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The Influence of High Fructose Corn Syrup on the Diabetes Epidemic

By

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An Honors Thesis Presented to the Honors Committee
of Western Oregon University
In Partial Fulfillment of the Requirements for
Graduation from the Honors Program

Dr. Tom Kelly, Thesis Advisor

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May, 2010

Acknowledgments

I would like to thank the people have been so supportive and helpful throughout the thesis process.

Mom and Dad, thank for always being supportive and pushing me to do my best. Dad, thank you for always being proud of everything I did. I know you would be so proud of me now. Mom, thank you for always being there, being supportive and encouraging me to do my best.

Dr. Tom Kelly, thank you for agreeing to be my thesis advisor and taking on the challenge of being an advisor for the first time. Your dedication and enthusiasm for teaching is refreshing and encouraging. Thank you for helping me nail down a subject when I had so many ideas and did not know where to start. You have been so helpful throughout the thesis process and I am grateful for all your time and support.

Dr. Gavin Keulks, thank you for always reassuring me that all would work out in the end when I began to feel panicked. Several times you reassured me that I just needed to take a deep breath and be confident in the direction that I was going.

Kurt, my fiancé and soon to be husband, thank you for being proud of me in all that I do. You have been my foundation and comfort when I began to doubt myself and my encouragement when all went well.

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Abstract

Over the past 30 years, the amount of high fructose corn syrup consumed in the United States has increased. During the same period the diabetes and obesity epidemic has emerged and risen to an all-time high. These epidemics are taking large tolls on the individual and on society. The compelling data showing the same upward trend of high fructose corn syrup, type 2 diabetes and obesity can hardly be ignored as many researchers try to uncover the link. Many have stated that the increase in high fructose corn syrup, especially that from soda pop, has led to the obesity epidemic and from there led to the diabetes epidemic. However, high fructose corn syrup could be directly leading to the diabetes epidemic or the two diseases could be so intertwined that the sweet syrup is causing both to occur. A large extent of research has been done in the area, but no strong evidence has been uncovered to show how the three are related. Much more research, especially on humans in the long-term, is needed to help find more answers. In the mean time, governmental bodies such as the Food and Drug Administration (FDA) and the presidential body need to make stronger efforts to reduce the amount of Americans diagnosed with type 2 diabetes or obesity.

Diabetes Defined

The term diabetes mellitus refers to a group of diseases that affect how the body can use glucose, more commonly referred to as blood sugar (Mayo Clinic Staff, 2009). All carbohydrates that enter the body eventually become metabolized into glucose to provide fuel for the cells, brain and body to carry out their physiological processes. Once glucose enters the blood stream, the pancreas releases insulin, which allows the uptake of glucose into the cells for energy (Insel, Turner, & Ross, 2006). Diabetes occurs when the body does not produce enough insulin, which in turn leads to high blood sugar because the cells cannot take up the glucose causing an abundance in the blood. If not well regulated, diabetes and high blood sugar can lead to a variety of other problems.

Type 1 diabetes, also known as insulin dependent diabetes mellitus (IDDM), effects five to ten percent of all individuals diagnosed with diabetes (Mayo Clinic Staff, 2009). There are two categories of type 1 diabetes: idiopathic type 1 diabetes and immune-mediated diabetes. However, immune-mediated diabetes is most common and the one generally referred to as type 1 diabetes (University of Virginia, 2004). Idiopathic type 1 diabetes, the rarest form of the disease, has no known causes. Immune-mediated diabetes is an autoimmune disorder in which the body's immune system attacks its own insulin producing pancreas cells in attempts to destroy them (University of Virginia, 2004). Though type 1 diabetes can develop at any age, it often appears during the early years of childhood or adolescence. Various factors are thought to contribute to the development of type 1 diabetes including genetics, viruses, and even possible environmental factors. At this time, type 1 diabetes has no cure, but can be managed with daily injections of insulin to maintain blood sugar level (Mayo Clinic Staff, 2007).

Type 2 diabetes, also called non-insulin-dependent diabetes mellitus (NIDDM), is a metabolic disorder in which the body becomes resistant to the effects of insulin or the body does not produce enough insulin to regulate blood sugar (Mayo Clinic Staff, 2009). Of the different types of diabetes, type 2 is most prevalent affecting 90 to 95% of all individuals diagnosed with diabetes (Mayo Clinic Staff, 2009). Unlike IDDM, type 2 diabetes often develops over a period of many years (University of Virginia, 2007). Before diagnosis of diabetes, individuals are often diagnosed with prediabetes, or blood glucose levels that are abnormally high, but not high enough to be defined as diabetes (University of Virginia, 2007). Exact causes of type 2 diabetes are unknown, but possible causes include genetics, obesity, and improper nutrition (University of Virginia, 2007).

Spread and Trends of Diabetes in the United States

The total number of individuals diagnosed each year with type 2 diabetes continues to increase affecting many people in the United States. In 1980, 5.6 million people were documented with diagnosed type 2 diabetes (Center for Disease Control [CDC], 2008). In 2002, more than 18 million Americans, or about 6.9% of the population, had diagnosed type 2 diabetes (Cheng, 2005). An estimate from the Center for Disease Control and Prevention stated that in 2007, 23.6 million Americans, or 7.8% of the population, had type 2 diabetes (CDC, 2007). Of that 23.6 million, 5.7 million were undiagnosed. The same survey showed that 10.7% of people 20 years and older have type 2 diabetes, and 23.1% of people 60 years and older have type 2 diabetes.

Though the seriousness of the epidemic was only recognized recently, the trends of the previous century already showed a threat. The incidence of type 2 diabetes in 1990 to 1992 was

6.4 times higher than the rates from 1935 to 1936 and that rate increased by another 40% from 1990 to 1999 (Cheng, 2005). Assuming the trends continued in a similar fashion, the predicted risk of developing type 2 diabetes for an individual born in 2000 was estimated to be 32.8% for males and 38.5% for females (Cheng, 2005).

Complications Associated with Diabetes

Diabetes is the fifth leading cause of death by disease in the United States and also contributes to higher rates of morbidity (American Diabetes Association [ADA], 2003). Chronic elevation of blood glucose will eventually lead to tissue damage, which can then lead to disease. Though many of the organ systems can be damaged, the kidneys, eyes, peripheral nerves and vascular tree, are the most effected with significant, and sometimes fatal, diabetes complications (International Diabetes Federation [IDF], 2009). Based on numbers from 2004, heart disease was noted on 68% of diabetes-related death certificates among people 65 years and older (CDC, 2007) and accounts for about 50% of all diabetes fatalities and much of the disability associated with the disease (IDF, 2009). Death rates from heart disease in adults with diabetes are two to four times higher than adults without diabetes (CDC, 2007). Likewise, the risk for stroke is two to four times higher for diabetic individuals when compared to non-diabetic individuals, and accounts for 16% of diabetes-related deaths (CSC, 2007). In 2004, 75% of adults with diabetes had blood pressure greater than or equal to 130/80 mm Hg (healthy is considered 120/80 mm HG), or used prescription medications for hypertension (CDC, 2007). High blood pressure can lead to a variety of other problems and has been linked to several other complications such as heart attacks, blood clots, and strokes (CDC, 2007). Diabetes is the leading cause of new cases of blindness in adults aged 20 to 79 years old, causing 12,000 to 24,000 new cases each year (CDC, 2007). High blood sugar can lead to fluid build up behind the retina of the eye or

repeated hemorrhages in the back of the eye, both of which lead to blindness (IDF, 2009). The single most common cause of kidney failure is diabetes, accounting for 44% of new cases in the United States in 2005 (CDC, 2007). Many people with diabetes also suffer from some form of nervous system disease or damage. Around 60 to 70% of individuals with diabetes have mild to severe forms of nervous system damage (CDC, 2007). Results from this damage cause impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, erectile dysfunction, and many other nerve problems (CDC, 2007). Severe forms of diabetic nerve disease are a major contributor to lower-extremity amputations. More than 60% of non-traumatic lower-limb amputations occur in people with diabetes leading to about 71,000 lower-limb amputations in 2004 alone (CDC, 2007).

Other complications from diabetes include higher risk from periodontal disease, complications during pregnancy (including major birth defects and spontaneous abortions), biochemical imbalances which can cause acute life-threatening events such as ketoacidosis or coma, higher susceptibility to many other illnesses along with worse prognosis of the illness, and increased inability to do everyday tasks (CDC, 2007).

Diabetes complications can also greatly affect children in different ways than adults. Unstable metabolic and blood sugar control in children can result in stunted growth (IDF, 2009). Exposure to both severe hypoglycemia and chronic hyperglycemia can adversely affect neurological development (IDF, 2009). Children are more sensitive to a lack of insulin than adults and are at a higher risk of a rapid and dramatic development of diabetic ketoacidosis (diabetic coma) (IDF, 2009).

The mechanism by which diabetes leads to the above complications is very complex, and not yet fully understood. Thoughts are that complications arise from mechanisms that involve

the direct toxic effects of high glucose levels, the impact of elevated blood pressure, along with abnormal lipid levels on both functional and structural abnormalities of small blood vessels (IDF, 2009).

