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# The Relationship Between Fructose and the Metabolic Syndrome Risk Factors

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THE RELATIONSHIP BETWEEN FRUCTOSE AND THE METABOLIC SYNDROME  
RISK FACTORS

by

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B.S., Human Nutrition and Dietetics

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A Research Paper

Submitted in Partial Fulfillment of the Requirements for  
the Master of Science

Department of Animal Science, Food and Nutrition  
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RESEARCH PAPER APPROVAL

THE RELATIONSHIP BETWEEN FRUCTOSE AND THE METABOLIC SYNDROME RISK  
FACTORS

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Lauren Kania

A Research Paper Submitted in Partial  
Fulfillment of the Requirements  
for the Degree of  
Master of Science  
in the field of Food and Nutrition

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## AN ABSTRACT OF THE RESEARCH PAPER OF

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TITLE: THE RELATIONSHIP BETWEEN FRUCTOSE AND THE METABOLIC SYNDROME RISK FACTORS

MAJOR PROFESSOR: Dr. William Banz

Up until the last few decades, fructose was pretty much nonexistent in the human diet. Today it can be found in various processed foods and beverages including soft drinks, juice, and baked goods. These products comprise a large proportion of the human diet these days and consumption is high in children, adolescents, and young adults. Naturally, fructose is found in plant sources such as fruits and sugar cane. Today, high fructose corn syrup is used as a sweetener in many processed foods and drinks such as soda and fruit juices. High fructose corn syrups' low production cost has increased its' use in the food production industry. When added together, the consumption of snacks and sweets make up more than 75 percent of intake of added sugars. Fructose is part of the macro nutrient group carbohydrate which are polyhydroxy aldehydes, or ketones, or substances that produce such compounds when hydrolyzed. The category fructose belongs to is the monosaccharide group. Structurally the simplest form of carbohydrate, monosaccharides cannot be reduced in size. However, it can still be utilized as an energy source for the body once it enters the glycolytic pathway. Since the consumption of fructose and high fructose corn syrup has risen, there has been a rise in the incidence of metabolic syndrome risk factors which can lead to the diagnosis of metabolic syndrome. Numerous studies with human and animal models have confirmed fructose is associated with the risk factors for the metabolic syndrome. For this paper, various articles pertaining to the increased consumption of fructose and high fructose corn syrup and the risks of the metabolic syndrome were read. These risks include obesity, hypertriglyceridemia, low HDL levels,

hypertension, and insulin resistance. Even though fructose intake may impact the risk factors, they do not always occur with a consumption of fructose and high fructose corn syrup.

Therefore, the main objectives of this research paper was to clarify what are fructose and high fructose corn syrup and also, what is the impact they have on the metabolic syndrome risk factors.

## ACKNOWLEDGMENTS

I want to take the time to thank those who believed in me and supported me these during my graduate school career. Without them I do not know how I would have gotten through it. First, I would like to thank my family and friends, who were there to pick up the pieces when I could not do it myself. Secondly, I would like to thank my professors who have given me guidance when I needed it most. Lastly, I would like to dedicate this paper to my fellow graduate students who have gone through the same struggle I have gone though. Do not worry, it gets better.

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# CHAPTER 1

## INTRODUCTION

Up until the last few decades, the main source of sweetening agents for various processed foods was sucrose. However, because of its sweeter taste and cheaper production cost, fructose or high fructose corn syrup are now the primary sources for sweetening agents. They are found in most added sugar beverages, baked goods, ice cream, candies, jams, and other various processed foods. The consumption of fructose and high fructose corn syrup has increased over the last couple decades, which is associated with health issues such as obesity and insulin resistance as well as in rise in rates of metabolic syndrome. In this paper, the main focus of discussion will be on fructose and high fructose corn syrup. What is fructose and high fructose corn syrup? How does it affect the human body? Therefore, the objectives of this research paper are to clarify what fructose and high fructose corn syrup are and also, what is the impact these substances have on the metabolic syndrome risk factors.

Research paper question:

1. How does consumption of fructose and high fructose corn syrup affect metabolic syndrome risk factors?

### **Background**

While virtually absent in our diet a few hundred years ago, fructose and other added dietary sugars have now become a major constituent of our modern diet (Tappy et al., 2010a). Dietary sugars either as a naturally occurring component of many foods or as an addition during processing and preparation are ubiquitous in the food environment (Malik and Hu, 2012).

### **Fructose and High Fructose Corn Syrup Consumption**

Currently, added sugars account on average for almost 270 calories, or more than 13% of total calories consumed per day by the U.S. population (2015-2020 Dietary Guidelines). Below is a graph from the 2015-2020 Dietary Guidelines depicting intake as a percent of calories. The intakes for children, adolescents, and young adults for both male and females is the highest of all the age groups.

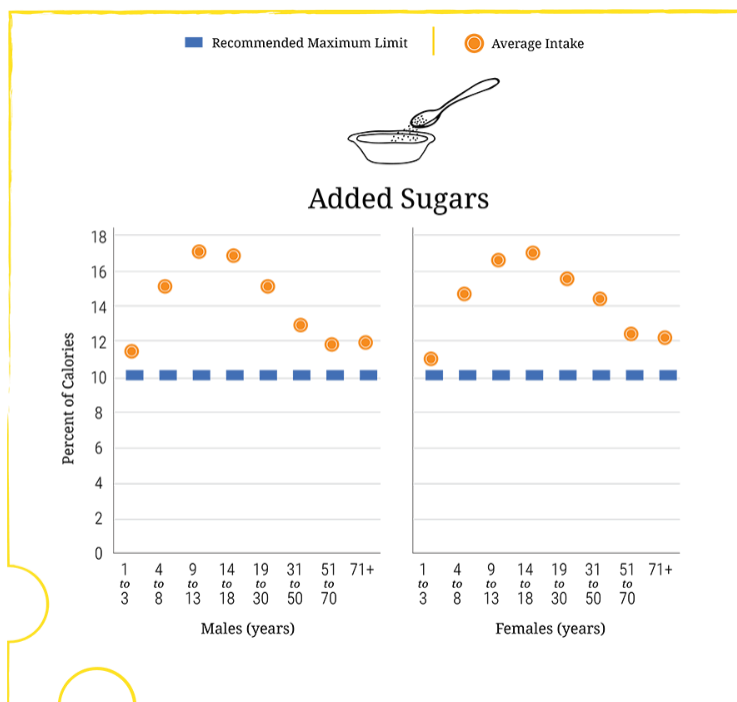


Figure 1: Adapted from Dietary Guidelines for Americans 2015-2020 (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015)

Dietary sources of fructose are sucrose from beet or cane, high fructose corn syrup, fruits, and honey (Tappy et al., 2010a). Over the past several years the use of fructose in processed foods, soft drinks, and an assortment of desserts has increased significantly. The introduction of high-fructose corn syrup (HFCS) as a cost-effective sweetener in the American diet has gradually led to a great increase in its use (Bantle, 2009). High-fructose corn syrup is produced by the isolation of starch from corn and hydrolysis of glucose. One predominant product of consumption by the public which uses high fructose corn syrup is sugar-sweetened beverages.

