LITERATURE REVIEW Open Access

Pengaruh Diet Tinggi Sukrosa dan Fruktosa Terhadap Obesitas Pada Hewan Coba: Kajian Pustaka

The Effect of Sucrose and Fructose Diet on Obesity in Animal Trial: A Literature Review

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ABSTRAK

Latar belakang: *Obesitas merupakan kondisi yang disebabkan berbagai faktor. Salah satu faktor penyebab obesitas adalah pola makan. Diet tinggi sukrosa dan fruktosa dapat meningkatkan resiko komplikasi akibat berat badan berlebih, seperti obesitas, penyakit komorbid lainnya, dan penyakit metabolik.*
Tujuan: *Artikel ini bertujuan untuk membahas pengaruh dari diet tinggi sukrosa dan fruktosa terhadap obesitas pada hewan coba.*
Ulasan: *Hasil pencarian literatur memberikan bukti bahwa diet tinggi sukrosa dan fruktosa dapat mengakibatkan peningkatan berat badan, menyebabkan status gizi berlebih, obesitas, peningkatan lingkar pinggang, jaringan adipose dalam tubuh, serta peradangan pada jaringan adipose. Komplikasi tambahan lainnya dari diet tinggi sukrosa dan fruktosa dapat mengakibatkan penurunan pengeluaran energi, menyebabkan peningkatan stress oksidatif pada ginjal, dan penyakit hati berlemak non-alkohol (non-alcoholic fatty liver disease) yang dapat merusak hati.*
Kesimpulan: *Artikel penelitian menunjukkan bahwa ada hubungan antara diet tinggi sukrosa dan fruktosa dengan obesitas, serta penyakit komorbid lainnya, yaitu penyakit metabolik. Penelitian lebih lanjut disarankan untuk dilakukan dengan melibatkan zat gizi lain untuk melihat mekanisme interaksi zat gizi sebagai faktor determinan obesitas baik pada penelitian menggunakan hewan coba maupun penelitian pada manusia.*

Kata Kunci: *Sukrosa, Fruktosa, Obesitas, Hewan Coba*

ABSTRACT

Background: Obesity is a multi-factorial condition. One of the factors that can cause obesity is dietary habit. High sucrose and fructose diet can increase the risk of overweight complications, namely obesity and its comorbidities, metabolic diseases.
Objective: This article aims to discuss the effects of high sucrose and fructose diet on obesity in animal testing.
Discussion: The results from several literature search provided evidence that high sucrose and fructose diet can result in an increase of body weight, causing the nutritional status to be overweight, obesity, an increase of waist circumferences, adipose tissue within the body, and inflammation in adipose tissue. Other additional complications from high sucrose and fructose diet may result in reducing energy expenditure, cause an increase of oxidative stress in kidney, and non-alcoholic fatty liver disease which can damage the liver.
Conclusion: Research articles suggest that there are relations between high sucrose and fructose diet with obesity as well as the comorbidities, namely metabolic diseases. Further research is suggested to be carried out to involve other nutrients to see the mechanism of nutrient interaction as a determinant factor of obesity either in animal or human studies.

Keywords: Sucrose, Fructose, Obesity, Animal Trial

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INTRODUCTION

Obesity is a public health problem caused by many factors. The incidence of obesity is increasing in developing and developed countries [1]. The imbalance of energy consumed and expended is the main cause of obesity[2]. In addition, genetic and environmental factors that interact with each other can also cause obesity, namely diet, composition of food consumed, lifestyle, and physical activity that affect the body's energy expenditure[3]. The risk of obesity can be caused by an individual's diet. Individual diet is formed from the availability of food in the vicinity, both from economic aspects and physical aspects[4,5]. Foods that are more affordable are consumed more frequently and increase one's level of consumption than foods that are more expensive. However, foods with lower prices tend to be foods that are high in fat and sugar than vegetables and fruits. Choosing foods high in sugar can be one of the causes of obesity[6].

