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From Sweet to Deadly

How Fructose Can Lead to Health Problems

By Nestor Batres

Recall to a time when you were younger, every adult telling you sugar is bad for you. As you got older, you realized that it was because of the high amount of calories the sugar contributes. However, it goes deeper than the simple mantra, “excess calories going in equals fat.” When consumers are told that sugar is “bad” for you, often times they picture the ubiquitous solid, crystalline, sweet compound. However, research shows that it is not the whole sugar compound that can be detrimental for one’s health, but only part of it. More specifically, the part that can be harmful is fructose which along with glucose makes the compound sucrose (table sugar). There are numerous inherent problems with the digestion of fructose, such as the fact that it is only metabolized in the liver, its ability to create free fatty acids, and its potential to yield large amounts of uric acid. These problems are further exacerbated by the prevalence of fructose in many food stuffs. To understand the extent of the damage done by fructose, we must observe what happens to fructose once inside the body.

Fructose in the Liver

A first step to understanding the dangers of fructose is to explore how its unique metabolism occurs in our body. One of the main problems of fructose is that, unlike glucose which can be metabolized by any cell in the body, fructose is primarily metabolized in the liver. The main purpose of fructose is to replenish glycogen and to produce energy through the synthesis of triglycerides. Glycogen is a molecule stored in the body for later use as energy. The metabolism can be divided into two main parts: fructolysis and pyruvate’s fate in the Krebs cycle.

When a person ingests fructose, the transporter protein GLUT5, sends almost all of the fructose to the liver. Once in the liver, fructose gets converted to fructose-1-phosphate by the enzyme fructokinase and

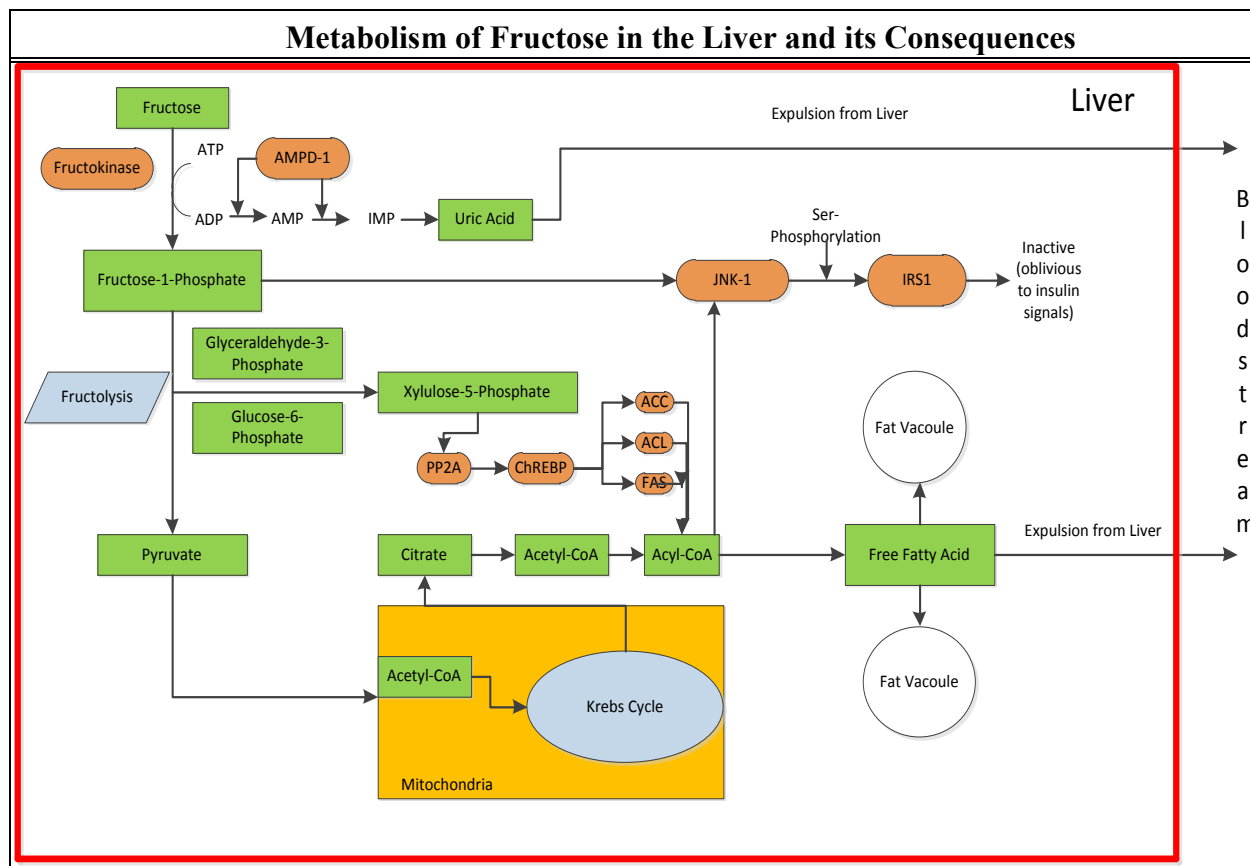
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Sugar exists in two main forms; syrup (top) or in a crystalline solid (bottom).