Sugar-sweetened beverages, which include the full spectrum of soft drinks, fruit drinks, energy and vitamin water drinks, are composed of naturally derived caloric sweeteners such as sucrose, high fructose corn syrup, or fruit juice concentrates. Collectively they are the largest contributor to added sugar intake in the US diet (Malik and Hu, 2012). Among the dietetic factors, sucrose- and fructose-rich soft drinks typically consumed in addition to meals are leading to enhanced energy uptake and emerge as the most consistent factor causing obesity (Ritze et al, 2014). There are three types of HFCS, each with a different proportion of fructose: HFCS-42, HFCS-55, and HFCS-90. The number for each HFCS corresponds to the percentage of synthesized fructose present in the syrup. HFCS-55 is used as a sweetener in soft drinks; whereas HFCS-42 is used in many processed foods and baked goods (Das, 2014). HFCS-90 (90% fructose and 10% glucose) which is used in specialty applications but more importantly is blended with glucose syrup to yield HFCS-42 (42% fructose and 58% glucose) and HFCS-55 (55% fructose and 45% glucose) (Parker, Salas, Nwosu, 2010).

The other major source of added sugars is snacks and sweets, which includes grain-based desserts such as cakes, pies, cookies, brownies, doughnuts, sweet rolls, and pastries; dairy desserts such as ice cream, other frozen desserts, and puddings; candies; sugars; jams; syrups; and sweet toppings. Together, these food categories make up more than 75 percent of intake of

all added sugars (2015-2020 Dietary Guidelines). Below is a graph showing food category sources of added sugars in the U.S. population ages 2 years and older.

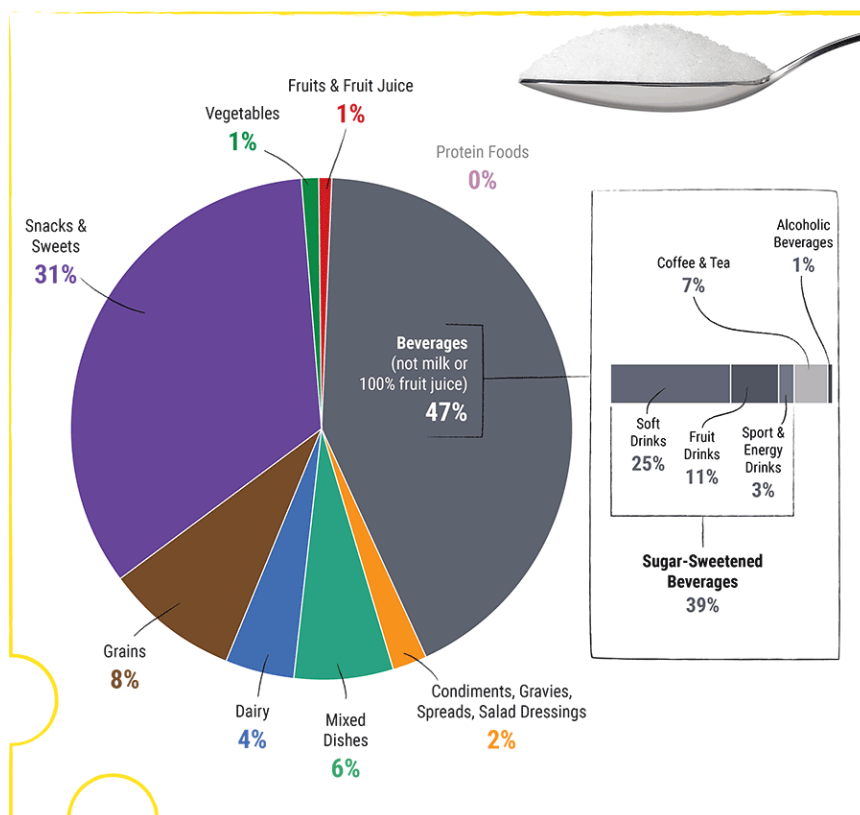


Figure 2: Adapted from Dietary Guidelines for Americans 2015-2020 (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015)

Various dietary guidelines have addressed sugars. Most have focused on the reduction of added fructose-containing sugars to maintain a healthy body weight (Cozma et al., 2013). In the past, dietary intake of fructose was 16-20 grams per day, mainly from fresh fruits and vegetables (Hosseini-Esfahani et al., 2011). It has been shown that an increased consumption of fructose may lead to increased levels of inflammatory mediators and reactive oxygen species, which in turn can influence the onset of metabolic syndrome. There is compelling evidence that a hypercaloric, high-fructose diet can induce, not only in animal models, but also in humans, a whole range of metabolic alteration, the most prominent being a disturbance of hepatic lipid metabolism and of plasma lipid profile (Tappy et al., 2010b).

Table 1: Adapted from the Summary of Current Dietary Guidelines Regarding the Consumption of Sugars and Fructose and the Prevention of Chronic Disease (Cozma et al., 2013)

Guideline	Sugars	Fructose
General Dietary Advice		
WHO/FAO 2003 USDA 2010 IOM 2002	<10% energy free sugars ≤25% energy free sugars ≤25% energy free sugars	- - -
Diabetes Recommendations		
ADA 2013 CDA 2013 EASD 2004	Avoid excess energy from sucrose ≤ 10% energy add sucrose ≤ 10% energy total free sugar	≤12% energy naturally occurring fructose ≤10% energy added fructose ≤30g/day fructose
Cardiovascular Recommendations		
AHA 2006 AHA 2009	Minimize added sugars from beverages and foods ≤100-150 kcals/day (~5%) added sugars	- -
Hypertension		
JNC7 CHEP	- ≤5 Servings per week sweets and added sugars	- Have 4-5 servings of fruit a day
Dyslipidemia Recommendations		
CCS 2009 CCS 2012 NCEP-ATP III AHA 2011 (fasting TG) Borderline (150-199mg/dL) High (200-499mg/dL) Very High (≥500mg/dL)	A diet low in simple sugars - Reduce sugar-containing beverages	- - - <100g/day fructose 50-100g/day fructose <50g/day fructose

## Fructose Composition

Carbohydrates are polyhydroxy aldehydes, or ketones, or substances that produce such compounds when hydrolyzed. There are different categories of carbohydrates which are included in the carbohydrate family. The categories are monosaccharides, disaccharides, polysaccharides, and oligosaccharides. The carbohydrate this paper will focus on is fructose which is part of the sugar carbohydrates. The sugar carbohydrates include monosaccharides and disaccharides.

