Does fructose promote obesity?

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Abstract

Today the largest source of fructose can be found in soft drinks, desserts and candies where it serves as a sweetener together with glucose. Fructose is not metabolized the same way as glucose and does not stimulate production of several key-hormones such as insulin, leptin and ghrelin, regulating energy balance. Because of these differences it might be asked whether there is a connection between the increased consumption of high fructose corn syrup (HFCS), a common used sweetener, and the epidemic-like increase in obesity throughout the world. Several studies indicate that fructose gives rise to more deleterious metabolic effects than glucose, consequently leading to obesity. At the same time no differences between HFCS and sucrose has been shown indicating that HFCS are not likely contributing to the development of obesity as believed. The biggest use of fructose is in the form of HFCS, suggesting no reason to worry. Instead we should focus on our total consumption of sugar, try to stay away from soft-drinks and candy, and continue to eat adequate amounts of fruit. However, further investigations needs to be done to fully understand and determine the metabolic effects of prolonged consumption of fructose.

Sammanfattning

Idag kan man hitta den största mängden fruktos i läsk, olika efterrätter och godis där den används tillsammans med glukos som sötningsmedel. Fruktos metaboliseras inte på samma sätt som glukos och stimulerar heller inte produktionen av insulin, leptin och ghrelin, vilka alla är viktiga hormoner som reglerar energibalansen. På grund av dessa skillnader diskuteras en koppling mellan den ökande konsumtionen av fruktossirap (HFCS), ett vanligt sötninsmedel, och den epidemiartade ökningen av fetma runt om i världen. Flera studier visar att fruktos ger uppkomst till fler skadliga metaboliska effekter än glukos, vilket i sin tur har lett till fetma. Samtidigt har ingen skillnad påvisats mellan HFCS och sukros vilket indikerar att HFCS inte har bidragit till ökningen av fetma som man tidigare trott. Eftersom den högsta mängden fruktos som används idag är den som förekommer i HFCS, behöver vi antagligen inte oroa oss. Istället borde vi; tänka på vårt totala intag av socker, försöka hålla oss undan läsk och godis samt fortsätta äta lagom mängd frukt. Fler undersökningar av de metaboliska effekterna som långvarigt intag av fruktos kan ge uppkomst till behöver dock göras för att få bättre förståelse och säkrare resultat.

Introduction

Fructose is a monosaccharide found in many foods such as honey, tree fruits, berries and melons. It can also be found together with sucrose and glucose in some root vegetables like beets, sweet potatoes, parsnips and onions. Today the largest source of fructose in the diet is though in the form of added fructose as a sweetener in desserts, candies and soft drinks (Lindqvist et al., 2008). Sucrose, which is a disaccharide consisting of 50 % fructose and 50 % glucose, also contributes to a portion of fructose when digested.

Fructose is a hexose with the same empirical formula as glucose but with a different structure. It can be found as a strait chain but most commonly it forms a furanose ring which has sweeter taste than both glucose and sucrose (McDonald et al., 2002).. Fructose does not have much impact on the level of blood sugar relative to glucose, due to its unique metabolic pathway and are often recommended for, and consumed by, people with diabetes (Gaby, 2005). However, eventually oxidation of fructose generates energy and it might be asked whether there might be a connection between the increased consumption of products that carry a high content of fructose and the epidemic-like increase in obesity throughout the

world. Another concern would be that consumption of fructose does not induce the same endocrine response as does glucose.

The use of high fructose corn syrup (HFCS) has increased considerably in the United States during the past several decades and is now used extensively as a sweetener in carbonated beverages and other sweetened drinks, baked goods, canned fruits, candies, jams, jellies and dairy products. It is inexpensive to produce and mixes well in many foods and are therefore often preferred to sucrose by the manufacturers of processed food (Gaby, 2005). From 1970 the per capita use of sucrose in the United States decreased moderately from 46,4 kg to 30,5 kg in 1997 whereas the use of HFCS during the same period increased from 0,23 kg to 28,4 kg (Putnam and Allshouse, 1999).

HFCS is made by enzymatic isomerization of some of the glucose in corn syrup to fructose. In many sweetened beverages HFCS-55, consisting of 55 % fructose and 42 % glucose, is used. Other products such as confections are usually sweetened with HFCS-42 (42 % fructose and 53 % glucose) (Melanson et al., 2008).

