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Consumption of sucrose and high fructose corn syrup does not increase liver fat or ectopic fat deposition in muscles

Running title: Consumption of sucrose and high fructose corn syrup consumption does not increase liver fat or ectopic fat deposition in muscles

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ABSTRACT

Background: Fructose induced triglyceride synthesis has been postulated to be augmented when accompanied by glucose. Chronic elevations could lead to excess fat accumulation in the liver and ectopic fat deposition in muscles which in turn could contribute to induction of abnormalities in glucose homeostasis, insulin resistance and the subsequent development of type 2 diabetes.

Objective: Evaluate the effect of the addition of commonly consumed fructose/glucose containing sugars in the usual diet on liver fat content and intramuscular adipose tissue (IMAT).

Materials and Methods: For ten weeks, sixty-four individuals (42.16 ± 11.66 years) consumed low-fat milk sweetened with either high fructose corn syrup (HFCS) or sucrose such that the added sugar matched the 25th, 50th and 90th percentile population consumption levels of fructose. Fat content of the liver was measured utilizing unenhanced CT Imaging and fat content of muscle was assessed by using magnetic resonance imaging (MRI).

Results: Over the course of 10 weeks, fat content of the liver (13.32 ±10.49% vs 13.21 ± 10.75%, $p > 0.05$), the vastus lateralis muscle (3.07 ± 0.74 vs. 3.15 ± 0.84g/100ml) and gluteus maximus muscle (4.08 ± 1.50 pre vs 4.24 ± 1.42g/100ml) were all unchanged ($p > 0.05$) when the six HFCS and sucrose groups were averaged. Group assignment did not affect the result (interaction > 0.05).

Conclusions: These data suggest that when fructose is consumed as part of a typical diet in normally consumed sweeteners such as sucrose or HFCS, ectopic fat storage in the liver or muscles is not promoted.

Keywords: fructose, high fructose corn syrup, sucrose, liver fat, muscle fat

INTRODUCTION

Increased hepatic triglyceride synthesis resulting in fat deposition in the liver and ectopic deposition of intramuscular fat have been demonstrated to contribute to abnormalities in glucose homeostasis, insulin resistance, and the subsequent development of type 2 diabetes **(Korenblat et al 2008; Peterson and Shulman 2006;van Herpen et al 2011).** Recently it has been argued that excessive fructose consumption may contribute to increased hepatic triglyceride synthesis contributing to non alcoholic fatty liver disease (NAFLD) and increased intramuscular adipose tissue (IMAT) **(Lim et al 2010; Stanhope et al 2009;Teff et al 2009).** In has been further postulated that when fructose is consumed along with glucose, as it invariably is in the human diet, these conditions may be exacerbated **(Hudgins et al 2011; Lustig 2011).**

The total consumption of sugars has risen in the United States and other countries since 1970. The U.S. Department of Agriculture's Economic Research Service estimates that between 1970 and 2005, sugar sweeteners available for consumption increased 76 kcal/day/person from 400 kcals to 476 kcals **(Wells, Buzby 2008)** While total caloric sweetener consumption in the United States has increased during this period of time, sucrose remains the leading added sugar consumed in the American diet and the leading source of fructose. Worldwide consumption of sucrose is nine times as much as high fructose corn syrup. **(White 2008)**

Non alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease with an estimated prevalence between 20%-25% in adults **(Clark 2006; McCullough 2002; Angulo 2002; Clark et al 2002; Hiden et al 1977; Kooby et al 2003).** Increased fat in the liver (hepatic steatosis) has been associated with a variety of conditions including obesity, alcohol consumption, parenteral nutrition, and chemotherapy **(McCullough 2002; Kooby et al 2003).** NAFLD represents a spectrum of changes in the liver associated with fat accumulation within hepatocytes and includes both steatosis and steatohepatitis.

NAFLD may be a progressive disease which increases the risk of liver failure, cirrhosis and liver cancer **(McClough 2002; Regimbeau et al 2004; Bugianesi et al 2002).**

In the past decade a compelling body of literature has emerged linking ectopic deposition of intramuscular adipose tissue (IMAT) to insulin resistance. **(Korenblat et al 2008; Peterson and Shulman 2006; Milikovic-Gacic et al 2008; Goodpaster et al 2003; Gallagher et al 2005; Torrianai and Grinspoon 2005; Yim et al 2007; Song et al 2004; Berglun 2005; Albu et al 2005; Deivanayagam et al 2008).** It has been argued that IMAT is equivalent in volume to visceral abdominal tissue (VAT) **(Green et al 2005**). Several investigators have suggested that IMAT may contribute to as much as 75% of total body insulin resistance **(Peterson and Shulman 2006; Gallagher et al 2005).**

Insulin resistance is an important predisposing condition to type 2 diabetes. Type 2 diabetes mellitus (T2DM) (**Korenblat et al 2008; Peterson and Shulman 2006; Milikovic-Gacic et al 2008; Goodpaster et al 2003; Berglun 2005;Shulman 2000)** is a major cause of morbidity and mortality worldwide and a predisposing condition for high blood pressure, some dyslipidemias and coronary heart disease **(Shulman 2000; American Diabetes Association 2010; Brunner et al 2008; Weber et al 2010; Holman et al 2008; International Diabetes Federation 2011).** Prospective studies have demonstrated that insulin resistance is the best predictor of whether or not an individual will later become diabetic **(Warram et al 1990;Lillioja et al 1988; Haffner et al 1990; Reaven et al 1976).** Increased IMAT has been associated with obesity **(Song et al 2004**:**Berglun 2005; Albu et al 2005; Deivanayagam et al 2008**, aging **(Lim et al 2010)** and other conditions, and is more prevalent in certain population groups (e.g. African Americans**) (Milikovic-Gacic et al 2008; Torrianai and Grinspoon 2005; Song et al 2004**; **Berglun 2005)** than in others, although all age groups and ethnicities are significantly affected.