Below is a chart which list the various sugars that are part of the monosaccharides and the disaccharides.

Table 2: Adapted from Chemical Formulas for Sugar (<http://www.chemicalformula.org/sugar>, 2016)

Name	Type of sugar (mono=1 or di=2 sugar units)	Chemical formula of sugar
Glucose	Monosaccharide	C <sub>6</sub> H <sub>12</sub> O <sub>6</sub>
Fructose	Monosaccharide	C <sub>6</sub> H <sub>12</sub> O <sub>6</sub>
Galactose	Monosaccharide	C <sub>6</sub> H <sub>12</sub> O <sub>6</sub>
Lactose	Disaccharide	C <sub>12</sub> H <sub>22</sub> O <sub>11</sub>
Sucrose	Disaccharide	C <sub>12</sub> H <sub>22</sub> O <sub>11</sub>
Maltose	Disaccharide	C <sub>12</sub> H <sub>22</sub> O <sub>11</sub>

Fructose is part of the monosaccharide family, which is the simplest groups of carbohydrates. These simple sugars serve not only as fuel molecules but also as fundamental constituents of living systems (Tymoczko et al, 2010). Its backbone consists of alternating phosphoryl groups and deoxyribose, a cyclic five-carbon sugar (Tymoczko et al, 2010). An example of monosaccharides are glucose and fructose. Fructose is a hexose, with a chemical formula C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> identical to that of glucose. It differs from glucose by the presence of a keto group in position 2 of its carbon chain, versus an aldehyde group at position 1 of the glucose carbon chain (Tappy et al., 2010a).

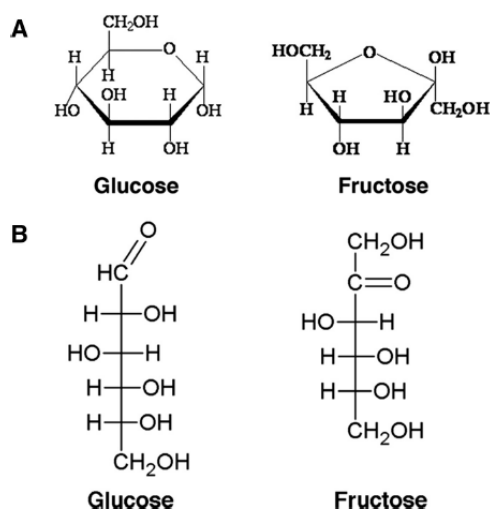


Figure 3: Adapted from The role of fructose in metabolism and cancer (Charrez et al., 2015)

Monosaccharides are structurally the simplest form of carbohydrate in that they cannot be reduced in size to smaller units by hydrolysis. Monosaccharides are called simple sugars and are sometimes referred to as monosaccharide units. The most abundant monosaccharide in nature- and certainly the most important nutritionally-is the 6-carbon sugar glucose (Gropper, et al., 2009, p. 63).

### **Fructose Metabolism and Absorption**

Although glucose is the monosaccharide most commonly used as an energy source, others also are important fuels (Tymoczko et al., 2010 p. 238). Fructose is another monosaccharide that can be used as a fuel source and can go through the glycolytic pathway. Fructose is a component of sucrose, or table sugar, and high-fructose corn syrup (Tymoczko et al., 2010 p. 238), which as stated above, is used to sweeten various foods and beverages. There has long been interest in the metabolic effects of dietary fructose, particularly in people with metabolic syndrome and diabetes (Bantle, 2009). Fructose is a highly lipogenic sugar that had profound metabolic effects in the liver and has been associated with many of the components of the metabolic syndrome (Dekker et al., 2010). Fructose metabolism is an unregulated metabolic pathway (Khitan et al., 2014) and the results from this process can be devastating to those who consume amounts greater than what is recommended. When ingested by humans, fructose is absorbed by an active transport system but at a slower rate than is glucose (Bantle, 2009). Fructose alone is poorly absorbed, but enhanced by glucose in the gut, thus accounting for the rapid and complete absorption of both fructose and glucose when consumed as sucrose or high fructose corn syrup (Malik and Hu, 2012).

Unlike glucose, fructose does not have a pathway which is dedicated specifically to its' metabolism. Before the metabolism of fructose can begin, it must be transported into the mucosal cell by GLUT5 which is a specific facilitate transporter. GLUT5 is expressed in insulin-sensitive



tissues (skeletal muscle and adipocytes) of humans and rodents, where it mediates the uptake of substantial quantities of dietary fructose (Litherland et al, 2004). GLUT5 is found in the small intestine. Since the entry of fructose is not dependent on the concentration of glucose, this process still happens with a high concentration of glucose. To move fructose out of the mucosal cell, GLUT2 is used which also moves glucose out of the cell. From here, fructose moves to the liver where it is absorbed very efficiently and then phosphorylated.

There are two ways fructose can enter the glycolytic pathway. Much of the ingested fructose is metabolized by the liver, using fructose 1-phosphate pathway. The first step is the phosphorylation of fructose to fructose 1-phosphate by fructokinase (Tymoczko et al., 2010, p. 238). The phosphorylation of fructose to fructose 1-phosphate is the major means by which fructose is converted to glycolysis metabolites (Gropper et al., 2009, p. 84). Fructose 1-phosphate is then split into glyceraldehyde and dihydroxyacetone phosphate, an intermediate in glycolysis. This aldol cleavage is catalyzed by a specific fructose 1-phosphate aldolase.

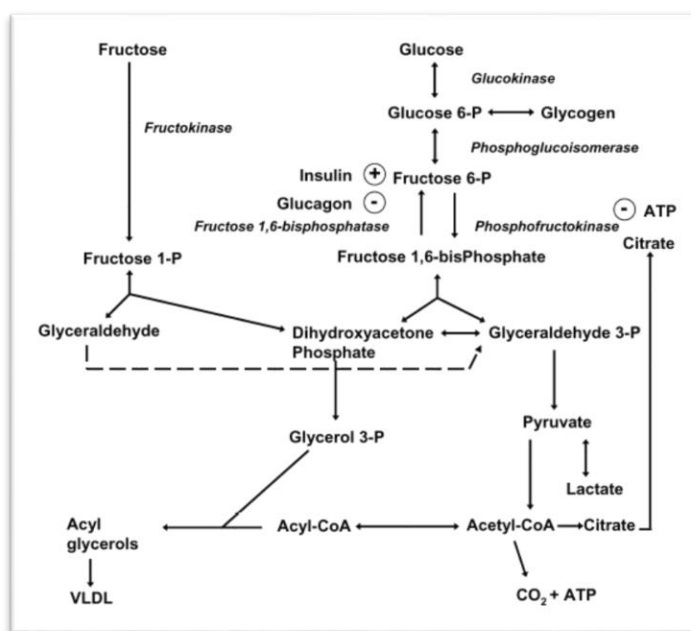


Figure 4: Adapted from Fructose and glucose metabolism as reported by Elliott, 2002

