reduction of the deleterious metabolic effects promoted by cafeteria diet (Cigarroa *et al*., 2016; Brandt *et al.,* 2010). The great palatability together with the easy availability of these foods results in the creation of an obesogenicenvironment which leads to the greater desire of the individuals to consume the cafeteria diet, modifying the feeding behavior (Scheggi *et al*., 2013). There have been studies showing that animals submitted to cafeteria dietcombined with 10% of sucrose solution obtained an increase in the gene expression of inflammatory markers such as TNF-α and IL-1β in the hippocampus region, suggesting that cafeteria dietcan promote population expansion of microglia cells (macrophages) in the hippocampus (Beilharz *et al.*,2014). Results indicated that the uptake of carbohydrates through the consumption of refined sugar and others harmful to health may be an important factor in the development of some neuropathology associated with the metabolic syndrome (Smith *et al*., 2016). According to studies conducted with rats during 3 months of cafeteria diet, this period is sufficient to develop metabolic syndrome, however, healthy lifestyle is able to reverse the effects of cafeteria diet, cafeteria dietwas able to increase the density of microglia cells Iba1, which would be a marker of macrophages in the CA1 region of the hippocampus, which was not observed in animals that were submitted to a standard diet (Smith *et al*., 2016).

Conclusion

This review study has shown that experimental animal models of obesity with diets rich in refined carbohydrates have revealed important deleterious effects to the metabolism, generating systemic and tissue damages mainly at adipose, cardiac and hepatic levels, higher expression of proinflammatory cytokines, greater visceral adiposity, and other consequences arising from the inflammatory process.
Such studies in animal models have been effective in representing the physiological changes of obesity that can be extrapolated to humans, especially demonstrating proinflammatory action after ingestion of diets rich in refined carbohydrates. However, few studies have addressed diets that act preventively or in the treatment of obesity, such as fiber consumption or type of carbohydrate and its beneficial influence on the inflammatory process. Considering that high carbohydrate consumption is a characteristic of the Western diet, and that this type of diet is predominant in developing countries, and its relation with non-transmissible chronic diseases, it is necessary new studies that evaluate the insertion of protective foods, acting on the metabolism as a whole, especially with anti-inflammatory action, improving the picture of obesity and another chronic diseases.

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