Economic Impact of Diabetes in the United States

The cost of diabetes for both the individual and the U.S. are substantial. An estimate by the American Diabetes Association for direct medical and indirect expenditure costs for diabetes in the United States in 2007 was \$174 billion (ADA, 2007). Comparatively, the same estimate done in 1997 totaled \$98 billion (Skyler & Oddo, 2002). Of the \$174 billion spent in 2007, \$116 billion went towards direct medical expenditures alone (ADA, 2007). Broken down, the \$116 billion went towards diabetes care (\$27.5 billion), chronic complications attributable to diabetes (\$29.1 billion), and excess prevalence of general medical conditions (\$52.2 billion) (ADA, 2007). Indirect expenditures, including lost workdays, restricted activity days, mortality, and permanent disability due to diabetes made up the remaining \$58 billion (ADA, 2007). Per capita medical expenditures in 2003 totaled \$13,243 for people with diabetes and \$2,560 for healthy people without diabetes. When adjusting for differences in age, sex, and race/ethnicity between the population with and without diabetes, people with diabetes had medical expenditures that were about 2.4 times higher than expenditures that would be incurred by the same group in the absence of diabetes (ADA, 2003). In comparison, 1997 estimates were \$10,071 per capita for those with diabetes, and \$2,669 for people without diabetes (Skyler & Oddo, 2002). When individuals with undiagnosed diabetes, pre-diabetes and gestational diabetes are factored in as well, the estimate of national costs of diabetes in 2007 would total \$218 billion (ADA, 2007).

Though the estimates in 2007 were \$174 billion, this number is likely an underestimate of the true burden of diabetes. Not included in this number are intangibles such as pain and suffering, care provided by nonpaid caregivers, and several areas of health care spending where people with diabetes probably use services at higher rates than people without diabetes (e.g., dental care, optometry care, and the use of licensed dieticians) (ADA, 2003). This estimate also excludes any undiagnosed individuals suffering from diabetes and related complications. The cost of diabetes affects not only the person and their families, but society as well. Lost work days or decreased production due to diabetes affects the individual, but also the community in which they work (ADA, 2003). Also, unmet costs on healthcare expenditures incurred by individuals with diabetes must be met somehow. This is often absorbed by society with taxes and higher medical costs overall (ADA, 2003).

Insulin Resistance and Pre-Diabetes

Both insulin resistance and pre-diabetes can lead to type 2 diabetes if life style changes are not made. Insulin resistance is a condition in which the body produces insulin, but cannot use it properly because the tissues do not respond well to the insulin resulting in higher blood glucose levels (National Institute of Health [NIH], 2008). The higher blood glucose levels cause the pancreas to produce more and more insulin to keep up with the high levels of glucose in the blood. Over time the pancreas can no longer keep up with the body's need for insulin resulting in excess glucose build up in the blood (NIH, 2008). A long-term, substantial increase in glucose in the blood elevates the chance of developing type 2 diabetes (NIH, 2008). The most common cause associated with insulin resistance is excess weight and lack of physical activity (NIH, 2008). Pre-diabetes is a condition where the levels of blood glucose are higher than

normal, but not quite high enough to be diagnosed as diabetes (NIH, 2008). Other common names for pre-diabetes are impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (NIH, 2008).

Most people with insulin resistance or pre-diabetes are not aware that they have the conditions because there usually are no symptoms (NIH, 2008). The U.S. Department of Health and Human Services estimates that approximately 57 million people, or one in four adults 20 years and older, in the U.S. had pre-diabetes in 2007 (NIH, 2008). Studies have shown that most people with pre-diabetes usually develop type 2 diabetes within ten years, unless they change their lifestyle to loss around five to seven percent of their body weight (NIH, 2008).

Metabolic Syndrome

As the number of individuals in the United States diagnosed with type 2 diabetes continues to rise, many are searching for a cause and a solution. However, diabetes has been labeled as a multi-factorial disease and is commonly associated with a cluster of other pathologies including: obesity, hypertriglyceridemia, impaired glucose tolerance, and insulin resistance (Basciano, Federico, & Adeli, 2005). These diseases have been grouped together and are commonly called the metabolic syndrome, previously called syndrome X or insulin resistance syndrome (Basciano et. al., 2005). The metabolic syndrome is defined, by the American Heart Association and the National Heart, Lung and Blood Institute, as the presence of any of the three following conditions: waist measurement of 40 inches or more for men and 35 inches or more for women; triglyceride levels of 150 milligrams per deciliter (mg/dL) or above, or taking medication for elevated triglyceride levels; HDL, or “good”, cholesterol level below 40 mg/dL for men and below 50 mg/dL for women, or taking medication for low HDL levels; blood

pressure levels of 130/85 or above, or taking medication for elevated blood pressure levels; and/or fasting blood glucose levels of 100 mg/dL or above, or taking medication for elevated blood glucose levels (NIH, 2008).

Individuals with the metabolic syndrome are also at an increased risk of developing coronary heart disease, or other disease related to plaque buildup on the artery walls, and type 2 diabetes (American Heart Association, 2010). Though there is no well-accepted criteria for diagnosing the metabolic syndrome (many different criteria like the one above have been proposed, but no set one has been decided), it is estimated that over 50 million Americans have the disease (American Heart Association, 2010). The dominant underlying risk factors for the metabolic syndrome appear to be abdominal obesity and insulin resistance (why the metabolic syndrome is also called the insulin resistance syndrome) (American Heart Association, 2010). The metabolic syndrome has also been given the nickname “Diabesity” in reference to the increasing incidence of diabetes in combination with obesity as a result of changes in human behavior (Basciano et. al., 2005). A new consensus states that insulin resistance and obesity are actually part of one common pathologic mechanism of the metabolic syndrome and evidence shows that the process starts early in life during childhood and develops with time (Basciano et. al., 2005).

Obesity in the United States: Trends, Costs and Associated Problems

In the United States, obesity has become an epidemic as the number of individuals who are overweight, obese and extremely obese continue to rise. Obesity is defined as a body mass index (BMI) of greater than or equal to 30. Overweight is classified as a BMI between 25.0 and 29.9 and extremely obese is a BMI greater than or equal to 40. From 1960 to 2006, the percent

of people in the United States between the ages of 20 and 74 classified as obese rose from 13.4% to 35.1% (Health E-Stats, 2008). In that same time period, the number of overweight individuals in the same age category rose slightly and the percentage of extremely obese individuals rose from 0.9% to 6.2% (Health E-Stats, 2008). Though medical care costs related to obesity are hard to estimate because of related issues beyond obesity, some figures are available. In 1998, the medical costs associated with overweight and obesity accounted for an estimated 9.2% of U.S. medical expenditures with total costs possibly as high as \$78.5 billion (CDC, 2009). A study comparing health costs of obese individuals between 1997 and 2001 found that obese individuals spent more than \$1,000 per capita, or 37% more than a normal-weight individual in 2001 (Cheng, 2005). Associated health risks with obesity are: Coronary heart disease, type 2 diabetes, cancers (endometrial, breast, and colon), hypertension, dyslipidemia, stroke, liver and gallbladder disease, sleep apnea and respiratory problems, osteoarthritis, and gynecological problems (abnormal menses, infertility) among others (CDC, 2009).

Past research has shown an association between higher dietary energy from fat and higher body weight (Basciano et. al., 2005). This has led to an increase in production and promotion of low fat foods and diets (Basciano et. al., 2005). However, though consumers are buying low fat foods and the amount of dietary fat has declined, there is no corresponding trend to obesity, in fact, the opposite has occurred (Basciano et. al., 2005). This odd statistic quite clearly shows that fat intake is not the leading problem, or possibly even a problem worth focusing on. Increasing evidence suggests that the focus should be on the rise in consumption of carbohydrates, specifically refined carbohydrates, such as sugar, and those high in fructose (Basciano et. al., 2005).

High Fructose Corn Syrup History, Production Methods, and Consumption

High fructose corn syrup was discovered in 1957 by two researchers who made the sweet syrup using an enzyme called glucose isomerase (Orthodox Union). This enzyme is added to glucose rich corn syrup to rearrange the molecular composition of glucose and convert it to fructose (Orthodox Union). The result is a syrup sweeter than regular corn syrup and sugar and appropriately named high fructose corn syrup (Orthodox Union). The more glucose that is converted to fructose the sweeter the resulting syrup (Orthodox Union). On a 100 point scale, where sucrose is 100 in sweetness, high fructose corn syrup ranges from 120 to 160 depending on the percentage of fructose in the final product, and corn syrup (glucose) is 70 to 80 on the same scale (Orthodox Union). The sweeter syrup allowed companies to use less sugar to get the same sweetness and therefore save money. The high availability of corn, and rising prices on sugar, along with the increasing use of byproducts from corn, also contributes to the lower and more appealing price of high fructose corn syrup (Putnam & Allshouse, 1999). The economic impact of high fructose corn syrup caused many companies to switch their sweeteners over to high fructose corn syrup instead of corn syrup or sucrose (Orthodox Union). High fructose corn syrup is typically made at one of two different sweetness levels and named either high fructose corn syrup 42 or 55 referring to the amount of glucose converted to fructose (Orthodox Union).