Dihydroxyactone phosphate continues into stage 2 of glycolysis, whereas glyceraldehyde is then phosphorylated to glyceraldehyde 3-phosphate, a glycolytic intermediate, by triose kinase. In other tissues, fructose can be phosphorylated to the glycolytic intermediate fructose 6-phosphate by hexokinase (Tymoczko, Berg, & Lubert, 2010, p. 238). When fructose enters this pathway, it bypasses the two highly regulated steps of glycolysis, catalyzed by glucokinase/hexokinase and phosphofructokinase (Khitani et al, 2014). Once fructose enters the pathway and is converted, it continues along and is used to produce energy for the body. Below is a figure illustrating the both pathways fructose is metabolized in the body.

## **CHAPTER 2**

### **LITERATURE REVIEW**

There has been a wide range of research done concerning fructose and high fructose corn syrup and their effects on the human body. For that reason, this paper will discuss various findings in all areas regarding the consumption of fructose and high fructose corn syrup and their relationship with the metabolic risk factors.

#### **Metabolic Syndrome**

According to the National Heart, Lung, and Blood Institute, the metabolic syndrome is the name for a group of risk factors that raises a patient's risk of heart disease and other health problems such as diabetes and stroke. These risk factors include a large waistline, high triglyceride level, low HDL cholesterol level, high blood pressure, and high fasting blood sugar (National Heart, Lung, and Blood Institute, 2015). Based on the results of a physical exam and blood tests (National Heart, Lung, and Blood Institute, 2015), a doctor will be able to diagnose patients with metabolic syndrome. However, even though a patient may have only one of the risk factors may be present, it does not mean the patient will end up being diagnosed with metabolic syndrome. The dramatic increase in patients with metabolic syndrome recently seen in Western Societies is most likely due to alterations in lifestyle, which includes increased consumption of high-calorie diets and decreased physical activity (Axelsen et al., 2010).

In animal models, high-fructose diets almost invariably lead to the concomitant development of excess body fat and insulin resistance; an increased body fat mass, body fat distribution, and ectopic lipid deposition in liver and muscle can all play a role in the development of the metabolic syndrome (Tappy et al., 2010). In a study conducted by Ervin et al (2009), they found a little more than one-third of the adults in the United States could be

characterized as having metabolic syndrome. Metabolic syndrome incidence increased with age but increased more dramatically as BMI increased. The prevalence of metabolic syndrome varied by race and ethnicity but the pattern of incidence was different for males and females.

According to Hosseini-Esfahani et al. (2011), the higher intake of dietary fructose was associated with a higher risk of developing metabolic syndrome. Their study consisted of data collected from subjects of the Tehran Lipid and Glucose Study between 2006-2008. From the study, 2799 men and women aged 19-70 y, were recruited. Any subject who had an under- or over reporting of dietary intakes were excluded (Hosseini-Esfahani et al., 2011). In the end, a total of 2537 subjects (1141 men and 1396 women) were analyzed (Hosseini-Esfahani et al., 2011). Total dietary fructose was assigned as quartile intakes for men and women, based on their 25th-50th-75th percentile values. Total dietary fructose intakes in the 1st, 2nd, 3rd, and 4th quartiles were  $\leq 13.3$ , 13.4-17.5, 17.6-23.7, and  $> 23.7$  in men, and  $\leq 10.3$ , 10.4-15.2, 15.3-20.8, and  $> 20.8$  in women (Hosseini-Esfahani et al., 2011). The study used a validated semi-quantitative food frequency questionnaire which listed 168 food items. In this study, 45% and 55% of participants were men and women, with mean ages  $40.5 \pm 13.6$  and  $38.6 \pm 12.8$  years, respectively. Mean dietary intakes of total fructose were  $46.5 \pm 24.5$  g/d in men and  $37.3 \pm 24.2$  g/d in women; these intakes were approximately 8 and 7 percent of the total energy intakes, in men and women, respectively (Hosseini-Esfahani et al., 2011). Compared with those in the lowest quartile of fructose intakes, men and women in the highest quartile, respectively, had 33% and 20% higher risk of the metabolic syndrome; 39% and 20% higher risk of abdominal obesity; 11% and 9% higher risk of hypertension; and 9% and 9% higher risk of impaired fasting glucose (Hosseini-Esfahani et al, 2011). From this study, they concluded the increased risk of metabolic

syndrome and its components may be attributed to increase fructose intake from industrialized foods.

In a study performed by Axelsen et al. (2010), the authors investigated whether or not a high-fructose and high-fat diet would increase the risks of metabolic syndrome. The study, which used four-week-old male Sprague-Dawley rats that were stratified according to equal weight into two pools containing 10 groups each. One pool (n=8-12/group) received normal chow and water, and the other pool (n=8-12/group) received a high-fat diet with 10% fructose in the drinking water (Axelsen et al., 2010). The study found that a diet rich in fructose and fat induces metabolic syndrome in rats (Axelsen et al., 2010). The study concluded that male Sprague-Dawley rats receiving a high fat and fructose diet for 48 wks (FFFR) developed severe obesity ( $830.8 \pm 17\text{g}$ ) relative to rats fed normal chow ( $621.8 \pm 39\text{g}$ ). There was interaction between duration of feeding and diet, and the difference between groups was statistically significant from 20 wk of feeding (Axelsen et al., 2010). The study results showed fasting blood glucose levels were significantly increased in the FFFRs after 6, 12, and 18 wk of feeding. However, following 24, 36, and 48 wk of feeding, FFFRs had similar fasting blood glucose levels as control rats. Urine glucose content was significantly increased in FFFRs after 12 and 18 wk of feeding, and the urine protein content increased with age in both FFFRs and control rats, but no difference was observed between the two groups. Glucose tolerance was dependent on both diet and duration of feeding, and it was significantly decreased in FFFRs compared with control-fed rats after 18, 36, and 48 wk of feeding (Axelsen et al., 2010). Neither FFFRs nor control rats showed any change in mean arterial BP throughout the 48 wk of feeding, and no statistically significant difference between the two groups was found at any time point (Axelsen et al., 2010).