The current study was undertaken to see if any increase in liver fat or IMAT occurred from daily consumption of sucrose or high fructose corn syrup containing beverages given at three different levels up to the 90th percentile for fructose intake in the American diet **(Torrianai and Grinspoon 2005).** We hypothesized that neither increased liver fat nor increased IMAT would occur at these normal levels of fructose intake delivered through the most commonly consumed fructose containing sugars. We further hypothesized that there would be no differences between sucrose and high fructose corn syrup in terms of promoting liver or muscle fat accumulation.

Many of the studies which have demonstrated increases in triglyceride synthesis and increased accumulation of fat in the liver and muscle have been performed utilizing large quantities of pure fructose compared to pure glucose, neither of which is consumed to any appreciable degree in the human diet **(Teff et al 2009; Stanhope et al 2009)**. Very few data are available comparing high fructose corn syrup to sucrose, particularly in the areas of liver fat accumulation and ectopic deposition of fat in the muscle. To the best of our knowledge, this is the first randomized trial to compare fat deposition in the liver and muscle utilizing the two main sources of fructose in the human diet, HFCS and sucrose, delivered at doses within the normal range consumed.

MATERIALS AND METHODS

Subject Selection

Eighty men and women between the ages of 20 and 60 years of age were recruited to participate in the current study. Body mass index (BMI) was required to be between 23-35 kg/m^2. Subjects could not be taking any prescription medicine or over the counter products for weight loss, or be enrolled in a commercial weight loss program. Individuals were excluded who had any history of thyroid disease, diabetes or glucose intolerance, uncontrolled hypertension, any gastrointestinal disorder, history or presence of cancer, or currently consuming more than 14 alcoholic beverages per week. Women who were pregnant, lactating or trying to become pregnant were also excluded. The study was approved by the Western Institutional Review Board (WIRB), and all subjects signed an informed consent.

Intervention

This was a ten week, randomized, prospective, partially blinded, parallel investigation where individuals were required to consume one of three different levels of either SUC or HFCS (55% fructose) at 8%, 18% or 30% of the calories required for weight maintenance. These consumption levels are equivalent to the 25th, 50th, 90th percentile for fructose consumption respectively.

The sugar was supplied via sugar sweetened, low-fat milk. The energy intake required to maintain body weight was estimated for each participant using the Mifflin St Joer prediction equation (and appropriate activity factor based on self reported levels of habitual physical activity). The number of servings of the test beverage was then determined in an amount necessary to meet required HFCS

or Sucrose content of the diet, determined by the participant's group assignment. All participants were instructed to substitute the servings of test beverage for food or other beverages usually consumed, but otherwise were given no structured dietary plans to follow. Subjects and investigators were blinded as to which sugar the subjects were receiving. Subjects were further blinded to how much sugar they were receiving, although research staff needed knowledge of this to prescribe the daily servings of the test beverage.

HFCS or SUC products were provided to subjects on a weekly basis by study personnel in amounts appropriate for each individual's calorie level. Milk checklists were provided to keep track of consumption levels, and these were reviewed weekly. Cumulative consumption levels below 80%, or 5 consecutive days without consumption of a single serving of the test beverage led to automatic withdrawal due to lack of compliance.

CT Scans

Unenhanced CT scans of the liver were performed at baseline and week 10 utilizing the technique described by Kodama et al **(Kodama et al 2007).** Subjects were prospectively imaged on a Phillips Brillance-64 slice CT utilizing spiral technique without intravenous contrast media. Scans were performed at baseline and at week 10. Qualitative and quantitative analysis of the CT data were performed by a board certified radiologist who was blinded to the patient data. The value for pathologic fat content was assigned based on the linear regression equation calculated by Kodama **(Kodama et al 2007).**

Attenuation Measurements

CT was performed at 120 kVp, 240-340 mAs, 5.0 mm collimation, pitch of 1.5 and 5.0 mm reconstructed interval. Attenuation measurements were delineated in four regions of interest (ROI) within the liver. Air calibration of the CT was performed on a daily basis. Water phantom calibration was performed on a weekly basis. Each ROI measured 1.0+/- 0.2 cm^2. There were four sectors delineated as a modification of the Couinaud segmentation system. Segmentation of the sectors include a right posterior sector for segments VI and VII, right anterior sector for segments V and VIII, left medial sector for segment IV and left lateral sector for segments II and III. ROI measurements were randomly performed sampling the hepatic parenchyma, with absence of vessels or focal lesions within the representative sector measurement. Average attenuation values of the liver were compared with linear regression values conducted on a log-log scale as described by Kodama **(Kodama et al 2007).**