During 1960-2006 Swedish consumers have increased their energy intake by 7, 5 % measured in kilojoules (KJ) per capita. There is an increased amount from protein, a decreased amount from fat while carbohydrates still contribute to the same amount as in 1960. The National food administration recommends that carbohydrates should constitute 50-55 % of energy intake, whereas its actual contribution in 2006 was 48 %.

The direct consumption of sucrose has decreased from 30 to 7 kg/ person and year during 1960-2006, whereas the total consumption of sucrose and syrup has been relatively constant between 40-45 kg/ person and year. This is due to less baking, jam- and must- making at home, and instead we are buying these as pre made products in the grocery store. At the same time the consumption of products with high proportion of sugar such as cacao, chocolate and confectionery has increased. Also the consumption of soft drinks has increased dramatically from approximately 22 litre/ person to 90 litre/ person and year. Although the specific figures for fructose consumption are difficult to extract.

The National food administration recommends intake of sugar produced in pure form not to exceed 10 % of daily energy intake. This corresponds to approximately 20 kg/year for an adult woman and 25 kg/year for a man, including added sugar from all kinds of food.
Even if the estimated consumption from Swedish Board of Agriculture might be a bit high due to decrement in the grocery chain resulting in approximately 25-30 kg/person and year, this still exceeds the recommendations with 5 kg (Jordbruksverket, 2009).

Sugar in forage is mainly occurring as molasses and other products derived from food production. Grass and hay are other sources of sugar which can contain over 10 %. The sugar content of molasses is approximately 43 % (Nordic Sugar, 2009) and in 2001 the amount of molasses in feed mixtures constitute; 0,1 % to pigs; 2,9 % to cattle and 4.5 % to horses (Jordbruksverket, 2001). The sugar in forage eaten by ruminants is consumed by the micro organisms in the rumen which are using it as energy supply (Lärn-Nilsson et al., 2005). Thus, concerning the fructose consumption, monogastric animals are the ones we should focus on.

According to Hellberg (2009, personal communication) at Lantmännen, the sugar content in their forage is mainly molasses used as a pellet binder. They are also using a fructose-solution in forage for horses. This constitutes 2-3 % of the feed and is also working as a pellet binder.

Feed mixtures for dogs and cats from Royal canin, does not contain any adding's of sugar (Edoff, 2009. personal communication) whereas some dog feed from Dechra contains 2,5-3,5 % of added sugar (Madsen, 2009. personal communication).

The aim of this review is to investigate the literature on how fructose is metabolized, and in addition review studies comparing metabolic consequences between fructose and glucose and to find out if there are any differences between HFCS and sucrose. Finally, the aim was to explore whether the increased consumption of dietary fructose might be one of the factors contributing to the development of obesity. If this is an issue among humans, could it be a concern also among our domestic animals and should we still eat fruit?

Fructose metabolism

Fructose is absorbed in the small intestine and transported by the epithelial cells into the hepatic portal vein (Sjaastad et al., 2003). In contrast to fructose formed during glucose metabolism, fructose from extern sources is phosphorylated on carbon 1 to form fructose-1-phosfate, a reaction catalysed by the enzyme fructokinase. Fructose-1-phosfate is then split into glyceraldehyde and dihydroxyacetone phosphate and both of these products can be converted to glyceraldehyde-3-phosphate. Now, the carbon from fructose can readily converge with the glycolytic pathway (as either dihydroxyacetone phosphate or glyceraldehyde-3-phosphate). The most important thing here is the ability of fructose to by-pass the main regulatory step where glucose carbon enters glycolysis. It is the step where glucose-6-phosphate is converted to fructose 1,6-bisphosphate controlled by phosphofructokinase. Thus, while glucose metabolism is limited by feedback inhibition of phosphofructokinase by citrate and ATP, fructose may generate relatively unregulated amounts of glycolytic intermediate metabolites. This may result in great supply of the lipogenic substrates glycerol-3-phosphate and acetyl-CoA (Figure 1), thus fructose is a more lipogenic sugar than glucose (Elliot et al., 2002).