A study conducted by Ervin (2009), found that approximately 34% of adults met the criteria for metabolic syndrome. Males and females 40-59 years of age were about three times as likely as those 20-29 years of age to meet the criteria for metabolic syndrome. Males 60 years of age and over were more than four times as likely and females 60 years of age and over were more than six times or more likely as the youngest age group to meet the criteria. Non-Hispanic black males were about one-half as likely as non-Hispanic white males to meet the criteria for metabolic syndrome, while non-Hispanic black and Mexican-American females were about 1.5 times as likely as non-Hispanic white females to meet the criteria. Overweight males were about six times as likely and obese males were about 32 times as likely as normal weight males to meet the criteria. Overweight females were more than five times as likely and obese females were more than 17 times as likely as normal weight females.

In summary, the metabolic syndrome is diagnosed when a patient presents with at least three of the risk factors. The risk factors include a large waistline, high triglyceride level, low HDL level, high blood pressure, and high fasting blood sugar. The most likely cause of these risk factors could be due to lifestyle choices and dietary consumption of fructose which may negatively affect a persons' life. As age and BMI increase drastically, the prevalence of metabolic syndrome also increased. It has been shown at least 1 out of 3 adults may be characterized as having metabolic syndrome and prevalence varies by race, ethnicity, age, and gender. The following sections of this paper will be discussing the risk factors of metabolic syndrome and how it is associated with fructose and high fructose corn syrup.

## **Obesity**

Millions of Americans and people worldwide are overweight or obese (National Heart, Lung, and Blood Institute, 2012). In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these, over 600 million were obese (World Health Organization, 2015). The

terms "overweight" and "obesity" refer to body weight that's greater than what is considered healthy for a certain height (National Heart, Lung, and Blood Institute, 2012). The worldwide prevalence of obesity more than doubled between 1980 and 2014 (World Health Organization, 2015). Due to a rise in obesity rates among adults, metabolic syndrome is becoming more common (National Heart, Lung, and Blood Institute, 2015).

One way to help estimate whether or not one is obese is by using BMI. Although BMI is easy to measure, the measurement requires using a calibrated scale, obtaining the height and weight of a participant, and performing a calculation. Removal of shoes and heavy clothing is required by the participant (Camhi et al, 2008). Another way to help identify obesity is fat distribution waist circumference. Waist circumference may be a better predictor than BMI in detecting metabolic syndrome because of its association with increased visceral adipose tissue. Increased visceral adipose tissue is associated with insulin resistance, glucose intolerance, and abnormal lipid profiles (Camhi et al, 2008). In contrast, waist circumference is easier to obtain because it is a single measurement, requiring only an inexpensive tape measure. Obtaining the measurement poses minimal participant burden because clothing needs to be removed only from the abdominal area (Camhi et al, 2008). Throughout the past decades there has been a significant amount of research concerning obesity and the factors which cause it. One of the topics regarding obesity research has been added sugars, fructose, and high fructose corn syrup and their effects on obesity and obesity related diseases. Intake of high-fructose corn syrup (HFCS) has been suggested to contribute to the increased prevalence of obesity (Yu et al., 2013). Particularly, changes in dietary and eating behavior such as preferring sugar-sweetened beverages and sugar-rich processed food in addition to a sedentary life style, are associated with the sharp rise in obesity.

Ogden et al. (2011) found that 8.1% of infants and toddlers from birth to aged 2 years had a high weight for recumbent length. Findings also show that in 2011-2012, 31.8% of youth were either overweight or obese and 16.9% were obese (Ogden et al., 2014). Increases of body fat and weight are results of various factors in a person's life such as daily food intake habits. These habits can have negative effects on a patient's health and can progressively get worse if the same dietary habits continue. The health issues which can arise of this are but not limited to: Coronary heart disease, high blood pressure, type 2 diabetes, gallstones, breathing problems, and certain cancers (National Heart, Lung, and Blood Institute, 2012).

Bocarsly et al. (2010) studied the effects of a short- and long-term use of HFCS on body weight, body fat, and circulating triglycerides. There were 2 different experiments used for this study. Experiment 1 included weight-matched, male rats (300-375g, n+10/group) were fed either (1) ad libitum chow, (2) 24-h HFCS and chow, (3) 12-h HFCS and ad libitum chow, or (4) 12-h sucrose with ad libitum chow for 8 weeks (Bocarsly et al., 2010). For experiment 2, male rats (275-325 g, n=8/group) were maintained on either (1) 24-h HFCS and chow, (2) 12-h HFCS and ad libitum chow, or (3) ad libitum chow for 6 months. Female rats (150-200 g at the onset of the experiment, n=8/group) were also tested to determine if the findings applied to both sexes. They were given either (1) 24-h HFCS and ad libitum chow, (2) 12-h HFCS and 12-h chow, (3) 12-sucrose and 12-h chow, or (4) ad libitum chow (Bocarsly et al, 2010). Their results showed animals with 12-h 8% HFCS access gained significantly more weight in 8 weeks than animals with 12-h 10% sucrose access (Bocarsly et al, 2010). They also found that male rats with ad libitum HFCS for 6 months have increased body weight, abdominal fat and TG levels, compared to the controls (Bocarsly et al, 2010) with ad libitum chow alone. They found that female rats with 7 months of 24-h HFCS access to HFCS gained significantly more body weight, have more



abdominal fat and elevated TG levels Compared with chow- and sucrose-fed controls. The data collected from this study showed that access to HFCS can lead to the decreased maintenance of a normal body weight.

Lowndes et al. (2014) studied 355 overweight and obese individuals aged 20-60 years old who were placed on a eucaloric diet for 10 weeks, which incorporated SUC- or HFCS-sweetened, low-fat milk at 8%, 18%, or 30% of calories. There was a slight change in body weight in the entire cohort ( $169.1 \pm 30.6$  vs.  $171.6 \pm 31.8$  lbs). There were significant time X sugar level interactions for body weight, BMI and fat mass, with *post hoc* analysis revealing that the highest level of sugar intake produced greater increases in body weight and BMI than either the 8% and 18% groups and a greater increase in fat mass than in just the 8% group. Chan et al. (2013), they found an increased consumption of fructose-sweetened beverages was associated with increased waist and hip circumferences and body mass index.

After analyzing data from 2727 representative adolescents who were multistage sampled from 36 junior high schools, Lin et al (2012) found that 87.7% of adolescents were sugar-sweetened beverage drinkers, with 25.1% drinking >500ml per day of such beverages. The increased consumption was associated with increased waist and hip circumferences, body fat, and BMI. As compared with non-drinkers, sugar-sweetened beverage drinkers had a 3.2-4.9% elevated risk of obesity (Lin et al, 2012).