Fat Selective Magnetic Resonance Imaging (MRI)

Fat selective Magnetic Resonance Imaging (MRI) of the gluteus maximus and vastus lateralis muscle was performed according to the technique developed by Goodpaster et al **(Goodpaster et al 2004).**

MRI studies were performed using a 1.5-T scanner (Intera; Phillips, Andover, Massachusetts) utilizing a quadrature radiofrequency extremity coil. T1 weighted spin echo sagittal images with repetition time (TR)= 1270 MS, echo time (TE) =18 MS, flip angle = 90 degrees, field of view = 21.9 x 21.9 cm, 5-mm thick slices, 0-mm spacing, flip angle 90 degrees, matrix size = 336 x 300 were acquired of the lower extremity. Axial T1 weighted sequence was also performed with parameters TR =1270 MS, TE =18 MS, field of view 21.9 x 21.9 cm, flip angle = 90 degrees, matrix size = 200 x 180. Axial in and out of phase sequences were also obtained with TR = 500 ms, TE = 6.9 ms, matrix size = 124 x 124, flip angle = 35 degrees, field of view = 21.8 x 21.8 cm. 1.0 cm +/- 0.1 cm squared. Region of interest voxels were utilized to evaluate the signal intensity

of the gluteus maximus and vastus lateralis musculature. T1 weighted images were utilized to avoid subcutaneous adipose tissue and intramuscular adipose tissue in the analysis of the skeletal muscle lipid concentration. Lipid signal intensity of the muscles was converted to lipid concentrations in grams per 100 ml utilizing linear regression established by Goodpaster et al. **(Goodpaster et al 2004).**

All MRI images were read by a senior, offsite radiologist who was blinded to all study protocols.

Other Clinical Testing

All measurements were performed in the morning after a 1 hour fast. Measurements were taken baseline and again after ten weeks. Body composition was determined by iDXA (G.E. Medical Systems). In addition, blood samples for total cholesterol, LDL, triglycerides, HDL and glucose were obtained and analyzed using routine laboratory methods at a lipid certified laboratory. Nutritional intake was assessed using three day food records and analyzed by employing the Minnesota Nutrient Data Base System for Research (NDSR).

Statistical Analysis

Changes over the course of 10 weeks (main effect of time) and the effect of group assignment on the changes (main effect of group) were assessed by 2-way ANOVA (time x group). Significant time by group interactions were probed by testing within subject changes for each group separately and by calculating changes at week 10 minus baseline and testing for between group differences. Significant time effects with non significant interactions reflect changes in the

pooled data from the entire cohort. For all analyses an alpha level of 0.05 was set. Means and Standard deviations are reported in all tables.

RESULTS

Baseline Characteristics

Characteristics of all subjects who completed the study (n=64, Male=36 and Female=28) are shown in **Table 1**. There were no differences among the groups at baseline gender distribution or in any measured variable ($p>0.05$). The 16 individuals who did not complete the trial were dropped for a variety of reasons, either because of poor compliance with milk consumption, dissatisfaction with the protocol, inability to keep weekly appointments, or failure to complete both sets of CT and MRI evaluations. These individuals were not different in terms of age, BMI or any other clinically significant characteristic compared to the 64 finishers.

Effects on Energy and Macronutrient Intake

Energy intake increased significantly across the entire cohort (8450.8 ± 2997.4 vs 10228.2 ± 3136.3KJ, $p<0.001$), but this was not affected by group assignment **(Table 2).** This was driven by an increase in intake of total carbohydrate (247.0 ± 94.0 vs 350.8 ± 111.1g, $p<0.001$) and, more specifically, total sugar (97.1 ± 43.5 vs 215.5 ± 76.1gp<0.001). In both cases, within group increases were observed in both 18% and 30% groups, but not in the 8% groups.

Effects on Weight and Body Composition

Consistent with an overall increase in energy intake, an increase in body mass was observed in the entire pooled cohort (77.81 ± 13.86 vs 78.58± 14.21kg, $p<0.01$). Post Hoc analysis revealed it was only individuals in the 30% groups who gained weight. Of note, waist circumference, body fat percentage and fat mass did not increase. Increase in body mass index was accounted for by increases in both fat mass and fat free mass, although the time X group

interaction for these variables were not significant (p>0.05). These data are displayed in **Table 3.**

Effects on Measurement of Fat in the Liver and Skeletal Muscle

There were no significant changes in the measurement of fat in either the vastus lateralis (3.07 ± 0.74 vs 3.15 ± 0.84 grams/100 ml, p>0.05) or gluteus maximus (4.08 ± 1.50 vs 4.24 ± 1.42 grams/100 ml, p>0.05), or in the liver (13.32 ± 10.49 vs 13.21 ± 10.75%, p>0.05). These data are shown in **Table 4** and **Table 5**.

Effects on Lipids and Other Metabolic Factors

Ten weeks of consuming sugar sweetened, 1% fat milk did lead to an an average increase in triglycerides for the entire cohort (1.11 ± 0.46 vs 1.27 ± 0.73 mmol/L, p<0.05). However, this was comparable among the 6 groups (interaction p>0.05). There were no changes in any other lipid measurement. These data are displayed in **Table 6.**

DISCUSSION

Our findings confirm our hypothesis that at normal levels of consumption of the most common fructose containing sugars over a 10-week period there is no significant liver fat infiltration or increase in IMAT. Furthermore, our results demonstrate that there are no differences between HFCS and sucrose related to these two parameters.