Fructose consumption has increased sharply over the years. Excessive fructose consumption is a big contributor to the symptoms of metabolic syndrome, obesity, insulin resistance, and hypertriglycerides[7,8,9]. The increase in insulin in the blood is high enough to cause hypoglycemia. This condition causes the body to feel hungry, which triggers an increase in food intake. This condition can lead to excessive energy consumption, especially simple carbohydrates[10]. High consumption of sugar can disrupt metabolic processes, the balance between nutrient stores, and oxidation processes, thus affect hunger, satiety and energy intake to meet daily needs[11]. In addition, sucrose, also known as sugar, is also a sought-after carbohydrate, which has led to an increase in sucrose consumption over the past 50 years[12]. Regular consumption of sucrose can increase the severity of metabolic conditions, especially excess body weight. Diets that increase body weight can also lead to hyperinsulinemia and insulin resistance[13].

Based on the research, the group of mice fed a sugar diet caused high energy intake, poor nutritional quality, low micronutrient status in the blood, namely essential fatty acids, micronutrients, fiber and other important minerals. Human studies also show that a high sugar diet can increase energy by approximately 350 kcal / day, causing weight gain and increasing the size of adipose tissue[14]. Several epidemiological studies suggest that increased consumption of sugary drinks is associated with the risk of obesity because de novo lipogenesis is the main cause of fat accumulation in the body[14].The United States and Japan use High Fructose Corn Syrup (HFCS) as a source of fructose. HFCS is a mixture of fructose and glucose with different concentrations, whose fructose content reaches 90%[15]. However, in commercial products, generally the fructose content is 42-55%[16]. The consumption of HFCS in the United States increased sharply from 1970 to 1999[17].

Obesity is a nutritional problem that continues to grow throughout the world. Based on data from the Center for Disease Control and Prevention (CDC), as much as one third of the American population from early adulthood to middle age is obese[18]. Public health researchers claim that obesity occurs due to high-fat consumption and high-calorie sugary drinks. These foods and drinks contain added sugar, especially fructose. Over the past few decades, daily calorie intake has increased by 150 kcal to 300 kcal (based on age and gender) and as much as 50% of the increase in energy comes from consuming sweet, high-calorie drinks[19]. This research article aims to discuss the effects of a diet high in sucrose and fructose on obesity.

DISCUSSION

Literature Search

Initially, 856 articles were obtained, then they were selected into 126 articles based on titles and research abstracts that were suitable for further study. Finally, a total of 12 research articles were selected to compile a systematic review, described in more detail in tables 1 and 2. Table 1 contains seven articles on sucrose or fructose with obesity while table 2 contains five articles on sucrose or fructose with metabolic diseases.

Table 1. Effect of Diets High in Sucrose and Fructose on Obesity

Research Title and Author	Research methods	Result
Obesity Induction with High Fat Sucrose in Rats[20]	Design: Experimental study Subjects: 40 male wistar rats. Treatment: Rats were divided into 2 groups: 20 rats were given normal diet (control) and 20 mice were given additional sucrose supplement water (300g / L).	A diet high in sucrose increases body mass index and plasma triglyceride counted. The addition of sucrose to the diet led to obesity in mice, weight gain, and glucose intolerance.
Sucrose Counteracts the Anti-Inflammatory Effect of Fish Oil in Adipose Tissue and Increases Obesity Development in Mice[21]	Design: Experimental study Subject: male mouseC57BL / 6J 8 weeks of age per group. Treatment: Rats were given a protein (casein) diet or a high-fat sucrose-based diet supplemented with fish oil or corn oil for 9 weeks.	The mice fed a sucrose-rich diet became obese and had higher expression of inflammatory markers in adipose tissue. There was an increase in the expression of macrophage and inflammatory marker genes in obese mice.

