Effects of SGLT-2 Inhibitors and Visceral Fat on Glucose Metabolism

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Introduction

Abdominal obesity and excess visceral fat, termed "visceral adiposity", has strong associations with insulin resistance, hyperglycemia and type 2 diabetes. However, the amount of visceral adipose tissue (VAT) in most individuals represents only a relatively small fraction of body fat burden, generally less than 15%. Persistent turnover of mesenteric triglycerides from this fat depot in spite of hyperinsulinemia delivers glycerol and fatty acids directly into the portal circulation, providing both a substrate for gluconeogenesis in the liver.

A previous pilot study provided evidence that participants with high VAT would have lower ^{13}C enrichment in glucose, compared with participants with low VAT. This signifies a greater endogenous adipose contribution of glycerol to hepatic gluconeogenesis. Alternative pathways theorized to influence the development of insulin resistance and mitochondrial failure include both the pentose phosphate pathway and citric acid cycle.

This study aims to expand this pilot project to an increased number of subjects, but also to evaluate the effect of a SGLT-2 inhibitor on these three pathways. SGLT-2 inhibitors inhibit renal glucose reabsorption in the proximal nephron. Over time, this drug has been demonstrated to cause weight loss, decreased systolic BP, slow nephropathy, and decrease hemoglobinA1C by 0.5-1.0%. Observed differences in pathways between high visceral fat subjects on a SGLT-2 inhibitor compared to control high visceral fat subjects could provide insight into the metabolomic physiology provided by SGLT-2 inhibitors.

Figure 1.

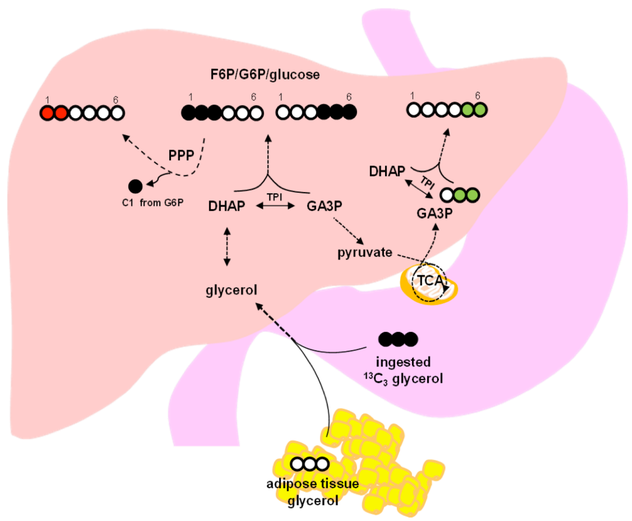

Figure 1. Glycerol-gluconeogenesis is directly interrogated by determining the fraction of $^{13}C_3$ enrichment in blood glucose using NMR spectroscopic quantification of ^{13}C-labeled glucose isotopomers. Total ^{13}C enrichment in plasma glucose is measured by the sum of all glucose isotopomers with excess ^{13}C. Additional information about specific pathways is derived from specific glucose isotopomers.

Methods and Results:

Subjects (n=15) participated after an overnight fast. These subjects were separated based on waist circumference, BMI, and other factors into high (n=8) and low (n=7) visceral adipose tissue groups. A peripheral intravenous catheter was placed, and 0.5mL of blood was drawn for glucose analysis. Glycerol was then provided following the formula below: Weight (kg) x 0.05 g/kg x 1 ml/1.302 g = [U-13C3] glycerol (ml). Participants drank the glycerol followed by 1 cup of filtered water to rinse the bottle. Blood samples were drawn at +15, +30, +60, +90, +120, +150, and +180 minutes for analysis. For each sample 0.5 ml of blood was used for blood glucose analysis and 40 ml of each sample was immediately centrifuged and stored on ice to be used for nuclear magnetic resonance (NMR) analysis described below.

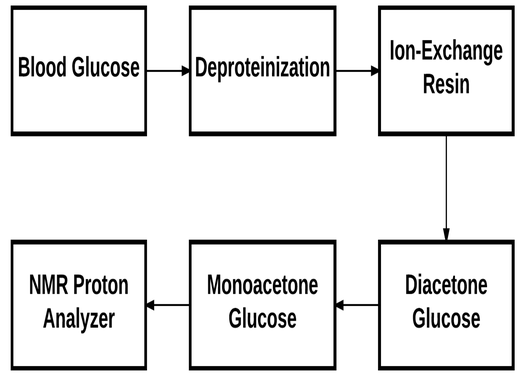

Figure 2.