Previous studies which have suggested that increased fructose could potentially contribute to NAFLD have often been criticized for using pure fructose (rarely consumed in the human diet) **(Teff et al 2009),** employing large doses (**Teff et al 2009; Hudgins et al 2011)** or using animal models which may not translate to human metabolism **(Sievenpiper et al 2011).** Little is known about the effects of fructose on fatty infiltration of the liver when it is consumed along with glucose in the common forms of food and beverages that are found in the human diet (e.g. foods sweetened with sucrose or high fructose corn syrup) particularly in otherwise healthy, normal individuals.

Recently investigators have postulated that there may be a link between excessive fructose consumption and NAFLD and IMAT **(Abdelmalek et al 2010; Vos et al 2011).** The underlying metabolic handling of fructose by the liver provides a putative pathophysiologic mechanism. In contrast to glucose, fructose is almost entirely metabolized by the liver. While most of the fructose is metabolized to glucose, glycogen or lactate, metabolic pathways exist which can shunt some of the fructose into the creation of free fatty acids which may ultimately be stored in the liver or exported to muscle as triglycerides**.** **(Stanhope et al 2009: McDevitt et al 2000).**

Recently it has been postulated that increased fructose consumption in the human diet, particularly in Europe and the United States, may have contributed to an increased prevalence of NAFLD **(Clark 2006)** and IMAT **(Lim et al 2010).** The theoretical basis for these assertions rests on differences of metabolism of fructose compared to glucose. Fructose metabolism differs from glucose in two

major ways **(Tappy and Le 2010).** First, there is nearly complete first-pass hepatic extraction of fructose. Secondly, while the majority of fructose is converted to glucose, glycogen and lactate, enzymatic reactions in the final steps related to fructose metabolism may also result in increased free fatty acids produced in the liver which, in turn, may be packaged into triglycerides and stored in hepatocytes or exported to muscles **(Tappy and Le 2010)**. It has been hypothesized that the process of *de novo* lipogenesis (DNL) resulting from fructose metabolism may lead to a variety of metabolic abnormalities (in addition to NAFLD and IMAT) including insulin resistance, dyslipidemias, diabetes and the metabolic syndrome **(Stanhope et al 2009).**

The studies which have been cited to suggest a link between fructose consumption and NAFLD and IMAT have been criticized on a variety of grounds. Particular concerns have been raised about studies that employ conditions that differ markedly from the way fructose is normally consumed in the human diet. Some of this work has been done in animals or humans employing large doses of pure fructose **(Stanhope et al 2009; Teff et al 2009)** (not normally consumed in the human diet) or using bolus dosages at higher levels than human beings typically consume from all sources **(Marriott et al 2009)** and particularly after an overnight fast **(Hudgins et al 2011).**

Within the human diet, fructose is almost invariably consumed in combination with glucose, including in the most commonly consumed sweeteners: sucrose and high fructose corn syrup as well as concentrated fruit juices, honey, molasses and other fructose/glucose containing sweeteners. It has been recently postulated that when fructose is consumed in the presence of glucose, the process of *de novo* lipogenesis may become even more significant **(Hudgins et al 2011; Lustig 2008).** One recent study suggested that when fructose and glucose are consumed together, DNL may triple **(Hudgins et al 2011)**, thereby exacerbating the likelihood of NAFLD and IMAT. Not all recent

studies, however, have supported a link between fructose consumption and fat deposition in the liver and muscle **(Silbernagel et al 2011; Leˆ et al 2006).**

The two largest sources of fructose in the human diet are sucrose (a disaccharide containing 50% fructose and 50% glucose) and high fructose corn syrup which is present in the human diet in two forms: HFCS-55 (which consists of 55% fructose, 42% glucose and 3% other carbohydrates) and HFCS-42 (which consists of 42% fructose and 58% glucose).

A recent study followed individuals for six months and compared sucrose-sweetened cola to water, milk and diet cola, all consumed in the amount of one liter per day (well within normal population consumption levels in the United States) **(Maersk et al 2012).** This study found that individuals in the sucrose-sweetened cola consuming arm had increased fat accumulation in the liver and muscle. The authors speculated that these findings might be even more pronounced if beverages had been sweetened with high fructose corn syrup since the form of high fructose corn syrup used to sweeten soft drinks (HFCS-55) has slightly more fructose than does sucrose. The authors also noted that their finding of increased fat accumulation in the liver and the muscle could be confounded by the fact that the sugar sweetened cola consuming group also increased absolute body weight and total fat mass**(Maersk et al 2012)**.