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Research Title and Author	Research methods	Result
Liquid Sucrose Consumption Promotes Obesity and Impairs Glucose Tolerance Without Altering Circulating Insulin Levels[22]	Design: Experimental study Subjects: 32 male rats aged 14 weeks. Treatment: 16 rats in group 1 were given standard feed, 16 rats in group 2 were given liquid containing 30% sucrose.	30% liquid sucrose caused the mice to be obese after 2 weeks of consuming sucrose solution. Respiratory Quotient (RQ) was higher in mice that consumed sucrose, indicating an increase in carbohydrate use.
High-fructose corn syrup causes characteristics of obesity in rats: Increased body weight, body fat and triglyceride levels Miriam[23]	Design: Experimental study Subjects: Male and female rats. Treatment: Group 1 (2 months treatment rats) were given ad libitum chow, 24-h HFCS, 12-h HFCS, or 12-h sucrose. Group 2 (treatment rats 6-7 months) were given 24-h HCFS, 12-h HFCS, or ad libitum chow.	Mice with 12 hours of access to HFCS experienced higher weight gain than the sucrose group. Male rats who received HCFS for 6 months had higher body weight, abdominal fat and triglyceride levels than controls.
Unexpected Long-Term Protection of Adult Offspring Born to High-Fat Fed Dams against Obesity Induced by a Sucrose-Rich Diet[24]	Design: Experimental study Subjects: 32 female Wistar rats and 8 male Wistar rats aged 8 weeks Treatment: 16 female rats were given diet C containing 55.9% fiber, 20% protein, 4.5% fat. 16 female rats were given a P diet containing 33% commercial food, 33% sweetened fat, 7% sucrose, and 27% water until the lactation period is complete. 8 male rats were given standard feed.	The mice consuming diet P were obese, overweight, experienced an elevated plasma levels of leptin, triglycerides, and insulin.
Potential effect of maternal dietary sucrose or fructose syrup on CD36, leptin, and ghrelin- mediated fetal programming of obesity[25]	Design: Experimental study Subject: 3 weeks old mouse. Treatment: 5 groups of mice were given a diet containing 13% fat, 60% carbohydrates (fiber and dextrose), and 24% protein (casein). The control group was given water, 3 groups were given sucrose (50% fructose bound), 100% free fructose, or HFCS (55% free fructose). 1 group was given maltodextrin isocaloric drink.	The highest body fat accumulation was found in rats given drinks in the form of HFCS, fructose, sucrose, compared to the control group and the group of mice given maltodextrin drinks. Energy intake was found to be greater in the group of mice that were given HFCS and sucrose drinks.
Effects if a High-Carbohydrate Diet Blood Glucose and Body Weight Wistar Rats[26]	Design: Experimental study Subjects: 15 male wistar rats for 6 weeks. Treatment: 5 rats were given standard feed of 20g / 200g BW of rats / day, 5 rats of treatment 1 were given corn starch 7.4g / 200gBB of rats / day and standard feed of 12.6g / 200gBB / day, 5 treatment 2 rats were given refined sugar liquid using a cannula of 6.7 g / 200 gBB / day and a standard feed of 13.3g / 200g BW / day.	The treatment group 2 rats experienced an increase in body weight. In addition, a high-sugar diet also raised the average blood sugar level. Both were statistically significant.

The research articles in Table 1 show an association between a diet high in sucrose or fructose in mice with weight gain. Continuous weight gain leads to the incidence of obesity. High consumption of fructose or sucrose can lead to weight gain. This is due to the activation of lipoprotein lipase (LPL) and limitation of the rate of enzymes involved in the uptake of triglycerides and circulating subcutaneous adipose tissue storage. Consumption of sugary drinks causes an increase in insulin so that sugar levels in the body are high[27]. This triggers an increase in visceral adipose tissue and an increase in subcutaneous adipose tissue[28].

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The addition of sucrose as much as 30% of total calories in a long time has been shown to increase body weight to cause obesity by causing an increase in plasma triglycerides[20]. Consumption of sucrose causes an increase in liver fat levels, body weight, fat mass increases pancreatic beta cells in mice[29]. and the presence of Ser-pinA12 gene expression associated with obesity and type 2 diabetes[30]. This study was in line with several other studies in which subjects given a diet with sucrose or simple sugars caused weight gain[26,24,25,21]. Another study said a sucrose diet led to significant weight gain and an increase in gonadal adipose tissue[31].

Foods that contain fructose can increase fat formation in the liver in obese or overweight individuals[32]. Fructose metabolism is regulated by phosphofructokinases[16]. When liver citrate and ATP levels are high, glucose metabolism in the liver is inhibited. Most of the glucose consumed will pass through the liver and reach the systemic circulation. In contrast, the metabolism of fructose converted to fructose-1-phosphate is regulated by fructokinase. Fructokinase is not inhibited by ATP or citrate. When the liver energy status is high, fructokinase continues to metabolize fructose to be converted into fructose-1-phosphate. Most of the fructose consumption is taken up by the liver and relatively little reaches the systemic circulation. In the liver, fructose can be metabolized to regulate the amount of substrate de novo lipogenesis, acetyl Co-A and glyceraldehyde triphosphate, thereby increasing the amount of de novo lipogenesis. Fructose can activate the sterol receptor element binding protein-1c (SREBP-1c), regardless of the presence of insulin[33].