uses a molecule of adenosine triphosphate (ATP) for each molecule of fructose. By turning fructose into fructose-1-phosphate, the molecule can now enter the fructolysis process. Two intermediates of this process, dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, lead the path towards the production of glucose-6-phosphate, which in turn can become xylulose-5-phosphate. The problem with xylulose-5-phosphate is that it stimulates protein phosphatase 2 (PP2A) and activates carbohydrate responsive element-binding protein (ChREBP) which releases fat producing enzymes ACC1, ACL and FAS. These enzymes become important in the production of free fatty acids from citrate.

The end product in fructolysis is pyruvate. Pyruvate is an important molecule for Krebs cycle, which occurs almost entirely in the mitochondria. Once pyruvate enters the



mitochondria, a significant amount of citrate is made. Citrate can then be transported out of the mitochondria's matrix and into the cell's cytoplasm. This citrate is immediately converted back into acetyl-CoA and then to acyl-CoA which along with the fat producing enzymes, ACC1, ACL and FAS, drives the synthesis of fat forward, a process called de novo lipogenesis. The fats produced are the triglycerides which form the backbone for low density lipoproteins (LDL's) and very low density lipoproteins (VLDL's), which are colloquially known as "bad" cholesterol.

These metabolic pathways are used to back the numerous studies done on subjects consuming high amounts of fructose. In a study done by John P. Bantle and others for the General Clinical Research Center at Fairview-University of Minnesota Medical Center, 12 healthy men were given isoenergetic meals but with varying fructose content. One

diet was composed of 17% fructose and the other 3% fructose, with the rest being glucose at the end of the study, six weeks, the daylong plasma triglyceride concentration was 32% higher in the high fructose diet. Similarly, Karen L. Teff and others at the General Clinical Research Center in Virginia conducted a study in which 12 healthy women were given meals with either 30% of the Calories being fructose or glucose. After 23 hours, it was found that subjects had lost about 2.1 grams/liter of triglycerides on the glucose diet, while subjects on the fructose diet had an increase of about 13.8 g/L of triglycerides.

The fat produced cannot stay in the liver, so the liver tries to remove the fat and send it into the blood stream for energy production or storage. However, not all the fat can be removed and over time there is accumulation of fat in the liver. This process is akin to the metabolism of alcohol and over

time can cause fatty liver disease. Fatty liver disease can further destroy the liver by causing inflammation, cirrhosis, and other complications.

Zvi Ackerman et al., decided to test how much fat actually stays in the liver. The researchers gathered 49 rats of similar weight and divided them into two groups. One group was fed normal rat chow, which is 41% glucose and the other group was fed a high fructose meal, which was 60% fructose. After five weeks, the fructose fed rats had high concentrations of lipids (28% higher), triglycerides (198% higher), and cholesterol (89% higher) in their liver than rats fed the rat chow. Additionally, in rat chow fed rats, the liver weight was recorded at 9.6 grams, while in fructose fed rats, the liver weight increased to 10.1 grams.

Conversely, the high amount of fat that does make it into the bloodstream promotes numerous health problems, such as heart disease and hypertension.