In the current study neither sucrose nor high fructose corn syrup at doses delivering 25th, 50th and 90th percentile population consumption levels of fructose in the context of mixed nutrient diets resulted in increased IMAT over a ten week trial. The average amount of IMAT in the vastus lateralis and the gluteus maximus both before and after the intervention in the current study was consistent with previous investigations utilizing MRI to assess IMAT. **(Goodpaster et al 2004;Schick et al 2002;Machann et al 2003).**

Our findings are at variance with recent findings of Maersk et al who found significant increases in ectopic skeletal muscle fat infiltration from consuming a liter of sucrose sweetened beverages daily over a six month, randomized intervention **(Maersk et al 2012).** The differences between our findings and those of Maersk et al may be a result of different study populations or the use of a different technology to assess muscle fat (MRS versus MRI). Our findings are consistent with those of Silbernagel et al who found no increase in IMAT in a four-week trial where 40% of calories were consumed as fructose **(Silbernagel et al 2011).** Silbernagel et al employed MRS to estimate IMAT. Furthermore, numerous other studies assessing changes in IMAT have employed intervals shorter than the ten-week intervention in the current trial to assess changes in IMAT in response to various interventions and have employed MRI, as we did, to assess muscle fat **(Goodpaster et al 2009; Greco et al 2002; Leˆ et al 2006)**.

It should be noted that studies to date, including ours, which have not shown increased liver or muscle fat accumulation in response to various doses of fructose have been limited in duration to no more than 10 weeks. In contrast the Maersk study which demonstrated increased liver and muscle fat accumulation documented these changes over a six month period **(Maersk et al 2012)**. Thus, our findings must be treated with caution since the duration of the study may not have been long enough to demonstrate accumulation of liver or muscle fat. Studies of longer duration utilizing commonly consumed sugars at normal consumption levels are clearly warranted.

It should be noted that a small, but statistically significant increase in energy consumption occurred in all groups despite the fact that individuals were counseled on a weekly basis to maintain a eucaloric diet (**Table 2**). This may reflect difficulty in incorporating the calories from sweetened milk in addition to the normal diet that subjects were accustomed to, particularly at high consumption levels of added sugars. The increase in body mass which occurred in several groups during the study period was the result of increases in both fat

mass and fat free mass which is consistent with the overall increase in caloric consumption which occurred over the 10 week trial.

In the current study, no changes in total cholesterol, LDL or HDL occurred. An increase in triglycerides occurred in the current study. Some studies have suggested that no increase in triglycerides occurs in response to fructose consumption levels up to those consumed by 95% of the population **(Dolan et al 2010(i); Dolan, Potter et al 2010(ii)** provided that the overall diet is isocaloric**.** Literature supporting no increased triglycerides at normal consumption levels of fructose in normal weight **(Dolan et al 2010 (i)** and obese **(Dolan, Potter et al 2010 (ii)** individuals has recently been reviewed. Other studies have suggested increases in triglycerides in response to fructose consumption **(Stanhope et al 2009; Teff et al 2009).** While the increases in triglycerides in the current study are not clinically important, this issue remains one of scientific discussion and debate. It should be pointed out that both the pre and post intervention triglyceride levels in the current study are well within population norms. Triglyceride levels have been routinely shown by multiple investigators to rise when carbohydrates are substituted for fat in the diet, particularly if those carbohydrates are simple sugars. In diets where carbohydrates are added through whole grains, fruits, vegetables and low fat unsweetened milk, such as the DASH Diet (Dietary Approach to Stop Hypertension), increase in triglycerides have not been reported, although HDL has declined (**Obarzanek et al 2001)**. In the Women's Health Initiative the high carbohydrate diet did not increase triglycerides although, once again, HDL declined (**Howard et al 2006).**

Our findings suggest that there is no increase in liver fat or IMAT over a 10-week period of consumption at any of these dosages of HFCS or sucrose, which would encompass consumption levels of fructose up to 90% of the population in the United States. Furthermore, there were no differences in liver fat accumulation or IMAT at any dosage, nor were there any differences between high fructose corn syrup and sucrose.

It has also been hypothesized that consumption of high fructose corn syrup could potentially create more adverse health consequences than sucrose because of the slightly higher percentage of fructose in the form of high fructose corn syrup (HFCS-55) most commonly utilized in soft drinks **(Maersk et al 2021).** This form of HFCS has 55% fructose compared to 50% of fructose in sucrose. However, this contention is controversial since a number of studies have shown the two sugars to be metabolically equivalent **(Melanson et al 2008;Soenen and Westerterp-Plantenga 2007)** and the current study did not demonstrate any differences.

To our knowledge, this is the first study to address whether or not there is an increase in liver fat or IMAT at normally consumed levels of fructose using the typically consumed sweeteners in the human diet. Strengths of this study are the rigorous control of the diet, high compliance of the subjects and measurement of a variety of parameters such as weight and body composition in addition to providing pre and post intervention CT and MRI scans in a blinded fashion. Weaknesses of the current study include the relatively small number of subjects and the fact that no adolescents were included in the study population. (Individuals between the ages of 15-19 consume the highest level of fructose containing foods and beverages of any age group) **(Marriott et al 2009).** The current study was also of relatively short duration (ten weeks), although other investigators have shown changes in liver fat infiltration in response to various interventions in periods ranging from 4-10 weeks **(Silbernagel et al 2011; Lim et al 2011; de Souza et al 2012).**