Table 2. Effect of Diets High in Sucrose and Fructose with Metabolic Diseases in Obesity Subjects

Research Title and Author	Subject and Treatment	Result
A Novel Wistar Rat Model of Obesity-Related Nonalcoholic Fatty Liver Disease Induced by Sucrose-Rich Diet[34]	Design: Experimental study Subjects: 60 male Wistar rats aged 28 days were given water and ad libitum food. Treatment: experimental group (EG), were given a high sucrose diet for 5 (EG5), 10 (EG10), 20 (EG20) and 30 (EG30) weeks (33% of condensed milk, 7% sucrose). The control (CG) group was given standard feed for 5 (CG5), 10 (CG10), 20 (CG20), and 30 (CG30) weeks. From weeks 25-30, the EG30 and CG30 mice were subjected to physical training.	Sucrose-rich diet with excess consumption led to obesity / central obesity in EG mice from week 10.
High-sucrose effect on bone structure, hardness and biomechanics in an obesity model using Wistar male rats[35]	Design: Experimental study Subjects: 34 male Wistar rats, 8 weeks old Treatment: the control group (C) was given a standard dietary diet and water, the HS group was given a commercial diet high in sucrose and 30% ad libitum sucrose solution, and the WHS group was given a water diet + a commercial diet high in sucrose.	Weight control group increased 36.2%, HS group increased 50.5%, and WHS group rose 77.3% from the first day. Sucrose solution caused weight gain, an increased in abdominal circumference and BMI, caused low satiety, and increased calorie intake.
Hepatic Adverse Effects of Fructose Consumption Independent of Overweight / Obesit [36]	Design: Experimental study Subjects: male rats aged 12 weeks. Treatment: standard diet mice group (SC: 9% fat, 15% protein, and 76% carbohydrate; 3802.8 kcal / kg), high fat diet group (HF, 42% lipids, 14% protein, and 44% carbohydrates; 4702.8 kcal / kg), the high-fructose diet group (HFr: 9% fat, 15% protein, 76% carbohydrates, 34% fructose; 3802.8 kcal / kg), the high-fat and high-fructose (HF / HFr) diet group : 42% lipids, 14% protein and 44% carbohydrates, 34% fructose; 4702.8 kcal / kg).	The HF / HFr group showed the largest values of the PPAR-γ and PPAR-α ratios. HFr mice exhibited intrahepatic macro and microfat vesicles and intralobular inflammation. HF / HFr mice have increased hepatic ROS and a NASH-like phenotype (nonalcoholic steatohepatitis) with fibrosis of nonalcoholic steatohepatitis.

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Research Title and Author	Subject and Treatment	Result
Comparison of free fructose and glucose to sucrose in the ability to cause fatty liver[37]	Design: Experimental study Subjects: 12 male Sprague-Dawley rats weighing 150 g Treatment: group 1 received a 60% (S) sucrose diet or 30% fructose + 30% glucose (FG) diet, group 2 rats received a standard dietary diet (control group).	Serum uric acid increased with FG, consistent with the effect of fructose addition. Serum uric acid was correlated with markers of metabolic syndrome such as serum TGs ($p < 0.001$), cholesterol ($p < 0.001$), insulin ($p = 0.004$), abdominal fat ($p = 0.007$) and total fat ($p = 0.008$). Both diets induced fatty liver and increase liver TG, especially in postprandial and periportal mild inflammation of the liver tissue. There was a strong positive correlation between hepatic uric acid and TG ($p < 0.001$).
Differential Effect of Sucrose and Fructose in Differential Effect of Sucrose and Fructose in Combination with a High Fat Diet on Intestinal Microbiota and Kidney Oxidative Stress[38]	Design: Experimental study Subjects: 24 male Wistar rats aged 5-7 weeks. Treatment: 8 mice were fed a diet high in fat and 5% sucrose in drinking water (HFS), 8 mice were fed a diet high in fat and 5% fructose in drinking water, 8 mice were fed a control diet (C) for 4 months.	A high-fructose sucrose diet increased fat mass (51% and 40%). Obesity due to consumption of HFS or HFF resulted chronic inflammation mediated by LPS. The mice fed HFS showed decreased renal UCP-1, increased oxidative stress by induction of SREBP-1 involved in renal lipogenesis, and increased NADPH oxidase expression and ROS production.