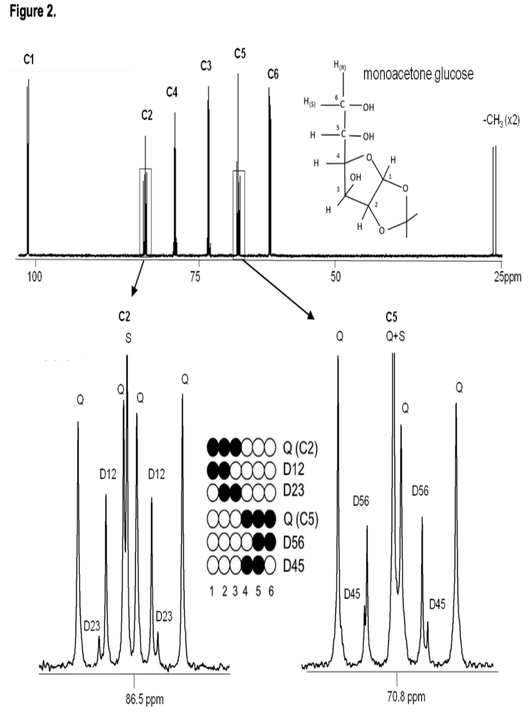

Figure 2. ^{13}C An overnight fasted participant with high VAT ingested [U-$^{13}C_3$] glycerol and blood was drawn at multiple time points. Glucose was converted to MAG for ^{13}C NMR analysis and the spectrum is from blood drawn at 180 min after the oral load of [U-$^{13}C_3$] glycerol. [1,2,3-$^{13}C_3$]- and [4,5,6-$^{13}C_3$] glucose were produced through gluconeogenesis directly from [U-$^{13}C_3$] glycerol. Gluconeogenesis via the TCA cycle produced double-labeled ([1,2-$^{13}C_2$], [2,3-$^{13}C_2$], [4,5-$^{13}C_2$] and [5,6-$^{13}C_2$]) glucose. Hepatic PPP activity produced additional [1,2-$^{12}C_2$] glucose.

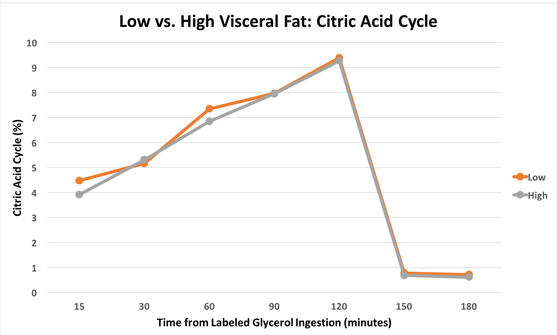

Figure 3. Contribution of the citric acid cycle to enriched glucose production. No observed difference was statistically significant during analysis of the preliminary data.

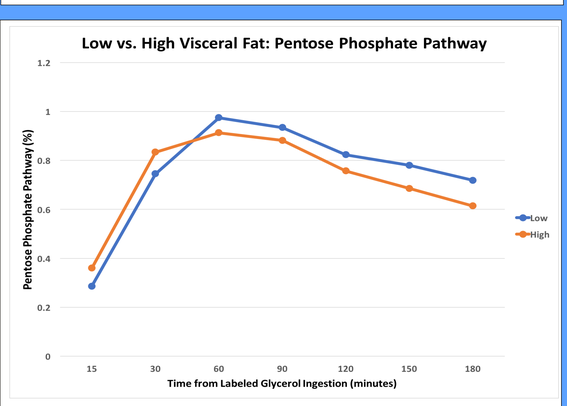

Figure 4. Contribution of the pentose phosphate pathway to enriched glucose production. Initial uptake arcs overlap; however, two-sample t-test using an average of values over 60min-180min interval demonstrates a p-value of <0.01.

Figure 5. Contribution of [U-$^{13}C_3$] Glycerol to Glucose Production. Initial uptake arcs overlap; however, two-sample t-test using an average of values over 60min-180min interval demonstrates a p-value of <0.001.

Discussion

Abdominal obesity and excess visceral adiposity (VAT) have strong associations with insulin resistance, hyperglycemia and type 2 diabetes. A previous pilot study showed that participants with high VAT have less enrichment in glucose, reflecting an abundant endogenous substrate pool from adipose turnover for gluconeogenesis compared with participants with low VAT.

Preliminary data from this experiment demonstrates significantly lower enrichment ($p<0.001$) and pentose phosphate activity ($p<0.01$) in the high VAT group when compared to low VAT.

This study aims to evaluate the effects of a SGLT-2 inhibitor, known to modify markers of VAT on gluconeogenic pathways in the liver. SGLT-2 inhibitors inhibit renal glucose reabsorption in the proximal nephron, inducing weight loss and decreasing systolic blood pressure. This medication has been suggested to reduce CVD event rates and lower hemoglobinA1c levels up to 1%. Observed differences in pathways between high visceral fat subjects on a SGLT-2 inhibitor compared to control high visceral fat subjects could provide insight into the physiologic changes provided by SGLT-2 inhibitors.

References

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