It could also be argued that an alternative methodology for measuring liver fat such as Magnetic Resonance Spectroscopy (MRS) might provide a more accurate estimation of triglyceride accumulation within hepatocytes **(Abdelmalek et al 2010; Vos et al 2011; McDevitt et al 2000).** Nonetheless, we believe that utilization of an established and commonly performed CT

measurement provides accurate information to answer the fundamental question of whether or not liver fat accumulation occurs at normally consumed levels of fructose via normally consumed sugars (HFCS and sucrose). Moreover, other investigators have demonstrated a high concordance between MRS and CT scans of the liver to determine hepatic fat content (r^2=0.81; unpublished observations DE Larson-Meyer, SR Smith and BR Newcomer, 2005) and other researchers have utilized this technology to track changes in hepatic fat content in response to short term dietary interventions **(Silbernagel et al 2011; Elias et al 2010).**

Numerous studies have investigated the effects of alterations in dietary carbohydrate on fasting blood TG concentrations (**Parks et al, 2000**). It is widely accepted that when the content of dietary carbohydrate is increased above levels of typical consumption (>55%), blood concentrations of triglycerides rise. Further, epidemiological evidence and clinical trials have showed that triglyceride levels are markedly affected by body mass and fat distribution. In the present investigation, ten weeks of consuming sugar sweetened, 1% fat milk did lead to an average increase in triglycerides for the (1.11 ± 0.46 vs 1.27 ± 0.73 mmol/L, $p<0.05$) and an increase in body mass (77.81 ± 13.86 vs 78.58± 14.21kg, $p<0.01$) in the entire pooled cohort . Interestingly, change in TG correlated with change in weight (($r=0.258$, $p<0.001$), change in BMI ($r=0.251$, $p<0.001$), change in FM ($r=0.165$, $p<0.05$), but did not correlate with change in total energy intake ($r=0.027$, $p>0.05$) or change in sugar intake ($r=0.002$, $p>0.05$). Of particular importance despite the reported elevated triglycerides for the entire cohort there were no similar changes observed in liver of muscle fat. It is not possible to explain these observations since the study was not designed to explore the kinetics of triglycerides. (**Parks et al 2000**)

In summary, the current study did not find any increase in liver fat or intramuscular adipose tissue over a ten-week intervention at fructose levels consumed by up to 90% of the population when consumed in the two largest

sources of fructose in the human diet – sucrose and HFCS. Furthermore, no differences were found between sucrose and high fructose corn syrup consumed with regard to liver or intramuscular adipose tissue accumulation and blood lipid indicators, and no differences were found at three different levels of consumption of either sugar. These findings are consistent with previous studies from our research group and others suggesting no metabolic differences between sucrose and high fructose corn syrup **(Melanson et al 2008;Soenen and Westerterp-Plantenga 2007).**

These studies suggest that fructose, when consumed at normal levels up to 90% of the population consumption levels in the commonly consumed sweeteners sucrose and HFCS, does not result in increased liver fat or intramuscular adipose tissue accumulation. These data also raise questions about the quantitative significance of *de novo* lipogenesis in response to normally consumed levels of fructose in the human diet. Further studies with larger sample sizes, longer duration and including adolescents would appear warranted.

CONFLICTS OF INTEREST AND FUNDING DISCLOSURE:

Steve Bravo: Has received consulting fees and equipment support from Siemens Inc.

James M. Rippe: Dr. Rippe's research organization has received funding and Dr. Rippe has received consulting fees from ConAgra Foods, PepsiCo International, Kraft Foods, the Corn Refiners Association and Weight Watchers International.

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TABLES

Table 1

Demographics of Study Group: Group assignment indicates the percentage of calories in the total diet consumed as either HFCS or sucrose during the 10 week intervention

	8% HFCS (M=4, F=4)	8% Sucrose (M=10, F=3)	18% HFCS (M=10, F=2)	18% Sucrose (M=3, F=7)	30% HFCS (M=4, F=7)	30% Sucrose (M=5, F=5)
Age (years)	38.6 ± 10.7	33.9 ± 10.3	36.8 ± 10.5	42.3 ± 11.0	44.8 ± 9.7	37.0 ± 13.2
Body Mass (kg)	84.7 ± 14.1	79.0 ± 20.7	78.7 ± 14.6	79.8 ± 15.8	79.7 ± 13.9	71.8 ± 12.0
Waist Circumference (cm)	88.7 ± 11.8	84.5 ± 12.8	87.6 ± 7.7	85.5 ± 11.5	90.3 ± 5.9	79.9 ± 7.3
Cholesterol (mmol/L)	4.6 ± 1.1	4.6 ± 1.0	4.5 ± 0.9	4.7 ± 0.7	4.8 ± 0.9	4.8 ± 1.2
Triglycerides (mmol/L)	1.3 ± 0.4	1.1 ± 0.7	1.0 ± 0.4	1.2 ± 0.5	1.2 ± 0.4	1.1 ± 0.7
Glucose (mmol/L)	5.0 ± 0.2	4.9 ± 0.3	5.0 ± 0.3	4.9 ± 0.3	5.1 ± 0.2	5.0 ± 0.3
Insulin (pmol/L)	60.1 ± 29.8	44.7 ± 25.4	57.0 ± 42.5	41.7 ± 31.7	70.9 ± 36.6	58.4 ± 33.3