In summary, when consumed in large amounts over an extended period of time, fructose may indeed cause one to gain a great deal amount of weight. For example, drinking one or more sweetened beverages a day may lead to an increase of daily caloric intake which can turn into significant weight gain over time. In 2014, more than 1.9 billion adults were overweight or obese and the number keeps rising. Metabolic syndrome is becoming more common as the obesity

rates keep climbing. Suggested contributors to the rise in obesity rates include increased daily intake of food, decreased physical activity, and increased added sugars and fructose consumption. Various health issues, such as coronary heart disease, high blood pressure, type 2 diabetes, gallstones, breathing problems and certain cancers, may arise weight gain due to the contributors. Studies have shown when large daily amounts of fructose are consumed over a lengthy period of time, it may increase body weight significantly.

### **Hypertriglyceridemia**

The second risk factor this paper will be covering is hypertriglyceridemia. Triglycerides are a type of fat found in the blood. A triglyceride level of 150 mg/dL (or being on medicine to treat high triglycerides) is a metabolic risk factor (National Heart, Lung, and Blood Institute, 2015). Over the years, it has become apparent that an increased consumption of fructose had adverse metabolic effects in both rodents and humans. In humans, it has been shown that fructose, when substituted for starch, increases plasma triglycerides (Tappy et al, 2010).

During the review of a recent meta-analysis, Tappy et al (2010) concluded that a fructose intake >50g/d was already associated with altered plasma triglyceride concentrations. In an effort to gain additional insight into the effects of fructose on plasma lipids, Bantle (2000) compared high- and low-fructose diets in 24 healthy volunteers (12 men and 12 women: 6 of each gender aged <40 y and 6 of each gender aged >40 y). All participants consumed 2 isocaloric diets for 6 wk. One diet provided 17% of energy of fructose. The other diet was sweetened with glucose and was nearly devoid of fructose (Bantle, 2000). The fructose diet resulted in higher fasting total and LDL plasma cholesterol at d 28, but this effect didn't persist at d 42. The plasma triglycerides responses to the diets differed by gender. The fructose diet had no significant effect on fasting or postprandial plasma triglycerides in women. However, in men, the fructose diet produced significantly higher fasting and postprandial plasma triglycerides. This effect persisted

through d 42. On d 42 of the fructose diet, daylong plasma triglycerides in men were 32% greater than during the glucose diet (Bantel, 2000). In another study conducted by Crescenzo et al (2014), it found that plasma triglycerides were elevated after consuming a high-fat-high-fructose diet. In the same study, they also found the high-fat-high-fructose diet lead to higher non-esterified fatty acids (Crescenzo et al, 2014).

In a crossover design, both glucose-tolerant and glucose-intolerant individuals consumed 50g carbohydrates from honey, sucrose, or high-fructose corn syrup. Raatz et al. (2015) found when the sugar sources were consumed over 2 weeks with a 2 to 4 week washout period, all three treatment groups experienced an increase of triglyceride levels.

Swarbrick et al. (2008), studied the effects of an isoenergetic 10-week intervention, in which 25% of daily energy requirements was provided as fructose-sweetened beverages, on fasting and postprandial glucose, insulin, TAG and plasma apo-B concentrations. Seven overweight or obese (BMI 26.8-33.3 kg/m<sup>2</sup>) postmenopausal women (age 50-72 years) were recruited (Swarbrick et al, 2008). Subjects resided in a residential facility during the entire 14-week period, where body weight, food intake and blood pressure were monitored. Body composition measurements and 14 h postprandial blood collections were performed at the Ragle Human Nutrition Research Facility (Swarbrick et al, 2008). The diets the participants were given provided 15% of energy from protein, 30% from fat and 55% from carbohydrate. During the baseline period, the carbohydrate was composed almost entirely of complex carbohydrate (i.e. starches from bread, rice and pasta), and the fructose content was < 3%. During intervention, complex carbohydrate was replaced with beverages sweetened with free fructose (at 25% of daily energy requirements), while the protein and fat content of the diet were unchanged (M. M. Swarbrick et al, 2007). Relative to the baseline diet, consumption of fructose-sweetened

beverages resulted in a progressive increase of postprandial TAG concentrations (M. M. Swarbrick et al, 2007). Hallfrisch et al. (1983), found when hyper-insulinemic men consumed three different levels of fructose, total plasma cholesterol and low-density lipoprotein cholesterol increased significantly as the level of fructose increased and were higher than in the controls used in the study.

In a study designed to investigate the effects of long-term feeding of chitosan on plasma glucose and lipids in rats fed a high-fructose diet (63.1%) ad libitum for 21 weeks, Liu, Cai, and Chiang (2015) found the high-fructose diet increased hepatic lipids and plasma triglycerides were elevated. In a randomized, controlled study of 74 adult men who were administered 200g fructose daily for 2 weeks with or without allopurinol conducted by Perez-Pozo et al. (2009), they found that fructose, when ingested, it resulted in a mean increase in fasting triglycerides of  $0.62 \pm 0.23 \text{ mmol l}^{-1}$  ( $55 \pm 20 \text{ mg per } 100 \text{ ml}$ ) compared with the baseline line.

However, results from a study, which was conducted in 2014 by Tillman et al. using C57Bl/6 mice, showed there was no increase in triglycerides. They concluded this could have been due to the metabolic response the mice had to fructose, age-dependent response, or the different modes of fructose delivery. Jameel et al. (2014) found similar results in their randomized, single blinded, cross-over study of 14 healthy male and female adults between the ages of 18-60. They were given one of 3 different isocaloric drinks, one containing 50g of fructose, after an overnight fast. They concluded there were overall no significant differences in plasma triglyceride levels regardless of which drink the participants were given.

In summary, while most of the studies found concluded increased fructose consumption can lead to higher blood triglyceride levels, there is still evidence which shows there may also be a decrease in levels or no effect at all. This could possibly be due to various factors including

age, gender, length of consumption, and current health status. The longer the increased consumption lasted, the blood triglyceride level in study subjects were more likely to raise compared to a shorter time span. Metabolic response and subject type/species may also possible contributors to varied results.

## **Low HDL**

The third risk factor which will be covered is low HDL. High-density lipoprotein (HDL) particles contain more protein than any of the other lipoproteins, which accounts for their metabolic role as a reservoir of the apolipoproteins that direct lipid metabolism (Krause's, page 839). HDL cholesterol sometimes is called "good" cholesterol. This is because it helps remove cholesterol from your arteries. A HDL cholesterol level of less than 50mg/dL for women and less than 40mg/dL for men (or being on medicine to treat low HDL cholesterol) is a metabolic risk factor (National Heart, Lung, and Blood Institute, 2015).