As the production and use of high fructose corn syrup went up, so did consumption. Between 1970 and 1997 sucrose dropped from 83% of total caloric sweetener used, to 43% (Putnam & Allshouse, 1999). Per capita use of sucrose dropped from 102 pounds per person in 1970 to 60 pounds per person in 1986 (Putnam & Allshouse, 1999). At the same time corn sweeteners increased from 16% to 56% of total caloric sweetener used and 19 to 86 pounds consumed per capita (Putnam & Allshouse, 1999). Not only did the consumption of high

fructose corn syrup rise, so did total caloric sweetener intake. Between 1982 and 1997 the consumption of caloric sweeteners increased by 34 pounds, or 28%, resulting in an average of two-fifths of a pound (53 teaspoonfuls) per person per day in 1997 (Putnam & Allshouse, 1999).

Most of the displacement of sucrose by high fructose corn syrup is linked to soft drink manufacturers that reduce their use of sucrose between 1980 and 1997 from 19 pounds to 1 pound per capita (Putnam & Allshouse, 1999). The use of high fructose corn syrup per capita rose from 0.5 pounds in 1970 to 62.4 pounds in 1997 (Putnam & Allshouse, 1999). In 1997, beverages accounted for 72% of total high fructose corn syrup deliveries for domestic food and beverage use compared 36% in 1980 (Putnam & Allshouse, 1999). Total corn sweetener passed cane and beet sugar use for the first time in 1985 and gap continues to widen (Putnam & Allshouse, 1999). As of 2004, high fructose corn syrup represented over 40% of caloric sweeteners added to foods and beverages and was the sole caloric sweetener in soft drinks in the United States (Bray, Nielsen & Popkin, 2004). Two-thirds of all high fructose corn syrup consumed in the United States is in the form of beverages (Bray et. al., 2004). The average daily intake of calories from high fructose corn syrup for all Americans aged two years and older was 132 kcal, and the top 20% ingested upwards of 316 kcal per day in 2004 (Bray et. al., 2004).

Metabolic Differences between Glucose and Fructose

Glucose and fructose are metabolized and absorbed differently in the human body. Both glucose and fructose are absorbed in parts of the intestine and transported to the liver via the portal vein (Basciano et. al., 2005). However, that is where the similarities stop. Glucose is absorbed by a sodium-dependent process in the early parts of the intestine while fructose is absorbed further down the intestines in the duodenum and jejunum by a non-sodium-dependent

process (Bray et. al., 2004). Once in the liver, the monosaccharides are then either metabolized in the liver for energy storage or passed through the blood to other cells to be metabolized for energy. Glucose enters both liver and other cells by the transport mechanism Glut-4, which is insulin dependent in most tissues (Bray et. al., 2004). Insulin works to activate the insulin receptors on cells, which in turn cause the density of glucose transporters on the cells surface to increase, thus allowing for more transportation of glucose into the cells (Bray et. al., 2004). Once inside the cell, glucose is then phosphorylated by the enzyme glucokinase to become glucose-6-phosphate and from there the intracellular metabolism of glucose begins (Bray et. al., 2004). Glucose metabolism is tightly controlled by enzymes which regulate the conversion of glucose-6-phosphate into the glycerol backbone of triglycerides (three fatty acids linked to one glycerol) by modulating the enzyme phosphofructokinase (Bray et. al., 2004).

Phosphofructokinase is a rate limiting factor in the process of converting glucose to energy for fuel in the body. The glycolytic system is very tightly controlled so that usable energy is only made when needed and excess glucose is stored in the body as glycogen for later use. If energy is needed glucose-6-phosphate is converted to fructose-6-phosphate and then to fructose 1,6 biphosphate (Elliott et. al., 2002). From there fructose 1,6 biphosphate is converted into either glyceraldehyde 3-phosphate or dihydroxyacetone phosphate (Elliott et. al., 2002). *(See figure 1)*

In contrast, fructose enters the liver cells via the Glut-5 transporter which is not dependent on insulin (Bray et. al., 2004). Once inside the liver cells fructose is phosphorylated by adenosine triphosphate to form fructose-1-phosphate and is catalyzed by the enzyme fructokinase (Elliott et. al., 2002). Fructose-1-phosphate is then split by aldolase B into glyceraldehyde and dihydroxyacetone phosphate, which can both enter the glycolytic pathway and be converted into glyceraldehyde-3-phosphate (Elliott et. al., 2002). Glyceraldehyde and

dihydroxyacetone phosphate enter the glycolytic pathway distal to phosphofructokinase and thus bypass the main rate-controlling step in glycolysis (Elliott et. al., 2002). These two trioses, glyceraldehyde and dihydroxyacetone phosphate, are the backbone for phospholipid and triacylglycerol synthesis and fructose also provides carbon atoms for synthesis of long-chain fatty acids (Bray et. al., 2004). Thus, fructose facilitates the biochemical formation of triacylglycerols more efficiently than does glucose through excess energy flux of unregulated fructose metabolism and the formation of trioses (Bray et. al., 2004). (*See figure 1*)

The differences in metabolism and absorption between glucose and fructose in the body affect other aspects of the hormones, particularly insulin, which help control hunger and provide satiety signals. As stated, fructose enters the cells via a Glut-5 transporter which is not dependent on insulin and is also not found in the pancreatic beta cells or the brain cells (Bray et. al., 2004). The absence of the transporter in the pancreatic beta cells and the brain cells results in very limited entry of fructose into these cells (Bray et. al., 2004). Glucose provides “satiety signals” to the brain by entering the brain cells, while fructose cannot provide these same signals because it is not able to be absorbed in the brain cells (Bray et. al., 2004). Along with two other peptides, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, circulating glucose increases insulin release from the pancreas (Bray et. al., 2004). Fructose does not stimulate insulin secretion, most likely because the beta cells of the pancreas are lacking the fructose transporter Glut-5 (Bray et. al., 2004).

Insulin plays an important role in regulating food consumption in two ways. First, insulin concentrations in the blood have been shown to have a direct inhibitory effect on food intake (Bray et. al., 2004). Second, insulin may affect the secretion of leptin, a hormone which inhibits food intake by signaling a sign of fullness or satiety in the brain (Bray et. al., 2004). There is a

time delay between when insulin increases and leptin releases, but the amount of leptin released is dependent upon the amount of circulating insulin (Bray et. al., 2004). Leptin has been illustrated as important in food consumption and body weight regulation by individuals who lack leptin and as a result are morbidly obese (Bray et. al., 2004). Individuals with low leptin levels have also been shown to have greater amounts of adiposity (Bray et. al., 2004). As expected, studies examining the effects of leptin have shown that administration of leptin to those who lack the hormone results in a dramatic decrease in food intake (Bray et. al., 2004). Thus, low insulin release after fructose ingestion would lead to low levels of leptin concentrations and an increase in food consumption when compared to glucose (Bray et. al., 2004).

Fructose has also been shown to reduce adiponectin responses, an adipocyte hormone that plays an important role in lipid homeostasis and insulin action (Basciano et. al., 2005). Adiponectin is stimulated by the insulin sensitizer agonist, which then functions to reduce circulating fatty acids and increase fat oxidation (Basciano et. al., 2005). The net effect is to decrease liver triglycerides and increase insulin sensitivity (Basciano et. al., 2005). Fructose works to reduce the adiponectin response, which in turn contributes to insulin de-sensitivity (Basciano et. al., 2005).

Type 2 Diabetes and Obesity

Though the exact molecular and cellular connection between obesity and type 2 diabetes is still very unclear and cannot yet be entirely explained, the causes appear to be circular (Cheng, 2005). Ceramide, a downstream product of fatty acid metabolism, down regulates the insulin signaling in the muscle (Cheng, 2005). As stated, fructose has been shown to increase free fatty acids, thus more fatty acid metabolism occurs and causes insulin resistance in the muscles,

insulin resistance in turn further exacerbates abnormalities in fat metabolism (Cheng, 2005). Fat accumulation also has harmful effects on beta cells which produce insulin (Cheng, 2005).

Again, these diseases appear to be intertwined and determination of which one develops first could be hard to untangle. However, it is clear that development of one (type 2 diabetes or obesity) may lead to development of the other and causes for both begin early in life and develop slowly over time. There is also an agreement that the American lifestyle of eating more and exercising less is the major contributor to both these disease.

Physiological Effects of Different Sugars on the Body in Relation to Obesity

Effects of different sugars on satiety, satiety hormones, and food intake

The differences in release of satiety hormones by glucose and fructose, lead some to believe that ingesting different sugars would lead to different amount of food eaten at subsequent meals. It would follow that if fructose does not cause a large release in insulin and accompanying leptin, the amount of satiety a person would have after consuming something with fructose (such as a beverage sweetened with fructose) would be considerably less than someone who consumed a glucose sweetened item, thus, causing the fructose-individual to eat more at a subsequent meal. Many have hypothesized the reason for an increase in obesity, and related type 2 diabetes, is correlated with a higher use of high fructose corn syrup in soda and an increase in soda consumption. However, multiple studies have shown that the type of sugar used to sweeten beverages does not make a difference in food intake in subsequent meals (Monsivais, Perrigue & Drewnowski, 2007; Akhavan & Anderson, 2007; Soenen & Westerterp-Plantenga, 2007; & Melanson, Zukley, Lowndes, Nguyen, Angelopoulos & Rippe, 2006).