Table 2

Change in energy intake over ten weeks of consuming sugar-sweetened low-fat milk

	Group	Pre	Week 10	Interaction p value
Energy Intake (KJ)	8% HFCS	8281.34 ± 2796.6	9083.9 ± 2599.1	0.277
	8% Sucrose	9674.7 ± 333.9	10215.2 ± 3727.5	
	18% HFCS	7618.6 ± 2978.6	10184.7 ± 3476.1	
	18% Sucrose	7918.6 ± 2324.6	9329.5 ± 2451.0	
	30% HFCS	7638.7 ± 1447.2	10781.3 ± 2469.4	
	30% Sucrose	9445.8 ± 4313.7	10228.2 ± 3136.3	
Fat (g)	8% Sucrose	86.1 ± 43.4	84.0 ± 48.7	0.598
	8% HFCS	65.0 ± 35.9	63.7 ± 26.1	
	18% HFCS	67.7 ± 33.4	78.2 ± 52.7	
	18% Sucrose	78.2 ± 36.1	60.4 ± 18.9	
	30% HFCS	68.9 ± 24.0	68.3 ± 26.7	
	30% Sucrose	74.8 ± 33.4	63.3 ± 20.7	
Carbohydrate (g)	8% Sucrose	269.3 ± 89.0	304.6 ± 93.5	0.017
	8% HFCS	247.0 ± 65.6	277.3 ± 67.2	
	18% HFCS	222.1 ± 92.1	347.4 ± 87.6**	
	18% Sucrose	214.9 ± 36.6	333.7 ± 95.8**	
	30% HFCS	231.7 ± 44.6	394.1 ± 78.5***	
	30% Sucrose	293.0 ± 168.0	431.5 ± 162.5*	
Protein (g)	8% Sucrose	98.4 ± 35.2	119.2 ±41.6	0.817
	8% HFCS	101.2 ±45.3	121.7 ±48.7	
	18% HFCS	79.4 ± 20.2	98.4 ± 28.1	
	18% Sucrose	72.6 ±22.8	100.2 ± 31.0	
	30% HFCS	78.1 ±16.1	113.4 ± 29.5	
	30% Sucrose	103.2 ±45.0	124.3 ± 50.8	
Total Sugar (g)	8% Sucrose	103.8 ±44.9	181.9 ± 61.2**	<0.001
	8% HFCS	102.7 ± 40.1	139.9 ± 22.1	
	18% HFCS	92.1 ± 51.2	202.9 ± 54.1***	
	18% Sucrose	85.3 ± 22.6	207.8 ± 54.8***	
	30% HFCS	97.5 ± 26.5	270.1 ± 48.2***	
	30% Sucrose	100.1 ± 67.8	272.2 ± 103.4**	

Within group difference compared to pre, $p<0.05$ *, Within group difference compared to pre, $p<0.01$**, Within group difference compared to pre, $p<0.001$***

Table 3

Change in body mass and measures of adiposity over ten weeks of consuming sugar-sweetened low-fat milk

	Group	Pre	Week 10	Interaction p value
Body Mass (kg)	8% HFCS	77.09 ± 16.70	76.67 ± 16.43	0.034
	8% Sucrose	84.44 ±14.62	84.77 ± 15.03	
	18% HFCS	78.70 ± 14.59	79.01 ± 15.45	
	18% Sucrose	74.61 ± 10.17	75.33 ± 9.40	
	30% HFCS	79.65 ± 13.92	81.97 ± 14.86**†	
	30% Sucrose	69.89 ± 10.69	71.01 ± 11.37*	
BMI(Kg/m^2)	8% HFCS	27.12 ± 5.66	26.99 ± 5.63	0.030
	8% Sucrose	28.42 ± 4.02	28.55 ± 4.20	
	18% HFCS	27.54 ± 3.21	27.61 ± 3.45	
	18% Sucrose	25.97 ± 3.17	26.24 ± 3.09	
	30% HFCS	28.59 ± 3.71	29.43 ± 4.17*†	
	30% Sucrose	25.61 ± 2.62	26.03 ± 3.04*	
Waist Circumference (cm)	8% HFCS	84.52 ± 12.18	83.51 ± 13.03	0.548
	8% Sucrose	88.53 ± 12.24	88.98 ± 12.17	
	18% HFCS	87.59 ± 7.70	87.77 ± 8.24	
	18% Sucrose	81.61 ± 7.11	82.35 ± 8.47	
	30% HFCS	90.30 ± 5.86	91.67 ± 6.31	
	30% Sucrose	78.58 ± 6.16	79.57 ± 6.53	
Body Fat %	8% HFCS	32.72 ± 11.24	32.51 ± 11.27	0.343
	8% Sucrose	31.07 ± 11.24	30.18 ± 11.54	
	18% HFCS	29.78 ± 8.95	30.29 ± 8.85	
	18% Sucrose	34.31 ± 11.08	35.06 ± 11.37	
	30% HFCS	39.24 ± 7.67	39.24 ± 7.65	
	30% Sucrose	29.54 ± 8.29	30.27 ± 7.52	
Fat Mass (kg)	8% HFCS	25.19 ± 11.44	24.86 ± 11.42	0.245
	8% Sucrose	28.36 ± 15.68	25.27 ± 11.98	
	18% HFCS	22.47 ± 7.62	23.04 ± 7.87	
	18% Sucrose	24.19 ± 7.61	25.24 ± 7.95	
	30% HFCS	30.26 ± 8.83	31.77 ± 10.70	
	30% Sucrose	19.69 ± 5.74	20.55 ± 5.44	
Fat Free Mass (kg)	8% HFCS	52.20 ± 9.99	51.98 ± 10.16	0.140
	8% Sucrose	57.89 ± 9.59	59.21 ± 9.62	
	18% HFCS	55.92 ± 13.46	55.69 ± 12.41	
	18% Sucrose	49.64 ± 11.70	50.10 ± 11.77	
	30% HFCS	49.12 ± 9.66	50.03 ± 9.82	
	30% Sucrose	50.28 ± 10.66	50.68 ± 10.89	