Uric Acid

The first step in the metabolism of fructose requires a molecule of ATP per molecule of fructose. The ATP, a purine-based molecule, provides the energy and the phosphate group for the reaction to proceed. Thus, the ATP molecule is converted to ADP. The body, with time, can usually recycle the ADP by bonding with a phosphate unit, creating ATP once again. However, since there is a huge volume of ATP being used in a short amount of time, there is not time or energy to recycle the ADP's. There-

This process is akin to the metabolism of alcohol and over time can cause fatty liver disease.

fore, the body further hydrolyzes the ADP into AMP, releasing an additional phosphate group. Excess AMP activates AMP deaminase, an enzyme that removes an amine (NH_2) from AMP, effectively converting it into IMP (inosine monophosphate). Consequently, the removal of ribose and further oxidation of IMP forms uric acid. Normally, uric acid is excreted through urine. However, since large amounts are being synthesized, some of the acid may not leave the body and cause hyperuricemia, elevated levels of uric acid in the blood stream. Hyperuricemia can lead to gout, a type of arthritis, and to kidney stones when uric acid crystallizes in the kidneys. Additionally, studies have shown that uric acid is indirectly involved in endothelial dysfunction, damage to the inner lining of blood vessels, and to inactivation of nitric oxide. These two conditions can lead to hypertension and other blood vessel related complications.

Using the National Health and Nutrition Examination Survey, conducted between 2001 and 2002 on 4073 subjects, researchers Xiang Gao Et Al found a correlation between fructose intake and uric acid production. The researchers found that between the highest and lowest fructose intake, about a 70 gram difference, produced a 22 $\mu\text{mol/L}$ difference in uric acid production. These findings were consistent with previous research done on the subject. In 1989, Sheldon Reiser et al found that a fructose rich diet produced about 13% more uric acid than a starch (glucose) rich diet.

Disruption of Hormones

Insulin is an important hormone that controls the level of blood glucose and suppresses ghrelin, a hormone that stimulates hunger. Insulin is released from the pancreas when the β -cells are stimulated. Nonetheless, fructose cannot enter the β -cells and thus no insulin is released upon the consumption of fructose. As a consequence,

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enzyme c-Jun N-Terminal Kinase 1 (JNK-1). JNK-1 can be destructive in that it allows the protein, insulin receptor substrate 1 (IRS1), to become phosphorylated at the Ser-307 site as opposed to the tyrosine site. A serine-phosphorylated IRS1 is rendered inactive, thereby no interaction between IRS1 and the insulin receptor. As more IRS1 become inactive, the more insulin needed to send a signal across and in essence IRS1 inactivity creates insulin resistance.

Once insulin resistance has been established, the pancreas has to work harder to release more insulin. However, an over excretion of insulin can be destructive for the body because insulin promotes fat production.

A basic outline on how the appetite hormones function in relation to each other and food. Also, this diagram demonstrates how all the hormones reach the brain.

ghrelin is not suppressed leaving a sensation of hunger and can lead a person to overeat.

Mohammed Saad's 2002 study demonstrated that when insulin levels increased, ghrelin levels decreased and vice versa. With the eight subjects, the researchers noted that when insulin levels increased from around 78pmol/L to 564 pmol/L, ghrelin levels diminished from 85pmol/L to 73pmol/L. Additionally, 90 minutes after the insulin spike was observed, ghrelin levels went as low as 61pmol/L.

As stated before, fructose drives the production of citrate forward, which in turn becomes acetyl-CoA. In addition to synthesizing fat, acetyl-CoA can also activate the

Insulin's main function is to force glucose from the blood into the liver, muscle, and fat cells thus lowering blood-sugar levels and allowing the body to create glycogen storages. Conversely, insulin also stops the use of stored fat as an energy source. If an excess of insulin is observed in the body, not only will cells create more fat but they will also stop the use of fat as energy.