In a study conducted by Lowndes et al. (2014), 355 overweight or obese individuals aged 20-60 years old were placed on a eucaloric diet for 10 weeks. By the end of the study they saw a decrease in HDL levels (Lowndes et al, 2014). In a randomized, controlled study of 74 adult men who were administered 200g fructose daily for 2 weeks with or without allopurinol conducted by Perez-Pozo et al. (2009), they found that fructose administrated resulted in a reduction of HDL cholesterol of  $0.06 \pm 0.02 \text{ mmol l}^{-1}$  ( $2.5 \pm 0.7 \text{ mg per 100ml}$ ) compared with the baseline. However, results from another study found that a consumption of fructose did not lead to a decrease in HDL levels but in fact lead to an increase (Naz et al., 2013). During the course of a 12-month study conducted by Jameel et al. (2014) also showed there was no decrease in HDL but however, there was an increase of HDL. An increase was also shown in a study by Bremer et al. (2011), but eventually ended in a decrease of HDL levels.

In summary, a consumption can influence the plasma HDL levels. However, various variables within the study can cause both an increase or decrease of HDL levels. Length of the study, gender, age, or even the population being tested can influence the outcome of the study.

## **Hypertension**

High blood pressure, or hypertension, is a disease. Even though it typically has no symptoms, high blood pressure can have deadly health consequences if not treated (American Heart Association, 2015). Out of every 3 people in the U.S., at least 1 of them is suffering from high blood pressure. This equates to about 70 million people. Over time, if the force of the blood flow is often high, the tissue that makes up the walls of arteries gets stretched beyond their healthy limit and damage occurs (American Heart Association, 2015). High blood pressure is called the "silent killer" because it often has no warning signs or symptoms, and many people do not know they have it (Centers for Disease Control and Prevention, 2014). Hypertension can be classified as primary or secondary hypertension. Primary hypertension or essential hypertension is idiopathic, which means the cause is unknown, and accounts for a large portion of all cases. Secondary hypertension is the result from a primary issue or disease. A blood pressure of 130/85 mmHg or higher) or being on medicine to treat high blood pressure) is a metabolic risk factor. If only one of your two blood pressure numbers is high, you're still at risk for metabolic syndrome (National Heart, Lung, and Blood Institute, 2015).

In a study conducted by SE Perez-Pozo et al. (2009), they found that a fructose ingestion of 200g daily for 2 weeks was associated with a significant increase in ambulatory BP compared with the baseline. 24-h ambulatory systolic BP (SBP) increased by  $7\pm 2$  mm Hg and diastolic BP (DBP) by  $5\pm 2$  mm Hg ( $P < 0.004$  and  $0.007$ , respectively). BP increased by 5.5-7.1% with slightly greater increases in DBP during the day (SE Perez-Pozo et al, 2010). When the results of the

study were compared to the criteria for metabolic syndrome, the number of participants who fit the criteria at baseline was 9 and that afterwards was 21 (SE Perez-Pozo et al, 2009).

In a meta-analysis conducted by Malik and Hu (2012), they pooled findings from three studies including 19,431 participants and 5803 cases of metabolic syndrome and observed an increased risk of about 20% comparing highest to lowest categories of intake. Two of the studies also looked at sugar-sweetened beverage consumption in relation to individual components of metabolic syndrome. The first study conducted found that individuals who consumed  $\geq 1$  sugar-sweetened beverage per day had a marginal 18% risk of developing hypertension compared to non-consumers after adjusting for baseline hypertension, age, sex, physical activity, smoking, intake of saturated fat, trans fat, fiber, magnesium, total energy, and glycemic index. The second study also found a marginal effect of sugar-sweetened beverages on incident hypertension comparing daily consumers to non-consumers.

Conti et al. (2014) took 21 day old female rats which were obtained from the Animals Facilities of the Institute of Cardiology of Rio Grande do Sul. The rats were randomly divided into hypertensive (H; n=8), hypertensive ovariectomized (HO; n=8) and hypertensive hypertensive ovariectomized undergoing fructose overload (FHO; n=8). FHO rats received D-fructose (100 g/L) in drinking water for 19 weeks. H and OH animals received standard laboratory chow and water ad libitum. Consumption of chow and water was measured weekly. Results from the study showed body weight and adipose tissue weight were higher in FHO group when compared to other groups. The FOH group presented resting tachycardia when compare to the other groups DAP and MAP were higher in HO group when compared to the H group and the FHO group. The study also found the triglyceride levels were increased in the FHO group when compared to all other groups (Conti et al. , 2014).

Results from a study conducted by Wu et al. (2014) showed a high fructose diet did increase blood pressure. The study was a 12-week long study using male, adult Wistar Kyoto rats to study whether fructose affects ATP content in rostral ventrolateral medulla and its significance in the increase in central sympathetic outflow and hypertension induced by the high fructose diet. Animals were divided randomly into the normal diet and high fructose diet groups. In the high fructose diet group, animals received 60% fructose as sole food source. The normal diet animals received regular chow. Both food and water were provided ad libitum. In comparison to the normal diet group, animals received high fructose diet for 12 weeks induced a significant increase in SAP, accompanied by an increase in the sympathetic vasomotor activity. In addition, animals subject to the 12 weeks high fructose diet developed characteristics of metabolic syndrome.

However, in a systematic review and meta-analysis of three large cohorts in 37,375 men and 185,855 women, providing a total 2,502,357 person-years of follow-up and 58,162 cases of incident hypertension conducted by Jayalath et al (2014), they found no association between fructose intake and incident hypertension, where fructose constituted up to 14% of the total energy intake, equivalent to the 90<sup>th</sup> percentile intake in the United States. In another study conducted by Angelopoulos et al (2014) supported this outcome. The authors concluded that 10 weeks of consumption of fructose at the 50<sup>th</sup> percentile level, whether consumed as pure fructose or with fructose-glucose containing sugars, does not promote increased blood pressure.

A majority of the research done on fructose intake and blood pressure has focused on towards adults thus far. To test whether or not these same findings could be used in the adolescence population, Bobridge et al. (2013) examined cross-sectional associations between dietary intake of fructose, serum uric acid and blood pressure in 814 adolescents aged 13-15



years participating in the Western Australian Pregnancy Cohort (Raine) Study. They found there is no direct relationship between fructose intake and blood pressure. However, their data suggests that gender may influence these relationships in adolescents, with significant associations observed more frequently in boys than girls. The same results regarding gender was also found during a study conducted by Conti et al (2014). They found that, before the age of 45, occurrence of hypertension is lower in women than in men. From age of 45 to 54 and from the age of 55 to 64, the percentage of hypertensive men is comparable to that of hypertensive women, a period which corresponds with the start of menopause. After the age of 65, blood pressure levels increase slower in men than in women.