Soenen and Westerterp-Plantenga (2007) found no differences in satiety or energy intake after high-fructose corn syrup, sucrose, or milk preloads. The study consisted of 15 men and 15 women who consumed a 4800 mL drink containing no energy (zero calories) or 1.5 MJ from sucrose, high fructose corn syrup, or milk. Satiety was measured by both circulating hormones related to satiety and by visual analog scales on appetite. Soenen and Westerterp-Plantenga found no differences between the effects of the sucrose- and high fructose corn syrup- containing drinks on changes on insulin, glucose, glucagon like peptide 1, and ghrelin concentrations (Soenen and Westerterp-Plantenga, 2007). Any change in satiety and energy compensation where due to the change in circulating satiety hormones (insulin, glucose, glucagon like peptide 1, and ghrelin) from ingestion of food stuffs and not any differences between what was in the food stuffs (Soenen and Westerterp-Plantenga, 2007). A similar study done by Monsivais et. al. (2007) compared the effects of drinking cola beverages sweetened with sucrose, high fructose corn syrup 42 (42% from fructose), or high fructose corn syrup 55 (55% from fructose) on subsequent food intake. The results were the same as the study by Soenen and Westerterp-Plantenga: no statistical evidence was found proving that commercial cola beverages sweetened with either sucrose or high fructose corn syrup (42 or 55) have different effects on hunger, satiety, or short-term energy intakes (Monsivais et. al., 2007).

Melanson et. al. (2006) examined the effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women and also found no statistical difference between the two sugars. The thirty women studied were housed in the study facility for two days and were given control meals along with their test drink on the first day (Melanson et. al., 2006). The test drinks were sweetened with high fructose corn syrup-55 or with sucrose to make up 30% of each individuals daily caloric

needs (Melanson et. al., 2006). The control meals were based on each individual based on body weight and basal metabolic rate for amount of calories needed to consume (Melanson et. al., 2006). The subjects were given three meals each of which contained one third of their daily caloric needs (Melanson et. al., 2006). Percentages of calories coming from fat, protein, and carbohydrate were 30%, 15%, and 55%, respectively (Melanson et. al., 2006). The total carbohydrate component consisted of 25% from complex carbohydrate and 30% from high fructose corn syrup-55 or sucrose, which were used to sweeten the beverages served with the meals (Melanson et. al., 2006). On the second day, the women were allowed to eat ad libitum and told to eat as much as they would like while food intake was recorded (Melanson et. al., 2006). Blood samples and satiety assessments based on visual analog scales were taken at scheduled times (Melanson et. al., 2006). However, the authors assessed that more research is needed to examine if the same response holds true for obese individuals, males or over longer periods of time (Melanson et. al., 2006).

A study examining the effects of sugars on young men completed by Akhavan and Anderson (2007) also showed no difference in the effects of different solutions of glucose-to-fructose ratios on subjective satiety based on visual analog scales, food intake, and satiety hormones (blood glucose, insulin, ghrelin, and uric acid). In two different experiments Akhavan and Anderson compared sugar solutions of 300 kcal/300 mL of 20:80 percent glucose to fructose (G20:F80), high fructose corn syrup 55 (G45:F55), sucrose, and G80:F20 (experiment one, 12 participants); and G20:F80, G35:F65, G50:F50, sucrose, and G80:F20 (experiment two, 19 participants). Average appetite, blood glucose and food intake after 80 minutes was measured in all subjects, and hormonal responses were measured in seven subjects in experiment two (Akhavan and Anderson, 2007). Results showed no differences between sugar solutions on

short-term effects of subjective and physiologic measures of satiety and food intake at subsequent meals (Akhavan and Anderson, 2007).

The above studies all come to the same conclusion that beverages sweetened with different sugars have no effect on meals eaten after the ingestion of the sugar solutions. However, all the studies outlined above were short in duration as observations were only made on a range from one meal to two days. Similar studies should be done over longer periods of time to see if constant sugar sweetened beverage consumption has an impact on food choice and amount of food eaten. The effects of the different sugars should also be examined in specific different populations, such as normal weight compared to overweight and obese individuals.

Fructose, high fructose corn syrup and body weight

The connection between the increase in sugar intake, especially from soft drinks or other sugar sweetened drinks, and the increase in obesity has led many researchers to examine the direct connection between sugar intake and body weight. A few long-term studies have shown a positive connection between increased soda/sugar or fruit juice/punch consumption and weight gain (Tordoff & Alleva, 1990; Ludwig, Peterson & Gortmaker, 2001; Berkey, Rockett, Field, Gillman, Colditz, 2004 & Schulze, Manson, Ludwig, Colditz, Stampfer, Willett & Hu, 2004).

Schulze et. al. (2004) followed 51,603 women over the course of nine years tracking their soft drink and fruit punch (juice with added sugars) consumption along with weight gain and new cases of type 2 diabetes. After nine years the results showed positive correlation in an increase in soda/fruit juice consumption with an increase in body weight. Results showed that those who had stable consumption patterns had no difference in weight gain, but change in consumption did have an effect on weight gain (Schulze et. al., 2004). The higher the increase in

consumption the higher the weight gain, with the most weight gain in those who increased their soft drink consumption from one or fewer drinks per week to one or more drinks per day (average of 4.33 kg in 4 years) and the lowest in those who decreased their intake (average of 0.75 kg in 4 years) (Schulze et. al., 2004). Increase in consumption of fruit punch and fruit juice also showed similar results. Women who increased their consumption of fruit punch or fruit juice from one of fewer drinks per week to one or more drinks per day, gained more weight (3.69 kg and 4.03 kg in 4 years, respectively) than those who decreased their consumption (2.43 kg and 2.32 kg in 4 years, respectively) (Schulze et. al., 2004). Contrastingly, women who increased their diet soda consumption one of fewer drinks per week to one or more drinks per day, gained less weight (1.59 kg in 4 years) than those who decreased their diet soda intake from one drink or more per day to one drink or less per week (4.25 kg in 4 years) (Schulze et. al., 2004). Results also showed a strong link between greater sugar sweetened soft drink consumption and progressively higher risk of type 2 diabetes (Schulze et. al., 2004), which will be discussed in a future section.

Sugary drink consumption is not only a problem in adults, but children as well, as the number of obese children rise. Ludwig et. al. (2001) examined 548 ethnically diverse schoolchildren from four different public schools in the Massachusetts area over 19 months tracking change in BMI and soda consumption. Results showed that with each additional serving of sugar-sweetened drinks consumed, BMI and frequency of obesity increased (Ludwig et. al., 2001). Again, a negative correlation was found between diet soda drinks and weight gain. However, Ludwig et. al. also comment on the limitations of the study including the small sample size and the challenge of gathering data and factoring in changes in the body due to growth, puberty, or fitness training and the observational nature which cannot prove causality, only

correlation. A larger, similar study, called Growing Up Today, including over 10,000 children and adolescents also illustrated that increased BMI was associated with high consumption of sugar sweetened beverages (Berkey et. al., 2004). The Growing Up Today study results found a positive correlation between children who increased their sugar-sweetened beverage consumption and an increased weight gain (Berkey et. al., 2004). Though larger in numbers, this study also can only prove correlation, not causation because of other uncontrolled factors.

Tordoff and Alleva (1990) studied the effects drinking soda sweetened with either aspartame (a no calorie sweetener) or high fructose corn syrup on food intake and body weight. The subjects, nine females and twenty-one males, were given 1150 grams of soda (four bottles of about 300 mL) sweetened with aspartame or high fructose corn syrup per day in two separate three week trials while food intake and body weight were recorded and compared to the baseline three weeks of no soda drinking (Tordoff & Alleva, 1990). Caloric intake significantly increased (13%), as did body weight, for both males and females during the three week consumption of soda sweetened with high fructose corn syrup (Tordoff & Alleva, 1990). Whereas, three weeks of aspartame sweetened soda significantly reduce caloric intake (about 7%) of both males and females, and reduced body weight in males (Tordoff & Alleva, 1990). Interestingly, both types of soda reduced the intake of sugar (33%) in the diet without affecting any other nutrient intakes (Tordoff & Alleva, 1990).

If studies have shown that different sugars have no different effect on subsequent meals, then why is there a correlation between an increase in sugar-sweetened beverages and weight gain as shown by several studies above? It could be because the extra calories consumed in the beverages are not being made up for by a reduction in other intake of solid food. When rats are given sweetened beverages they reduce their intake of solid food, but not by enough to

compensate for the extra calories in the sugar beverages resulting in a positive calorie balance and slow weight gain (Bray et. al., 2004). However, solid sugar-sweetened foods appear to be different and cause the individual to consume less total calories. DiMiglio and Mattes (2000) looked at the different effects of solid versus liquid carbohydrate loads in 14 individuals. The participants were given either solid jelly beans or caffeine-free soda in the amount of 450 kcal per day for four weeks to consume as they wished with a four week washout period in between sessions (DiMiglio & Mattes, 2000). Results showed that a precise 118% energy compensation was seen during the solid phase and -17% energy compensation was seen during the liquid phase when compared to the previous “normal” feeding stage (DiMiglio & Mattes, 2000). Meaning that energy intake was reduced to compensate during the solid phase, where no compensation was made during the liquid phase resulting in weight gain (DiMiglio & Mattes, 2000).

