

## LAY ABSTRACT

**Background:** We are currently conducting a research study comparing the effects of consuming beverages sweetened with two different sugars, fructose or glucose, providing 25% of energy requirements for 10 weeks in older, overweight and obese men and women. Current results demonstrate that both groups of subjects gained comparable amounts of weight (3 pounds). However, only the subject consuming fructose-sweetened beverages had increased accumulation of fat within the abdominal cavity, increased levels of lipids (triglycerides and cholesterol) in the blood, and reduced sensitivity to the hormone, insulin. These are changes that can increase the risks of developing cardiovascular disease and diabetes. It is a widely accepted hypothesis that increased levels of intra-abdominal fat causes reduced sensitivity to insulin by releasing a type of lipid known as free fatty acids into the blood. It is thought, that these free fatty acids then cause triglyceride (TG) accumulation in the liver, which reduces the effectiveness by which insulin can remove glucose from the blood and into the cells. Unexpectedly, in the subjects consuming fructose, levels of free fatty acids measured in the blood over a 24 hour period were not increased, however free fatty acid levels were moderately increased in the subjects who consumed glucose. This finding suggests that fructose may cause TG accumulation in the liver by a method different from increased free fatty acid release from intra-abdominal fat. We hypothesize that fructose consumption can stimulate the conversion of fructose into TG within the liver, thus providing a more direct route by which triglyceride can accumulate within the liver and cause insulin resistance. Furthermore, we hypothesize that consumption of a high fructose diet would result in increased liver TG content and reduced insulin sensitivity more rapidly than a high fat diet or a high glucose diet, even when the same number of calories of all three diets are consumed.

**Questions:** We are asking the following important questions: 1) Will rats fed a high fructose diet develop increased liver TG accumulation and reduced insulin sensitivity before they develop an increased amount of fat within the abdomen and increased levels of free fatty acids? 2) Will rats fed a high fructose diet develop increased liver TG accumulation and reduced insulin sensitivity more rapidly than rats fed equal amounts (in terms of calories) of a high glucose diet or a high fat diet? These questions are important because they will help to answer the questions whether and how the high sugar and high fat diets that are commonly consumed in this country lead to the development of cardiovascular disease and diabetes.

**Approach:** We will feed obese Sprague Dawley rats, that are susceptible to becoming obese and insulin resistant as adults, equal amounts of calories from diets containing high levels of fructose, glucose or fat for 1, 2, 4 & 8 weeks. We will measure the size of the intra-abdominal and extra-abdominal fat stores, the TG content in the liver, the TG and free fatty acid concentrations in the blood, and the sensitivity to the effects of insulin in all animals.

**Expected results and their effects:** We expect to demonstrate that liver TG content increases and insulin sensitivity decreases in rats fed fructose, before they develop increased intra-abdominal fat and free fatty acid levels. This finding will be important for showing fructose does not promote liver TG accumulation and reduced insulin sensitivity by the commonly accepted mechanism (increased amounts of abdominal fat leading to increased circulating free fatty acids). This is important for determining the mechanisms by which obesity is associated with increased risk of insulin resistance, cardiovascular disease and diabetes. We expect to show that the high fructose diet can promote increased liver TG content and decreased insulin sensitivity more rapidly than the high fat diet and the high glucose diet. This result will be important in demonstrating that even when different diets result in the same amount of weight gain, their effects on liver fat accumulation and insulin sensitivity are not the same, and therefore their effects on the risks for cardiovascular disease and diabetes risk may be different. These results will lead the way to more studies in humans to determine the amounts of sugar and fat, and the types of sugar and fat that can be consumed with a healthy diet that does not increase the risks for heart disease and diabetes.