In summary, hypertension affects about 1/3 of the U.S. population. Since there are often no signs or symptoms with hypertension, it is referred to as a silent killer. When consumed over a long period of time and in large amounts, fructose could cause hypertension. However, it has been shown that fructose consumption does not always lead to hypertension. Results varied between genders and ages throughout various studies. There was a more significant association between boys than girls when looking at adolescents. This was also reported by a study utilizing older adults.

## **Insulin Resistance**

Lastly, the fifth and final risk factor which will be covered in this paper will be insulin resistance. Insulin resistance is a condition in which the body produces insulin but does not use it effectively. When people have insulin resistance, glucose builds up in the blood instead of being absorbed by the cells, leading to type 2 diabetes or prediabetes (National Institute of Diabetes and Digestive and Kidney Diseases, 2014). The good news is if people learn they have insulin resistance early on, they can often prevent or delay diabetes by making changes to their lifestyle.

Insulin resistance can lead to a variety of serious health disorders (National Institute of Diabetes and Digestive and Kidney Diseases, 2014), if it is not treated as soon as it starts developing.

Fructose is also known to increase plasma uric acid, and this effect may be involved in the development of insulin resistance (Tappy, 2010b). As the global obesity epidemic continues to worsen, the world is seeing an unprecedented rise in the prevalence of type 2 diabetes. Excess adiposity, particularly around the central depots, is one of the most well-established risk factors for development of type 2 diabetes (Malik and Hu, 2012). Temporal patterns over the past three to four decades have shown a close parallel between the rise in added sugar intake and the global obesity and type 2 diabetes epidemics (Malik and Hu, 2012). The insulin resistance syndrome is a cluster of related variables that appears to be of major importance in the pathogenesis of coronary artery disease. The syndrome originally included resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, hypertension, dyslipidemia characterized by high triacylglycerol concentrations, and low concentrations of HDLs (Elliott et al., 2002).

Using 32 male Wistar rats which were 3 weeks old, Dupas et al. (2015) reported after twelve weeks on either a fructose enriched drink (20% w/v from age 3 weeks to 9 weeks and 25% w/v from age 10 weeks to 15 weeks) or tap water, the fructose enriched drink group presented with insulin resistance. In another study using rats and a fructose rich diet, they also found that consuming a high-fructose diet can lead to an increase in higher plasma glucose and insulin response (Crescenzo et al, 2014). Bremer et al. (2011) found when monkeys are exposed to a high-fructose diet, it does not result in overt diabetes and fasting glucose concentrations will not change ( $72 \pm 2$  mg/Dl at baseline and 12 months). However, fasting insulin concentration increased dramatically (+121% at 6 months and +95% at 12 months).

In a study conducted by Stanhope et al. (2011), they found that when one is exposed to fructose-sweetened beverages for 10 weeks, fasting glucose concentrations were significantly greater in the subjects who consumed fructose-sweetened beverages than in those who consumed glucose-sweetened beverages. In a study conducted by Senador et al. (2011), fasting glycemia was also found in C57BL mice as a result from an increased consumption of fructose over a period of 8 weeks. Liu et al., (2015) also reported similar results from their long term study. They found when given a high fructose diet, it induced an increase in plasma glucose and impaired glucose tolerance.

In a clinical study, 12 week old mice were separated into 2 group where one group was given standard rat chow for 8 weeks and the other group was given high-fructose rich chow for 8 weeks. D'Angelo et al (2005), found that fasting plasma glucose ( $171\pm 10$  versus  $120\pm 10$  mg/dL), plasma insulin ( $1.8\pm 0.5$  versus  $0.7\pm 0.1$ ) were modestly elevated but significantly elevated in fructose-fed animals (D'Angelo et al., 2005).

Perez-Pozo et al. (2010), found there was no significant change in glucose but there was an increase in the number of patients with fasting glucose levels meeting the criteria for metabolic syndrome when compared with the baseline from 45% to 55% (Perez-Pozo et al, 2010). In another study, which can confirm the results from Perez-Pozo et al. (2014), Jameel et al. (2011) in fact found a consumption of fructose can produce lower levels of blood glucose level when compared to glucose consumption.

In summary, fructose can adversely affect insulin resistance and eventually causing type 2 diabetes. Increased plasma uric acid levels can also be a result of increased fructose consumption which has been shown to be involved in the development of insulin resistance. There has been a close parallel between the rise in added sugar intake and global obesity and

type 2 diabetes epidemics over the last three to four decades. Various studies report there is an association between increased fructose consumption and insulin resistance development. Results differed among study length and fructose consumption throughout the studies. The longer the study lasted and the higher the amount of fructose consumed during the study had an increased risk of developing insulin resistance.

## CHAPTER 3

### CONCLUSION

Up until the last few decades, fructose was pretty much nonexistent in the human diet. Today it can be found in various processed foods and beverages including soft drinks, juice, and baked goods. These products currently make up a large portion of the human diet these days and consumption is high in children, adolescents, and young adults. Naturally, fructose is found in plant sources such as fruits and sugar cane. Today, high fructose corn syrup is used as a sweetener in many processed foods and drinks such as soda and fruit juices. High fructose corn syrups' low production cost has increased its' use in the food production industry. When added together, the consumption of snacks and sweets make up more than 75 percent of intake of added sugars. Fructose is part of the macro nutrient group carbohydrate which are polyhydroxy aldehydes, or ketones, or substances that produce such compounds when hydrolyzed. The category fructose belongs to is the monosaccharide group. Structurally the simplest form of carbohydrate, monosaccharides cannot be reduced in sized. While glucose is the most commonly used carbohydrate used as a fuel source in the body, fructose can be utilized for energy as well. To be used as a fuel source, fructose must first enter the glycolytic pathway after being ingested using the fructose 1-phosphate pathway.

From the readings for this paper, one can conclude that indeed an increased consumption may lead to an increase in the metabolic syndrome risk factors and an increase of risk of metabolic syndrome. When fructose is consumed in large quantities over a long period of time, obesity rates are shown to rise. This may have led to various health issues which contribute to the risk of metabolic syndrome. Increased fructose consumption was also associated with hypertriglyceridemia. Nevertheless, results from different studies did not show any effect from

the fructose consumption on blood triglyceride levels. The same results were found in studies regarding fructose consumption and plasma HDL levels and hypertension. Studies on fructose consumption and insulin resistance showed there is a close parallel between the rise in added sugar intake and global obesity and type 2 diabetes. After the readings, it is clear the consumption of fructose does not always lead to the same results and outcomes. The length of the study, the amount of fructose consumed, participant/animal model, age, gender, and metabolic response can influence the outcome. Since study results seem to differ between species and affect rat models more, I believe additional future research should pertain to humans rather than animal models.

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