The above studies outline the reason why high fructose corn syrup, especially in beverages, is thought to lead to weight gain. Several studies showed that an increase in soda or sugar-sweetened beverages is positively correlated with weight gain (Schulze et. al., 2004; Ludwig et. al., 2001 & Berkey et. al., 2004). The explanation for the weight gain may lie in the lack of compensation for the added calories from the drinks as outlined in the solid verses liquid carbohydrate feeding comparison (DiMiglio & Mattes, 2000). The slightly inconclusive evidence suggests that more, well-controlled research needs to be done to examine the effects of fructose on diet and nutrient selection especially in the long-term. More studies need to examine the difference that solids and liquid foods have on calorie consumption as a possible strong explanation for an increase in soda/sugar beverages leading to an increase in weight.

Negative metabolic effects of fructose and high fructose corn syrup

Though many recent studies have shown that different sugar types do not affect satiety hormones differently and therefore do not cause individuals to eat more at subsequent meals, the correlation between sugar and body weight still exists. Many researchers are still trying to uncover the link between the increase in consumption of fructose/high fructose corn syrup (especially from soda pop) and increased weight gain. A study examining the effect of feeding immature female rats different sugar solutions of glucose, sucrose, fructose, high fructose corn syrup (55%) or no sugar (control) for eight weeks found that the high fructose feeding led to fat gain more than did the other sugars (Light, Tsanzi, Giglotti & Janet, 2007). During the trial, the rats did show some compensation for the extra calories from the sugar solutions, but did not account for all extra calories leading to greater energy intake compared to the control (Light et. al., 2007). Though the extra food intake led to extra calories, there were no significant differences between the calorie consumption of the fructose, sucrose, or high fructose groups (Light et. al., 2007). At the end of the eight weeks, the only group to have greater final body weight and fat mass was the high fructose group, though the fat pad caused no differences in serum lipids or fasting blood glucose (Light et. al., 2007). The authors attribute the higher body weight and fat mass to the ability of the high fructose corn syrup to directly stimulate lipogenesis or adipogenesis (Light et. al., 2007).

A similar study done on mice drinking ad libitum water solutions with fructose, sucrose, or an artificial sweetener, showed comparable results (Jurgens, Haass, Castaneda, Schurmann, Koebnick, Dembrowski, Otto, Nawrocki, Scherer, Spranger, Ristow, Joost, Havel and Tschop, 2005). The mice accounted for the extra calories by not eating as much chow, but only the

fructose group showed an increase in adiposity (Jurgens et. al., 2007). The results from these studies suggest that weight gain from an intake of high fructose corn syrup or fructose may lead to weight gain, not because it causes the individual to eat more, but rather some underlying differences in metabolism between sugars.

A recent study done by Figlewicz, Ioannou, Bennett-Jay, Kittleson, Savard, and Roth (2009) showed, even without significant weight gain, fructose may cause unfavorable changes in the plasma lipid profile. Rats were given solutions sweetened either with agave, fructose, high fructose corn syrup, a combination of high fructose corn syrup and Hoodia (a putative appetite suppressant) or a non-caloric sweetener, as their sole source of liquid three nights per week for ten weeks (Figlewicz et. al., 2009). At the end of ten weeks no significant differences in body weight were seen but, serum cholesterol was higher in the fructose and high fructose groups and serum triglycerides were higher in the agave, high fructose corn syrup and high fructose corn syrup/Hoodia groups (Figlewicz et. al., 2009). Thus, the results suggest that even moderate consumption of fructose-sweetened liquids may lead to unfavorable changes in the plasma lipid profile (Figlewicz et. al., 2009). These changes in the plasma lipid profile could lead to further problems such as obesity or insulin resistance, but more research would be needed to make that conclusion.

Physiological Effects of Different Sugars on the Body in Relation to Type 2 Diabetes

Fructose as sweetener in diabetic foods

Many earlier studies on the effects of fructose on the body were aimed at helping diabetics find a low cost alternative sweetener that produced a decrease in plasma glucose and insulin response when compared to traditional sweeteners (sucrose, sorbitol, etc.). The majority

of the results from these early studies showed that fructose did not produce as much serum glucose and insulin response as did many other traditional sweeteners. These findings lead to the recommendation of the use of fructose as a sweetener for diabetic patients when they wanted to eat something sweet. Several studies have shown that fructose produces lower plasma glucose (PG) and insulin levels when compared to sucrose (Akgun & Ertel, 1980; Carpo, Kolterman & Olefsky, 1980; Carpo, Scarlett & Kolterman, 1982; Akgun & Ertel, 1985), sorbitol (Akgun & Ertel, 1980), dextrose (Carpo, Kolterman & Olefsky, 1980), and high fructose corn syrup (Akgun & Ertel, 1985; Akgun & Ertel, 1981). Akgun & Ertel (1980) showed that when given a 400 calorie breakfast sweetened with sucrose, sorbitol or fructose, both normal and NIDDM individuals had lower PG after the sorbitol and fructose meals. Normal individuals also had a lower insulin response to fructose, while NIDDM individuals showed no significant difference in insulin levels between the two sweeteners. The sorbitol caused mild abdominal cramps or diarrhea, thus leading the authors to suggest that fructose be used as a sweetening agent for diabetic foods (Akgun & Ertel, 1980). Though this study reflected results of other similar studies, the authors warn that no long-term studies on the use of fructose in normal or NIDDM patients have been completed (Akgun & Ertel, 1980). A similar study comparing fructose and sucrose in either a cake or an ice cream treat in normal and NIDDM patients found the same results (Carpo, Scarlett & Kolterman, 1982). After ingesting the fructose sweetened treats both normal and NIDDM subjects had lower serum glucose and insulin responses when compared to sucrose (Carpo, Scarlett & Kolterman, 1982).

A study comparing the ingestion of dextrose, sucrose or fructose, alone, in a drink or in a meal (protein and fat liquid meal) also showed that fructose produced lower serum glucose in normal, glucose intolerant, and NIDDM subjects, and lower insulin levels in normal and glucose

intolerant subjects (Carpo, Kolterman & Olefsky, 1980). Though the results were similar for all tests subjects (fructose produced the lowest glycemic response) the response to fructose increased the more glucose intolerant the individual was (Carpo, Kolterman & Olefsky, 1980). Again, however, the authors point out that very few long-term studies examining the results of a fructose diet have been done on humans, and only suggest that fructose “appears to be an acceptable nutritive sweetener for mild or moderately well-controlled diabetes patients” (Carpo, Kolterman & Olefsky, 1980).

A study comparing sucrose and high fructose corn syrup to fructose also found that fructose was more effective in mild NIDDM patients (lower pre-meal PG level) because patients with a higher PG (over 140 ml/dl) showed similar increases in PG whether they were given sucrose, high fructose corn syrup or fructose (Akgun & Ertel, 1985). An earlier study by the same authors also showed that fructose was superior to high fructose corn syrup as a sweetening agent for patients with NIDDM (Akgun & Ertel, 1981). The results were disappointing because the cost of high fructose corn syrup (at the time) was one-seventh of the cost of fructose, and half the cost of sucrose (Akgun & Ertel, 1981). A study by Hung (1980) also showed that high fructose corn syrup was not a good alternative for fructose in diabetic foods. When examining the effects of high fructose corn syrup on PG, insulin and C-peptide in both normal and NIDDM subjects, Hung found that high fructose corn syrup is not a good substitute for fructose because of its higher glycemic index rating (resulting from the containing glucose) (Hung, 1980). However, high fructose corn syrup still showed lower levels of PG, insulin and C-peptide when compared to glucose (Hung, 1980).

Though several of the above studies show that fructose proves to be a good sweetener to use in deictic foods, Bukar, Mezitis, Saitas & Pi-Sunyer (1990), warn against the error of using

individual components of commercially prepared foods to recommend a product for diabetic patients. Bukar et. al. (1990) examined the glycemic response in both normal and NIDDM patients to plain glucose, a tofu-based desert sweetened with high fructose corn syrup and a dairy-based sucrose-sweetened ice cream. Results showed no significant statistical difference in PG and insulin between the sweeteners, but the tofu desert actually produced a higher glycemic response than the ice cream (Bukar et. al, 1990). The higher glycemic response of the tofu dessert, and not a lower one as anticipated, was most likely because of the maltodextrin (strings of glucose) and free glucose also in the product, thus resulting in 24% fructose and 75% glucose after hydrolysis (Bukar et. al, 1990). The ice cream, after hydrolysis, contained 54% glucose, 11.5% galactose, and 33.5% fructose (Bukar et. al, 1990). The results show the problem with examining the label to decide on “better” dessert selection for diabetic individuals. On the other hand, the study examined only desserts sweetened with sucrose and high fructose corn syrup when Akgun & Ertel (1981) and Hung (1980) showed that high fructose corn syrup is not a good substitute for fructose in dietetic foods. The study would have been more complete if it had also used an example of a fructose sweetened dessert as well. Nonetheless, Bukar et. al. still make a good point: just because the label has fructose listed as one of the ingredients, does not make it the “best” dessert choice for a diabetic.