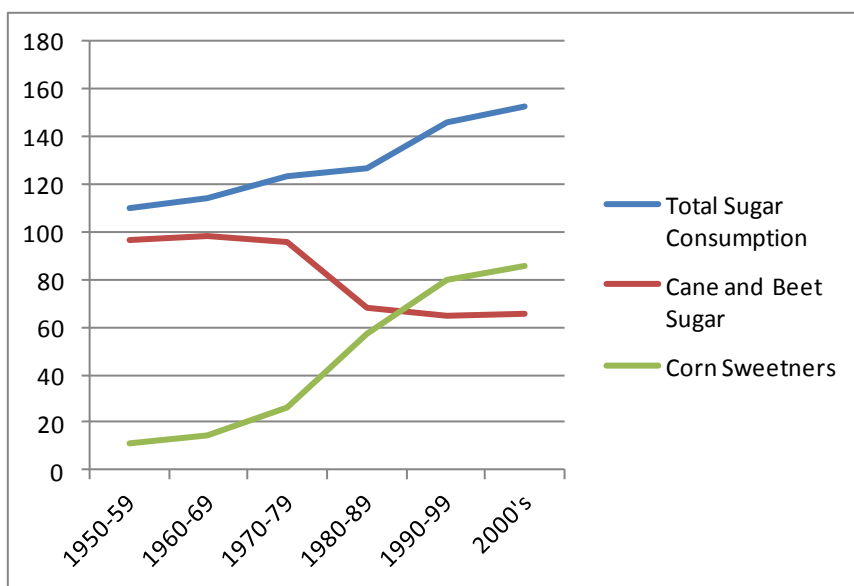
Research has shown that insulin spikes have stopped leptin recognition by the brain. Leptin is a signaling hormone that inhibits appetite. Once a person has had a full meal, leptin travels to the brain and signals satiety. However, when there is a large amount of insulin circulating in the body, the brain has

a high fructose diet compared to a high glucose diet (3261 to 6658 pmol/liter, respectively). Leptin concentrations also diminished, 300.8 ng/mL(glucose) to 218.5 ng/mL (fructose). Finally, the researchers also noticed a ghrelin disturbance. The subjects' baseline ghrelin concentration was observed, on average, at 308 pg/mL. However, on the glucose diet, after eating a meal, it was detected that ghrelin levels dropped, on average, 138 pg/mL. Meanwhile on the fructose diet, subjects' ghrelin level dropped, on average, only 46 pg/mL. The subjects in the restrained diet consistent mostly of fructose experienced more hunger sensations than the group eating a diet composed mostly of glucose.

Prevalence of Fructose

In 1977, the U.S. raised the tariffs on imported sugar, forcing companies to search for a cheaper alternative. Incidentally, a year before, the FDA had approved high fructose corn syrup (HFCS), providing these companies the inexpensive substitute they were desperately looking for. However, in finding this option, producers took advantage of the low cost of HFCS and used the syrup abundantly in their products. According to data gathered by the USDA, the amount of sugar consumed per capita has increased by almost 42.8 pounds since 1950. The graph above shows the increase of sugar consumption, specifically, the steep increase of corn syrup. Since people, for the most part use cane sugar and not corn syrup at home, they must be getting the HFCS from outside food stuffs. For example, in 1978, Kellogg's Special K had

U.S. Sugar Consumption Per Capita, in Pounds



around 9.6 grams of sugar per 100 grams of cereal. However, today, the cereal packs a whopping 17 grams of sugar per 100 grams of cereal, almost doubling the amount of sugar.

In the 1970's, Ancel Keys released a study claiming that the consumption of animal fats was strongly associated with coronary disease. This finding strongly influenced the US government and the population to demonize fat. The problem, nevertheless, was that manufacturers of food had to replace the fat with something else, to make the food item palatable once again. This replacement of fat also led to the increase in the usage of sugar. Additionally, this demonization of fats led people to look out for fats but completely neglecting their control of sugar intake.

Caveats

After all this information, there are several points that remain relevant. One of the most important ones is that table sugar is molecularly similar to high fructose corn syrup. Both compounds contain almost the same amount of glucose and fructose. Consuming one or the other makes no differ-

ence. You may also remember that fructose is found naturally in fruits. However, the amount found in fruits is trivial compared to processed food. For example, a 100g apple contains about 10.9 grams of sugar but only 5.9 grams of those are fructose. Also, fruit fiber stops some of the absorption of the sugar. Finally, we have to keep in mind that many factors increase the propensity of obesity, not just fructose. Such factors include a sedentary lifestyle, overconsumption of food, and overall negligence to health.

This research helps us shed light to the risks of excessive fructose consumption. Fructose can help us inch closer to hypertension, obesity, insulin resistance, and increased concentrations of triglycerides and LDL's. In short, fructose can lead us to the metabolic syndrome as well as an assortment of other dangers. However, it is almost impossible to run away from fructose, but you can curb its consumption. By being more informed, you can make healthier choices leading to a healthier lifestyle. Nutritionists and biochemists are hoping that one day; this information will be common knowledge.