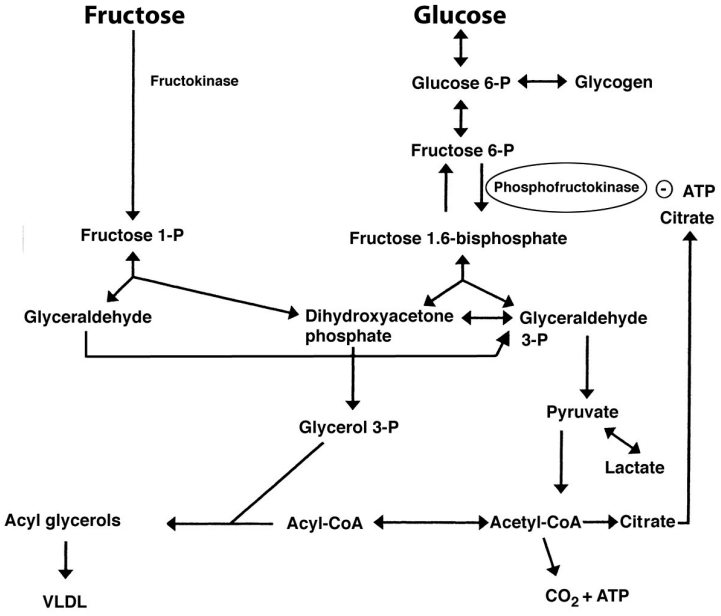

Figure 1. The utilization of fructose and glucose in the liver. Fructose carbon enters the glycolytic pathway without passing the main rate-controlling step of glucose controlled by phosphofructokinase (Modified from Elliot et al., 2002).

Results from studies in humans and animals

Fructose versus glucose

In contrast to glucose, fructose does not stimulate the secretion of insulin from pancreatic beta cells when digested and consequently the insulin-regulated hormone leptin will also have a reduced concentration. Areas in the central nervous system (CNS) involved in the control of food intake and energy homeostasis have insulin receptors which inhibits food intake when insulin is administrated. Leptin, synthesized in adipose tissue, has the same inhibiting effect as insulin and it also increases the thermogenesis. Insulin and leptin are inversely related to the orexigenic (causing hunger) hormone ghrelin, secreted from the endocrine cells of the stomach, possibly regulating food intake (as reviewed by Elliot et al., 2002). Thus, decreases of circulating insulin and leptin along with increased ghrelin concentrations may lead to increased caloric intake, due to their function as key signals to the central nervous system regulating long-term energy balance. In accordance herewith the consumption of foods and beverages containing fructose could contribute to weight gain and obesity (as reviewed by Teff et al. 2004).

In a short term study made by Teff et al. (2004) the plasma concentrations of glucose, insulin and leptin were measured to compare the differences after ingestion of fructose- and glucose-sweetened beverages with meals. Twelve normal-weight young women consumed sweetened beverages at 30% of energy requirements with 3 meals and plasma concentrations were compared over 2 separate 24-h periods. Compared with consumption of glucose-sweetened beverages, the consumption of fructose sweetened beverages resulted in lower 24-h circulating concentrations of glucose, insulin and leptin and resulted in less postprandial suppression of ghrelin.

In a long-term study in overweight and obese women, fructose-and glucose sweetened beverages constituting 25 % of energy requirements were compared during 10-weeks. Same result as from the short-term study showed significant reductions of postprandial glucose and insulin responses (Swarbrick et al., 2008).

To determine if a longer consumption of a diet high in fructose would lead to greater weight gain via increased caloric intake, decreased energy expenditure, or both when compared to a diet high in energy from glucose, Stanhope et al. (2008) made a study on rhesus monkeys. The study lasted for 12 months and the monkeys were fed an *ad libitum* standard chow diet supplemented with either glucose- or fructose-sweetened beverages contributing to about 40 % of total energy. After 3 and 6 months the monkeys fed fructose beverages had gained significant amounts of weight compared with their baseline weights and their energy expenditure was significantly decreased. Monkeys consuming glucose had none of these significant changes. Though, by the end of the study at 12 months, neither the weight gain nor the energy expenditure changes were significant different between the 2 groups (Figure 2).