Sugar-sweetened beverages and type 2 diabetes

Since the results of the above studies have been published, much research on the association between sugar-sweetened beverages and the risk for developing type 2 diabetes have been undertaken. The above studies suggest that fructose is a good alternative for diabetics because of the lower level of insulin response, but long-term effects were not studied. More

recent studies have uncovered negative results from long-term fructose feeding. The same study which followed over 51,000 women (Schulze et. al., 2004) that found a link between the number of sugar sweetened beverages, mostly soda pop, and weight gain, also found a connection between high intake of sugar sweetened beverages and the risk for type 2 diabetes. Over the course of the study and follow up, 741 new cases of type 2 diabetes were recorded and greater sugar-sweetened soft drink consumption was associated with a progressively higher risk of type 2 diabetes (Schulze et. al., 2004). The average, age-adjusted, rate ratio was 1.98 for women drinking one pop per day compared to women drinking only one pop per month (Schulze et. al., 2004). After adjustments for lifestyle and dietary confounds, the association was slightly attenuated to 1.83 and after controlling for BMI was 1.39 (Schulze et. al., 2004). Though the risk was reduced, the numbers were still significant and suggest that BMI accounted for only about half of the excess risk, but sugar-sweetened drinks remained significantly associated with an increase risk of diabetes (Schulze et. al., 2004). Another similar study following over 43,000 African American women between 1995 and 2001 also found a positive correlation between a higher intake of sugar-sweetened soft drinks and fruit drinks and type 2 diabetes (Palmer, Boggs, Krishnan, Hu, Singer & Rosenberg, 2008). The rate ratio for two or more soft drinks per day was 1.24 compared to less than one per month, while fruit drinks was 1.31 (Palmer et. al., 2008). However, Palmer et. al. found that the association of diabetes with soft drinks was almost entirely mediated by BMI, where fruit drink consumption was independent of BMI.

Similar correlation results were found in a study which followed 4,304 men and women between 40 and 60 years of age over a period of twelve years (Montonen, Jarvinen, Knekt, Heliovaara & Reunanen, 2007). The intake of different sugars was calculated and numbers of new diabetes cases was tracked. The combined intake of fructose and glucose was associated

with the risk of type 2 diabetes, but no significant association was observed for intakes of sucrose, lactose, or maltose (Montonen et. al., 2007). The relative risk between the highest and lowest amounts of combined fructose and glucose intake was 1.87 and the relative risks between the consumption of food items most contributing to sugar intakes were 1.69 for sweetened berry juice and 1.67 for soft drinks (Montonen et. al., 2007).

Carbonyl stress and high fructose corn syrup

Recent studies have been investigating the effect of carbonyls and carbonyl stress in relation to diabetes. Previous studies have shown a link between cellular and tissue damage caused by carbonyls and the implications of the damage triggering and/or contributing to diabetes and related complications (Kiefer, 2007). Carbonyl groups in tissues and plasma are a fairly stable marker of oxidative stress (Kiefer, 2007). Oxidative stress or oxidative damage occurs when free radicals, formed as a byproduct in energy production, present in the body interact with other cell molecules (Rutherford, 2007). Oxidative stress is present in all beings, but is more highly elevated in those with certain disease such as diabetes (Kiefer, 2007). Though carbonyl groups are not yet fully understood in their contribution to diabetes, there is a strong relation which has been shown in previous studies (Kiefer, 2007).

Recent research from Ho (2007) has shown that carbonated beverages containing high fructose corn syrup have been found to have very high levels of reactive carbonyls (Sampson, 2007). After testing eleven different carbonated soft drinks, Ho found very high levels of reactive carbonyls present. The amount in some was more than five times the amount present in the blood of an adult person with diabetes (Sampson, 2007). Non-carbonated juice beverages sweetened with high fructose corn syrup were only found to have one-third of the amount found

in carbonated soft drinks, and high fructose sweetened teas were found to only have one-sixth of the amount as the soft drinks (Sampson, 2007). Ho did not find the same reactive carbonyls in table sugar, which, like high fructose corn syrup is made up of both glucose and fructose. The hypothesized reason for the difference is that fructose and glucose are bound and chemically stable in sucrose, but are not as stable in high fructose corn syrup (Sampson, 2007). Ho also found that adding epigallocatechin gallate (EGCG), a component chemical found in some teas, significantly reduced the levels of reactive carbonyls in relation to the dose added (Sampson, 2007). Though this new insight may be promising, there are a lot of unanswered questions and much further research needed to understand how high fructose corn syrup sweetened beverages may cause oxidative stress.

Chronic fructose feeding and type 2 diabetes

As stated earlier, fructose has been shown to decrease levels adiponectin, an adipocyte hormone, which contributes to insulin resistance (Basciano et. al., 2005). There is also strong evidence that increase in free fatty acids (FFA) plays a role in insulin resistance and leads to diabetes (Basciano et. al., 2005). Increased FFA found in diabetics and fructose fed models (in rat studies) has been shown to play a role in the inflammatory state of insulin resistance (Basciano et. al., 2005). Fructose fed models cannot remove the FFA from the tissues, which causes an influx in energy and FFA leading to secretion of triglycerides (Basciano et. al., 2005). Insulin resistance has been correlated with intracellular triglyceride stores, which are involved in lipotoxicity and beta cell failure leading to diabetes (Basciano et. al., 2005). These results suggest that fructose leads to an increase in FFA, which in turn leads to secretion of triglycerides,

and this overabundance of triglycerides leads to negative effects in the body which can contribute diabetes.

More Research Needed

Sugars, obesity and weight gain

Many of the studies discussed provide compelling evidence clearly linking fructose and high fructose corn syrup increases with the increase of type 2 diabetes and related obesity. However, the understanding of the link still remains unclear as more research, especially long-term human research, needs to be done. It is clear that fructose has a different effect on circulating insulin and relating leptin, both satiety hormones which control food intake and feelings of fullness. However, short-term studies on beverages sweetened with different sweeteners given before meals showed no difference in food intake at subsequent meals, feelings of satiety, or on circulating satiety hormones (Monsivais et. al., 2007; Akhavan & Anderson, 2007; Soenen & Westerterp-Plantenga, 2007; & Melanson et. al., 2006). Though the results from these studies are interesting and opposite to what some may have predicted to occur, all studies were done in short-term setting lasting only one meal (Monsivais et. al., 2007; & Akhavan & Anderson, 2007; Soenen & Westerterp-Plantenga, 2007) or two days (Melanson et. al., 2006).

Other, long-term studies have shown a connection between ingesting soda sweetened with high fructose corn syrup and an increase in body weight assumed to be caused by a positive energy balance due to lack of compensation for the liquid calories. Two studies (Ludwig et. al., 2001 & Berkey et. al., 2004) examining the link between BMI and soda consumption in children found a correlation between higher BMI and increase soda consumption over periods just over a

year-and-a-half. Schulze et. al. (2004) found a strong positive correlation between increasing soda pop and fruit juice consumption and increased weight gain in their study lasting over eight years. Tordoff and Alleva (1990) also found that three weeks of drinking four bottles of soda sweetened with high fructose corn syrup caused an increase in caloric intake and body weight while soda sweetened with aspartame reduced calorie intake. A possible explanation is given by the results from the study by DiMaggio and Mattes (2000) showing that liquid calories may not be compensated for as much as solid calories, thus high intake of sugary soda causes weight gain because of lack of compensation, leading to extra calories. These long-term studies are more convincing, but the first three can only prove correlation not causation because they cannot account for other outside factors (such as puberty, growth, development, changes in eating habits, etc.). More studies like the one conducted by Tordoff and Alleva (1990) comparing body weight changes and energy intake to type of sweetener used beyond just high fructose corn syrup and aspartame need to be carried out. Tordoff and Alleva (1990) only compared high fructose corn syrup and aspartame, which is a no calorie sweetener. More studies need to look into other caloric sweeteners compared to high fructose corn syrup to see if the type of caloric sweetener makes a difference on weight gain. It would also be beneficial to see longer studies of the same nature carried out in larger populations and on obese individuals. In addition, while the results from DiMaggio and Mattes (2000) are very intriguing, more studies of a similar fashion need to be addressed. Such studies should include different forms of sugar, different populations, longer time periods, and larger study samples. Conclusions from these studies would help back up the results from the study by DiMaggio and Mattes (2000) and provide more insight into compensation from different forms of food.

Results on the negative metabolic implications of fructose and high fructose feeding are interesting, but very limited in scope and understanding. Light et. al. (2007) showed that when rats were given solutions sweetened with glucose, sucrose, fructose or high fructose corn syrup, only the high fructose corn syrup group had higher final fat pad and body weight. They attribute the reason to the ability of fructose to stimulate lipogenesis or adipogenesis. However, this does not explain why there was a difference between the high fructose corn syrup, which is both fructose and glucose, and fructose. If the reason is fructose is more easily turned into fat, then the same, or greater, higher body weight and fat mass should have been seen in the fructose group as well. Jurgens et. al. (2005) did show that, in mice, fructose sweetened solutions lead to an increase in adiposity when compared to sucrose or an artificial sweetener. Both studies suggest that an increase in body weight may not be due to an increase in food consumption but a difference the way the sugar is metabolized. Both studies provide interesting results that may explain why fructose could contribute to weight gain beyond just an increase in calories. Figlewicz et. al. (2009) also showed that even without weight gain, fructose may cause unfavorable changes in lipid profile. The negative effects that fructose may have on the body could be rooted deeper than just weight gain and changes in lipid profile could cause problems such as obesity or insulin resistance in the long run. However, these studies have only been done on rats and mice and the effect of fructose needs to be studied on humans to see if fructose or high fructose corn syrup would cause the same problems. The inconsistency between studies also needs to be cleared up as well. An explanation as to why Light et. al. (2005) only found increased weight gain in the high fructose group and not the fructose group needs to be more clearly stated and more trials comparing fructose and high fructose corn syrup need to be looked into.