Note: Group assignment indicates the percentage of calories in the total diet consumed as either HFCS or sucrose**.**

Within group difference compared to pre, $p<0.05$ *, Within group difference compared to pre, $p<0.01$**, Change (post-pre) different than HFCS 8%, $p<0.05$ †

Table 4

Change in skeletal muscle fat over ten weeks of consuming sugar-sweetened low-fat milk

		Pre	Post	Interaction p value
Vastus Lateralis (g/100ml)	8% HFCS	3.32 ± 0.83	3.05 ± 0.56	0.210
	8% Sucrose	2.74 ± 0.69	3.05 ± 1.10	
	18% HFCS	2.94 ± 0.83	3.00 ± 0.73	
	18% Sucrose	3.16 ± 0.50	3.50 ± 1.15	
	30% HFCS	2.95 ± 0.91	3.11 ± 0.80	
	30% Sucrose	3.41 ± 0.51	3.21 ± 0.43	
Gluteus Maximus (g/100ml)	8% HFCS	4.64 ±1.47	4.56 ± 1.31	0.603
	8% Sucrose	3.50 ± 1.22	3.85 ± 1.43	
	18% HFCS	3.75 ± 2.04	4.16 ± 1.51	
	18% Sucrose	4.06 ± 1.29	4.44 ± 1.90	
	30% HFCS	4.28 ± 1.53	4.26 ± 1.47	
	30% Sucrose	4.53 ± 1.22	4.29 ± 0.70	

Group assignment indicates the percentage of calories in the total diet consumed as either HFCS or sucrose**.**

Table 5

Change in liver fat content over ten weeks of consuming sugar-sweetened low-fat milk
Percent Liver Fat Pre and Post Intervention

	Group	Pre	Post	Interaction p value
Liver(%)	8% HFCS	7.70 ± 7.12	9.40 ± 4.65	0.208
	8% Sucrose	19.23 ± 14.61	16.15 ± 15.64	
	18% HFCS	13.23 ± 4.48	15.62 ± 9.33	
	18% Sucrose	14.75 ± 13.86	12.83 ± 13.57	
	30% HFCS	13.30 ± 9.38	14.70 ± 8.47	
	30% Sucrose	9.70 ± 5.60	9.00 ± 6.29	

Group assignment indicates the percentage of calories in the total diet consumed as either HFCS or sucrose**.**

Table 6

Change in serum cholesterol and triglycerides over ten weeks of consuming sugar-sweetened low-fat milk

	Group	Pre	Week 10	Interaction P
Total Cholesterol (mmol/l)	8% HFCS	4.55 ± 1.33	4.61 ± 0.92	0.881
	8% Sucrose	4.49±1.11	4.38 ± 0.97	
	18% HFCS	4.43 ± 0.86	4.67 ± 0.86	
	18% Sucrose	4.70 ± 0.79	4.68 ± 1.05	
	30% HFCS	4.78 ± 0.85	4.89 ± 0.83	
	30% Sucrose	4.58 1.18	4.54 ± 0.79	
Triglycerides (mmol/l)	8% HFCS	0.79 ± 0.36	1.00 ± 0.41	0.623
	8% Sucrose	1.27 ± 0.44	1.23 ± 0.80	
	18% HFCS	1.02 ±0.36	1.07±0.67	
	18% Sucrose	1.14± 0.49	1.32 ± 0.64	
	30% HFCS	1.16 ± 0.35	1.45 ± .0.70	
	30% Sucrose	1.12 ± 0.68	1.46 ± 1.01	
HDL (mmol/l)	8% HFCS	1.41 ± 0.58	1.34 ± 0.39	0.150
	8% Sucrose	1.16 ± 0.26	1.15 ± 0.24	
	18% HFCS	1.18 ± 0.35	1.24 ± 0.37	
	18% Sucrose	1.37 ± 0.29	1.36 ± 0.23	
	30% HFCS	1.22 ± 0.20	1.20 ± 0.23	
	30% Sucrose	1.50 ± 0.29	1.41 ±0.26	
LDL (mmol/l)	8% HFCS	2.78 ± 0.74	2.81 ± 0.68	0.930
	8% Sucrose	2.75 ± 1.05	2.76 ±0.84	
	18% HFCS	2.78 ± 0.81	2.95 ± 0.85	
	18% Sucrose	2.81 ± 0.71	2.71 ± 0.82	
	30% HFCS	3.03 ± 0.85	3.03 ± 0.80	
	30% Sucrose	2.57 ± 0.96	2.47 ± 0.65	

Group assignment indicates the percentage of calories in the total diet consumed as either HFCS or sucrose.

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