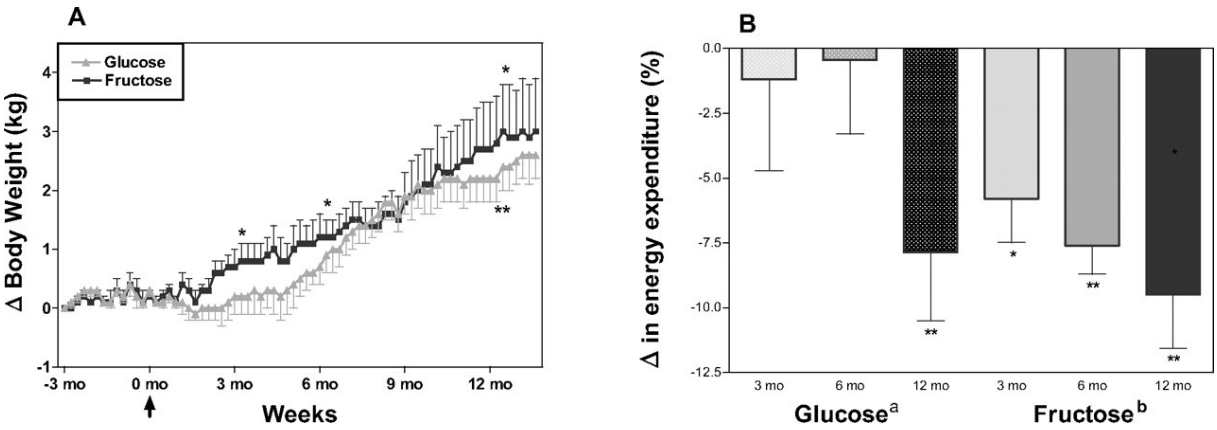

Figure 2. Results from the study in rhesus monkeys during 12 moths showing (A) change in body weight from baseline and (B) percentage change in energy expenditure from baseline (Stanhope et al., 2008).

In another study, mice were given fructose-sweetened beverages (15 % solution in water), sucrose (5 % fructose and 5 % glucose, popular soft drink) or artificial sweetener (0 % calories, popular diet soft drink) with the purpose to study differences of the solutions effecting body weight gain during 70 days. Average body weight of all 3 groups tended to increase, but this effect only reached statistical significant in the fructose group (Figure 3). The results indicate that body weight gain seems to depend on the fructose concentration (Jürgens et al., 2005).

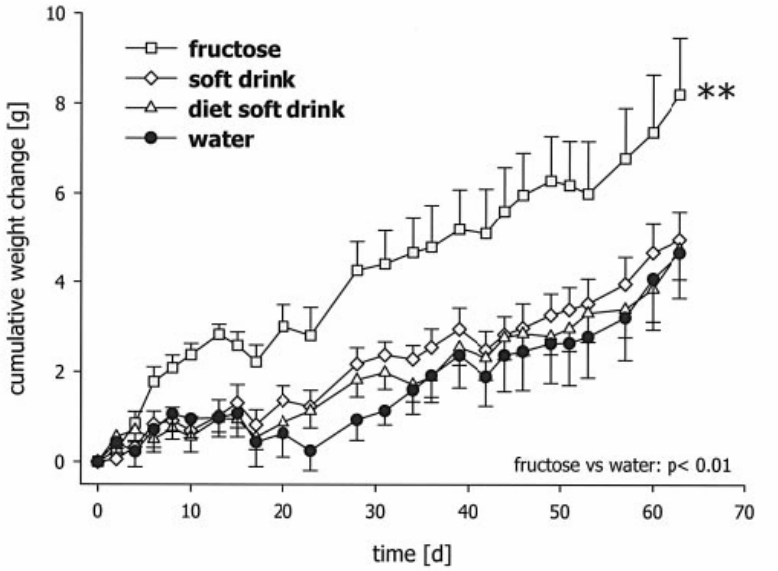

Figure 3. Cumulative change in body weight of the different groups of mice with a control group consuming water during 70 days (Jürgens et al. 2005).

A recent study made on obese humans consuming fructose- and glucose sweetened beverages during 10 weeks, showed significantly increased visceral adiposity of those consuming fructose (Stanhope et al., 2009).

Other important differences between fructose and glucose consumption deal with the lipid metabolism and were showed in the short-term study in normal weight women by Teff et al. (2004). Compared with glucose sweetened beverages, the concentrations of 24-h circulating plasma triacylglycerol were increased after consumption of fructose-sweetened beverages. Accordingly, in the long term study made by Swarbrick et al. (2008), the triacylglycerol exposure were increased by 140 % in overweight women consuming fructose-sweetened beverages whereas no increases of postprandial triacylglycerol profiles were observed in subjects consuming glucose-sweetened beverages. The significant increase of triacylglycerol levels when consuming fructose were also shown by Stanhope et al. in 2009. This raise of plasma- triacylglycerol levels after consumption of fructose could give rise to atherogenesis and cardiovascular disease (Teff et al., 2004).