Fructose and type 2 diabetes

Early studies on fructose recommended the sugar as a good alternative sweetener for diabetics because it produced lower glucose and insulin responses when compared to traditional sweeteners (Akgun & Ertel, 1980; Akgun & Ertel, 1981; Carpo et. al. 1980; Carpo et. al., 1982; Akgun & Ertel, 1985). Though fructose seemed to be a good alternative, Akgun and Ertel (1981) and Hung (1980) found that high fructose corn syrup was not. Bukar et. al. (1990) also cautions against using individual ingredients to recommend a food as other ingredients in the food could produce different glycemic responses that would outweigh the positive effects of fructose. Though possibly helpful for mild diabetics, these studies did not look into long-term effects of fructose feeding in normal populations or in diabetic populations and more than one study found that the more glucose intolerant an individual, the more response they had to fructose (Carpo et. al., 1980; and Akgun & Ertel, 1985). All above mentioned authors suggest that long-term research needs to be done in order to determine the effects of long-term fructose feeding in diabetes and its effects on the disease.

As it turns out, longer studies have shown an increase in risk of type 2 diabetes associated with a higher intake of sugar-sweetened beverages, especially those sweetened with high fructose corn syrup (Schulze et. al., 2004; Palmer et. al., 2008; and Montonen et. al., 2007). Schulze et. al. (2004) found a rate ratio of 1.98 for women drinking one soda pop per day compared to women drinking only one soda pop per month. After controlling for BMI, lifestyle and dietary confounds, the rate dropped to 1.39 which is still significant and suggests that only half of the risk for developing type 2 diabetes is related to BMI. Palmer et. al. (2008) also found that the rate ratio for two or more soft drinks per day was 1.24 compared to less than one per

month, while fruit drinks was 1.31 in African American women. However, contrary to Schulze et. al., the association of diabetes with soft drinks was almost entirely mediated by BMI, where fruit drink consumption was independent of BMI. Montonen et. al. (2007) found that the combined intake of fructose and glucose was associated with the risk of type 2 diabetes, though no significant association was observed for intakes of sucrose, lactose, or maltose. The relative risk between the highest and lowest amounts of combined fructose and glucose intake was 1.87 and relative risks found for sweetened berry juice and soft drinks were 1.69 and 1.67 respectively. Again, these links are very interesting and provide some proof that fructose and high fructose corn syrup could be contributing to type 2 diabetes independent of weight gain. More research needs to be done to clear up some inconsistencies between populations and to determine if fructose plays different roles in the pathogenesis of diabetes in different populations as suggested by the differences in findings between Schulze et. al. (2004) and Palmer et. al. (2007).

Carbonyls and carbonyl stress is a newer idea in the link between high fructose corn syrup and type 2 diabetes. In a study done by Ho (2007) carbonated beverages with high fructose corn syrup were found to contain very high levels of reactive carbonyls. Carbonyls are thought to cause tissue damage and possibly trigger or contribute to the onset of type 2 diabetes. Ho hypothesizes that the reason high fructose corn syrup and sucrose differ in the amounts of carbonyls even though they are both made up of glucose and fructose is because the chemical link is not as stable in high fructose corn syrup. This recent research could mean a great deal in relation to the diabetes epidemic and tie the link between soda pop consumption and type 2 diabetes, but more research is needed on the subject. Information on this particular research study was very hard to find and no follow up research was found. Studies need to compare the

chemical make-up of high fructose corn syrup compared to sucrose and how they react in the body and if carbonation changes the chemical make-up. Additionally, a better understanding of carbonyls and carbonyl stress in the body and its contribution to type 2 diabetes would need to be sought out. The amount of research needed to determine if there is a possible link might be great, but the results from such research could be tremendous.

Another newer idea that needs to be studied more in depth is the role increased free fatty acids in the blood have in the inflammatory state of insulin resistance. Free fatty acids have been shown to increase in several fructose-fed rat models. This increase in free fatty acids causes secretion of triglycerides and intracellular triglycerides are associated with insulin resistance which can lead to diabetes. This research is also more recent and needs to be studied more in depth to determine if the assumptions are correct. More research on humans on this topic needs to be looked into as well.

Overall, there is quite a bit of research that proposes promising information on the link between consumption of fructose or high fructose corn syrup and increased risk of type 2 diabetes, both in association with obesity, and as a separate cause. Most research presented provides a good starting block for future research ventures and applications. Future research needs to focus on long-term human trials in different populations and the differences and similarities between plain fructose and high fructose corn syrup. A better understanding of the causes and interconnectedness of obesity, type 2 diabetes and related metabolic symptoms would greatly advance the research in the field.

Possible Solutions

Though there have been no highly conclusive studies proving that high fructose corn syrup is contributing substantially to the diabetes, or obesity, epidemic there is enough compelling evidence to show that it may play a part. However, suggestions for preventing future spread are few and far between, and research on ways to “cure” or improve diabetes complications are contradicting. The most compelling and realistic, yet hard to attain, solution focuses on changing the American lifestyle through various measures to increase public awareness and encourage healthy changes.

Diets aimed at helping individuals with type 2 diabetes increase their insulin sensitivity and decrease negative factors related to type 2 diabetes mainly focus on a lower or restricted carbohydrate diet. These diets are typically 20% to 30% of energy from carbohydrates, but some go even lower. A study measuring the effects of a ketogenic (low carbohydrate) diet of 64 obese subjects with either high or normal blood glucose levels during a 56-week trial found positive results (Dashti, Mathew, Khadada, Mousawi, Talib, Asfar, Behbahani, & Al-Zaid, 2007). After the 56 weeks on the diet including 20 grams of carbohydrates for the first twelve weeks and 40 grams thereafter, and 80-100 grams of protein, body weight, BMI, blood glucose level, total cholesterol, LDL-cholesterol, triglycerides and urea were significantly decreased and HDL-cholesterol was significantly increased from week one (Dashti et. al., 2006). These results suggest the benefit of a ketogenic diet to aid with weight loss and blood glucose levels in diabetic patients. Though weight loss was induced over the 56-week trial mentioned above, two additional studies on low carbohydrate diets showed similar positive results without weight loss (Accurso, Bernstein, Dahlqvist, Draznin, Feinman, Fine et. al., 2008; and Gannon & Nuttall, 2006). Accurso et. al. (2008) review several studies on diet changes in diabetic patients and

conclude that a low carbohydrate diet is at least as effective as a low fat diet in for improving glycemic control and weight loss is not needed to gain benefits. Gannon and Nuttall (2006), in their search for a diet for people with type 2 diabetes that does not require weight loss, oral agents or insulin, but still controls blood glucose, have found that a lower carbohydrate and higher protein diet have a positive effect on blood glucose levels after five weeks. The diets found to be successful in reducing blood glucose were 20% and 30% carbohydrate diets where 30% came from protein and 50% and 40%, respectively, came from fat (Gannon, M., & Nuttall, F., 2006). The authors note, however, that their studies were only five weeks long and longer studies on different populations need to be conducted to determine the outcome (Gannon & Nuttall, 2006).

Though these studies suggest a low carbohydrate diet as a possible “treatment” option for those with type 2 diabetes, the American Diabetes Association does not recommend low carbohydrate diets (less than 130 grams per day) (American Diabetes Association, 2006). They warn that the long-term effects of these kinds of diets are unknown and most only show short-term weight loss with uncertain impact on cardiovascular disease risk (American Diabetes Association, 2006). The American Diabetes Association instead recommends medical nutrition therapy (MNT) to prevent and manage diabetes. MNT focuses on getting a healthy balance of all food groups with no more than 30% of energy coming from fat (American Diabetes Association, 2006). Also important in MNT is lifestyle changes that will produce moderate weight loss (7% body weight) which includes eating a well balanced diet and physical activity of at least 150 minutes per week (American Diabetes Association, 2006). After reviewing several articles, Cheng (2005) also agrees that lifestyle modification may be the best possible solution in preventing and managing type 2 diabetes. Several studies have shown that lifestyle

modifications in the form of either diet change or increase in exercise is more successful in preventing diabetes than control groups and medications (Cheng, 2005).

The above solutions are very probable and have been shown to work, however, lifestyle changes are hard to make and hard to stick too, especially in a society that wants immediate results without a lot of work. Bray (2004) suggests a change in which the individual does not have to work very hard consciously to make changes and receive benefits. Labeling his solution the “fluoride hypothesis” Bray explains his hypothesis has two meanings. The first refers to the environmental changes that were made to reduce the incidences of dental disease by adding fluoride to water and toothpaste (Bray, 2004). These environmental changes lead to a dramatic decrease in dental disease without the work of the individual. Bray suggests the same could be done to prevent obesity and diabetes. The second is an acronym using the first letters of fluoride: **F**or **L**owering **U**niversal **O**besity **R**ates are **I**mplement ideas that **D**on’t demand **E**ffort (Bray, 2004). It is obvious that telling people to change their lifestyle is not working because the rates of obesity and diabetes continue to go up. Most people know the basic ways to reduce their risks, but lack the motivation to make any changes or do not know where to begin making changes. Bray (2004) suggests that something needs to be changed in the environment rather than requiring lots of effort from the individual to make changes.