The research article in table 2 shows the effect of a diet high in sucrose and fructose on reducing energy expenditure which can lead to weight gain to obesity[32]. If this is allowed, it will have an impact on NAFLD (Nonalcoholic Fatty Liver Disease) which is characterized by the occurrence of steatosis, enlarged liver, increased thoracic circumference and BMI. This is associated with hyperleptinemia, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, increased VLDL cholesterol, reduced liver antioxidant enzymes, and increased liver malondialdehyde (MDA) expression as a marker of oxidative stress[39]. Hyperinsulinemia causes increased hepatic fatty acid synthesis, accumulation of triglycerides in hepatocytes and steatosis. High triglyceride levels are converted into VLDL lipoprotein. Hyperleptinemia occurs due to consumption of foods high in fructose[40]. A diet high in simple carbohydrates causes hypertriglyceridemia and results in reduced antioxidant reserves. Increased ROS will cause damage to membrane proteins and DNA which refers to the release of cytokines, pro-inflammation, activation of liver cells, fibrogenesis and liver damage[41]. This study is in accordance with other studies that a high-fructose diet shows changes in the metabolic system of the body and the liver. The effects of a high-fructose diet change show the same effect as a high-fat diet[42,38,36,43]. Long-term consumption of high-fructose foods will interfere with liver energy homeostasis, insulin resistance, reduce ATP levels in the liver and cause inflammation in liver tissue[44]. Low ATP levels can cause cell injury and NAFLD[45].

The impact of a high-fructose diet on obesity also causes oxidative stress which accelerates the incidence of degenerative diseases[38]. Obesity due to a diet high in sucrose or fructose results in a lipopolysaccharide-controlled, high-grade chronic inflammatory condition. This incident stems from dysbiosis in the gut microbiota. Subjects consuming a diet high in sucrose or fructose showed a significant increase in B bacteria product and a significant reduction in C-eutactus which was associated with irritable bowel syndrome (diarrhea)[46]. The undesirable effects of a diet high in sucrose and fructose were attenuated from increased L Reuteri and B fragilis in inhibition of growth of pathogenic bacteria, insulin sensitivity[36] and intestinal epithelial integrity [47,48,49]. As obesity progresses, biosis in the stomach microbiota increases lipopolysaccharide production in the high-sucrose diet group, which may activate TLR4 and induce NF-kB induction. It stimulates expression of inflammation-causing cytokines and production of ROS. Increased of interleukin-1β and 6, as well as TNF-α, are associated with insulin resistance and glucose intolerance[50]. The inflammatory process increases NADPH oxidase and the formation of ROS causes modification of antioxidant enzyme expression to different levels. This modification in the antioxidant response is associated with a redox imbalance that promotes a vicious cycle of oxidative stress. An imbalance between ROS levels and antioxidant enzymes leads to the formation of MDA (malondialdehyde), which is a marker of lipid peroxidation. High level of renal MDA is associated with renal stress and high urine H2O2 production[51] and TNF-α is associated with insulin resistance and glucose intolerance[50]. The inflammatory process increases NADPH oxidase and the formation of ROS causes modification of antioxidant enzyme expression to different degrees. This modification in the antioxidant response is associated with a redox imbalance that promotes a vicious cycle of oxidative stress. An imbalance

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between ROS levels and antioxidant enzymes leads to the formation of MDA (malondialdehyde), which is a marker of lipid peroxidation.

CONCLUSION

Based on research on experimental animals that have been analyzed regarding the diet composed in high sucrose and fructose, it can cause weight gain to and increase the risk of overweight and obesity conditions. The effect of diets high in sucrose and fructose on metabolic disease in obese subjects is to cause NAFLD (*Nonalcoholic Fatty Liver Disease*), liver damage, decreased energy expenditure on the body, and oxidative stress on the kidneys. The type of diet has an effect on weight regulation and its impact on health. One of the things to reduce the incidence of obesity is to change the type of diet or food consumed.

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