HFCS versus Sucrose

Many studies comparing the metabolic effects of beverages sweetened with fructose and glucose have been made, but fructose and glucose are not commonly used as sweeteners in their pure form. Therefore studies of HFCS and sucrose were made by e. g. Stanhope et al. in 2008 with the hypothesis that the sweeteners endocrine and metabolic effects would be quite equally due to their rather similar composition of fructose and glucose. They were also thought to produce responses intermediate between those of pure fructose and glucose. This was tested in a short-term study made on male subjects consuming beverages sweetened with HFCS, sucrose, fructose, and glucose constituting 25 % of the energy. As hypothesized, the consumption of both HFCS and sucrose produced postprandial glucose, insulin, and leptin profiles that were intermediate to those induced by pure fructose and pure glucose. Thus, the response of the two sweeteners was not significantly different. Melanson et al. found in 2007 similar results when investigating normal-weight women consuming 30% of energy from HFCS and sucrose during a 24-h period. Also White found these sweeteners similar in his review from 2008. In contrast, the responses to consumption of sucrose and HFCS were comparable to those of pure fructose in regard to the postprandial triacylglycerol concentrations, but further long-term studies needs to be done investigating this unexpected result (Stanhope et al., 2008).

Discussion

The differences between the metabolism of glucose and fructose have been shown to effect the concentrations of several important hormones in the body. The concentrations of glucose and insulin have been decreased in both short- (Teff et al. 2004) and long-term studies (Swarbrick et al. 2008) after consumption of fructose compared to glucose were they constitute 25-30 % of energy requirements. Short-term studies have also resulted in lower concentrations of leptin and simultaneously increased concentrations of ghrelin when consuming fructose compared to glucose. As both leptin and insulin inhibits food intake and ghrelin makes us feel hunger, the feed consumption could possibly be increased when consuming fructose in comparison to glucose. All of these substances play an important role in the long-term energy balance and since consuming fructose-sweetened beverages seems to have a negative effect on all of them it is likely that the balance could be disturbed. Consequently it could lead to obesity, which was shown by Stanhope et al. in 2009 where people who consumed fructose-sweetened beverages got significant increased visceral adiposity compared to those consuming glucose. Similar result was shown by Jürgens et al. in 2005 in their study on mice given different kinds of sweetened beverages. The mice who got fructose-sweetened beverages where the only ones that got significantly increased body weight which was also shown after 3 and 6 months in the study on rhesus monkeys by

Stanhope et al in 2008. However after 12 months, significant changes among the monkeys could no longer be seen between the fructose and glucose group. These results indicate that fructose consumption could have negative effects on the energy balance and possibly give rise to obesity.

Should we then stop eating fruit? This is a current topic where people have very different opinions. Some say you will get fat from eating it and others that it is healthy. Everything is relative, if you eat an apple instead of a cookie, you will get sugar but also fibres, antioxidants and vitamins. But if you consume large amounts of fruit every day, this would probably not be very good concerning weight gain or dental health. However, because of its contribution of fibre, micronutrients and antioxidants, fruit and vegetables should still continue to be encouraged. It is unlikely that the intake of naturally occurring fructose, approximately 15 g/d, should contribute significantly to the unfavourable metabolic consequences associated with the consumption of large amounts of fructose, according to Elliot et al. (2002).

In a debate article in the newspaper Dagens Nyheter, published 3 of May 2009, Enkvist claims that eating fruit will make you fat. The author bases his facts on the recent published article from Stanhope et al in 2009, comparing effects from consumption of fructose- and glucose sweetened beverages during 10 weeks. The study showed significant increased abdominal fat in the group consuming fructose. Thus, the National food administration answers the article from Enkvist and says that same parallel from fructose-sweetened beverages can not be made on fruit. The persons in the study would have to eat 25 apples a day to get the same amount of fructose as was consumed in the study. They say that fruit is healthy and still recommends an intake of 500 gram fruit and vegetables per day (Livsmedelsverket, 2009).