Nestle and Jacobson (2000) also agree that the focus on changing individual’s behaviors to reduce obesity is not working and some sort of public health policy needs to be implemented. Though the focus in the article is on obesity, the same ideas could help reduce the incidences of type 2 diabetes through the same mechanisms or with similar types of ideas. The article focuses on why past health initiatives have failed and how to make them more effective in the future and ideas for improving the health of America by changing lifestyles. Past initiatives, such as the

Healthy People 2000 initiative, have all addressed the issues of obesity and had the commitment and cooperation of government agencies only to be unsuccessful because lack of proper direction and funding (Nestle & Jacobson, 2000). Even the recent Healthy People 2010 plan offers little guidance on how the objectives are expected to be achieved mostly only calling for a “converted public effort” in the right direction (Nestle & Jacobson, 2000). Nestle and Jacobson (2000) push for change with better direction and stronger action to change the lifestyles of Americans, instead of a plan based on mostly wishful thinking. Among the ideas proposed are: reducing or eliminating the amount of “junk food” commercials on children’s TV channels, increase funding to state health departments for mass media health promotion campaigns that emphasize healthy eating and physical activity patterns, make a plant-based diet the focus of dietary guidance, declare and organize an annual national “No-TV” week, require more physical education and sports programs in schools even if it means extending the school day, require nutrition food labeling on all food including menu items and fresh meat, promote healthy eating in school and work cafeterias, encourage more healthy eating by creating taxes for “empty calorie” foods such as soft drinks and make healthy foods (fresh fruit and vegetables especially) lower priced and unhealthy foods higher priced, along with many other changes in the way society currently runs to promote and encourage healthy eating and a more active lifestyle (Nestle & Jacobson, 2000).

Some of the same initiatives stated by Nestle and Jacobson (2000) could be made to reduce the amount of high fructose corn syrup used consumed in the United States. As stated, it is obvious that relying on the individual to make changes is not effective in reducing the number of individuals with type 2 diabetes, so some other approach needs to be taken. The increase in consumption of high fructose corn syrup over the past four decades has not been the choice of the consumer. High fructose corn syrup is used in place of other sugars causing consumers to

start ingesting more without the conscious decision to do so. Though high fructose corn syrup has not been directly proven to increase risk of developing or causing diabetes, there is enough evidence to suggest that it has played some part, if not a major role. Therefore, something should be done to decrease the amount of high fructose corn syrup in the diet by reducing the amount available to consumers or somehow discouraging the consumption of products containing high fructose corn syrup. Soda pop should be the first target as it contributes the most to high fructose corn syrup consumption. A possible solution would be to add a tax onto the price of the soda pop as has been proposed before by those concerned with both the obesity and diabetes epidemic and those concerned with increased sugar intake. Several states have already implemented such a tax. California has a 7.25% sales tax on soft drinks raising about \$200 million a year and Arkansas has a two cent tax which raises about \$40 million a year (Nestle & Jacobson, 2000). These two states, along with several others, put the money into the general treasury while others, such as West Virginia, use it to support medical, dental and nursing schools (Nestle & Jacobson, 2000). All states should have such a tax on soda pop and the money generated should be put towards other efforts to reduce high fructose corn syrup consumption and increase other healthful food choice. Beyond soda pop, the tax should be spread to fruit juices and other beverages sweetened with high fructose corn syrup and possibly even to other items, such as baked goods and snacks, which also contain high fructose corn syrup. Not only would this reduce the amount that consumers purchase, but the money generated could also be used to help inform individuals to make better choices and warn them of the possible negative effects of long-term consumption of high fructose corn syrup.

Beyond taxing soda pop, other steps could be taken to reduce the availability of such items that contain high fructose corn syrup. Quick access soda pop and snacks in vending

machines should be replaced with healthier alternative or removed all together, especially in schools, where children are forming lifelong habits. The FDA could step in and require that other sources of sweeteners be used and the amount of those sweeteners be reduced. Cafeterias in schools, workplace, hospitals and other areas should reduce or eliminate the amount of items available which are sweetened with high fructose corn syrup and instead offer in their place other more healthy alternatives, preferably fresh fruits and vegetables. Of these cafeterias, the government should focus on school lunch places where children are often required to eat and where low income students may get their only well-balance meal of the day. By changing what is available to eat, students and consumers will effortlessly reduce the amount of high fructose corn syrup they are consuming and hopefully increase consumption of other healthful foods.

Society has created a toxic food environment, which includes high fructose corn syrup among many other unhealthy items, and the best way to change how people are eating is by changing society.

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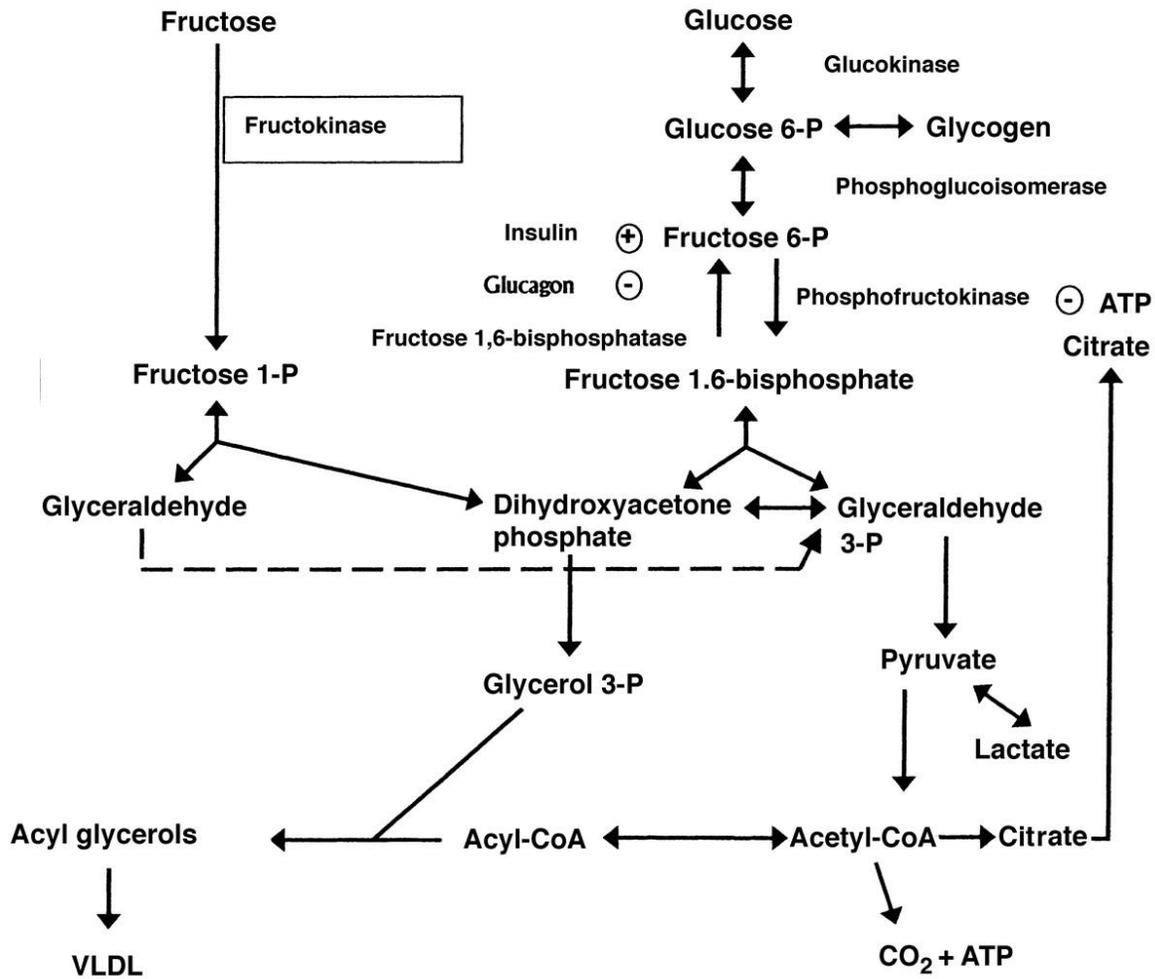
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Figure 1



Utilization of fructose and glucose in the liver. Hepatic fructose metabolism begins with phosphorylation by fructokinase (EC 2.7.1.4). Fructose carbon enters the glycolytic pathway at the triose phosphate level (dihydroxyacetone phosphate and glyceraldehyde-3-phosphate). Thus, fructose bypasses the major control point by which glucose carbon enters glycolysis (phosphofructokinase; EC 2.7.1.11), where glucose metabolism is limited by feedback inhibition by citrate and ATP. This allows fructose to serve as an unregulated source of both glycerol-3-phosphate and acetyl-CoA for hepatic lipogenesis. P, phosphate.

(Elliott et. al., 2002, 913)