Except from the differences between fructose and glucose regarding energy balance and obesity, the triacylglycerol levels have also varied. Both short- (Teff et al., 2004) and long-term studies (Swarbrick et al., 2008; Stanhope et al., 2009) show significant increases of triacylglycerol levels after consumption of fructose compared to glucose. Also consuming sucrose and HFCS seems to affect the triacylglycerol levels the same way as pure fructose (Stanhope et al., 2008). This result is a bit peculiar because they have very different composition and still gives the same response. The question is then; does this mean that HFCS and sucrose are as bad as fructose? Further long-term studies have to be performed to clarify this issue, but if this is the case then the amount of fructose in these sweeteners might be enough to cause atherogenesis and cardiovascular diseases.

Except for the triacylglycerol levels, the studies that have been made comparing HFCS and sucrose shows that they both contribute to metabolic changes intermediate to those of pure fructose and glucose (Stanhope et al., 2008). These results were as expected because both of them have a composition of approximately 50 % of each sugar. Neither the study by Stanhope at al. in 2008, nor the one by Melanson et al. in 2007 show significant differences between HFCS or sucrose. According to White (2008), “It is time to retire the hypothesis that HFCS is uniquely responsible for obesity”. In this review he states several reasons which supports this e. g. HFCS has the same sugar composition as sucrose and although pure fructose can cause unfavourable metabolic effects consumed in high concentration, it cannot be applied to HFCS containing both fructose and glucose. Since 1970 caloric intake has increased due to increased consumption of all caloric nutrients, particularly fats, flour and cereals and not because of added sugars such as HFCS. Further conclusions were that there is no longer an association

between the obesity in the United States and the consumption of HFCS as the obesity rates are continuing to rise, in contrast to the per capita consumption of HFCS that has decreased in recent years. Also, since HFCS is a minor sweetener in the global perspective with occurrence <10%, no association between HFCS consumption and worldwide obesity can be made.
These arguments along with the studies showing no difference between HFCS and sucrose may suggest that the increased use of HFCS as a sweetener, instead of sucrose, should not be of any concern regarding the rise of obesity.

The intake of carbohydrates in Sweden seems to be lower than recommended and total consumption of sugar does not seem to be increasing. But could it be the fact that the increased consumption of sugar in liquid form contributes to an increased consumption of calories from other sources e.g. protein and fat? Maybe the body does not recognise calories in e.g. soft drinks and other beverages the same way as when it comes from food. Then the intake of sugar could indirectly contribute to weight gain and obesity. Also the extreme increased consumption of soft drinks could probably continue to rise and eventually maybe increase the total consumption of sugar as well. Along with the fact that intake of sugar produced in pure form exceeds recommendations, there are several facts suggesting you should be careful with food and beverages sweetened with great quantities of sugar. Concerning our domestic animals, they do not seem to consume such large amounts of sugar that it would be of any concern.

Fructose seem to have more deleterious effects on weigt gain and obesity than glucose but today the biggest amount of fructose used in food and beverages are in the form of HFCS. Since HFSC does not seem to give rise to any different effects according weight gain and obesity compared to sucrose, we should probably not be worried. However, if the composition of sweeteners should change or maybe if fructose would be used in pure form, we would probably be able to see more of its negative consequences. Today, concerning weight gain and obesity, results presented in this review are consistent with the over-all conclusion that we should focus more about our total intake of sugar instead of fructose alone.

Conclusions

Fructose and glucose are metabolized differently; fructose can bypass the main rate-controlling step that glucose must undergo and does not induce the same endocrine response as does glucose. Several studies suggest that this may contribute to weight gain, obesity and cardiovascular diseases. Since our domestic animals seem to consume very small amounts of sugar, this should not be of any concern for them. No significant difference has been shown between HFCS and sucrose which indicates that consumption of HFCS does not constitute a specific risk factor for development of obesity that can be separated from the total intake of sugars. It remains, however, clear that fructose produces more deleterious effects than glucose, if consumed in high doses. This means that we can continue to eat fruit, in reasonable amounts and instead focus on the total intake of sugar and avoid over consumption of large amounts of e.g. soft drinks and candy. These conclusions are based on studies made so far, but some of them are equivocal and additional long-term studies need to be done to fully understand and determine the metabolic effects of prolonged fructose consumption.

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