M&R Week 2 Metabolism Challenge question Answers and Explanations

Learning Objectives:

1. Outline the pathways for fatty acid and triacylglycerol synthesis.
2. List the major metabolic effects of insulin signaling; indicate which tend to be diminished during insulin resistance and which aren't.
3. Describe why people with obesity, metabolic syndrome and selective insulin resistance usually have elevated blood triglycerides and low HDL-cholesterol levels.

An asymptomatic 48-year-old man, presented to the clinic for a routine physical exam after having an abnormal health screening test for his work, which showed high cholesterol and elevated blood glucose. Other than a steady weight gain since college, his past medical history is unremarkable. He completes an activity survey, the results of which indicate that he is relatively sedentary. When asked to describe what he typically eats, he says that he avoids red meat and fatty foods, but really loves bread.

Physical Exam:
VS: T 36.0, HR 78, RR 14, BP 142/94, O2 saturation 97% on room air, Height 175cm (5 ft 9 in) weight 95kg (209lbs), BMI 31 kg/m_2
GEN: alert, oriented, no acute distress
HEENT: fundoscopic exam shows arteriovenous nicking bilaterally
CV: regular rate and rhythm, normal S1 and S2; LVAI is palpable in the 5th intercostal space, mid clavicular line, normal amplitude and duration
PULM: normal breath sounds throughout all anterior and posterior fields, no wheezing or rales
ABD: protuberant abdomen, normoactive bowel sounds; non-tender, non-distended
NEURO: decreased sensation to monofilament on plantar aspect of feet bilaterally

Labs (fasting):
Glucose: 186 mg/dL
HbA1c: 8.1%.
Total cholesterol: 280 mg/dL
Triglycerides: 360 mg/dL
LDL: 180 mg/dL
HDL: 26 mg/dL

1. **Insufficient inhibition of which enzyme is most directly contributing to his elevated triglycerides?**
   A. Adipose triglyceride lipase (ATGL)
   B. Cholesterol ester transfer protein (CETP)
   C. Glucose 6-phosphatase
   D. Lipoprotein lipase (LPL)
   E. Pancreatic lipase
   F. Phospho(enol)pyruvate carboxykinase (PEPCK)

Choice A: Adipose triglyceride lipase (ATGL) hydrolyzes the first fatty acid from triacylglycerols (also called triglycerides) within adipocytes. Hormone-Sensitive Lipase (HSL) comes next in the pathway and hydrolyzes the second fatty acid, leaving a mono-acyl glycerol (which is subsequently hydrolyzed by a third lipase). Both ATGL and HSL are strongly

inhibited by the action of insulin signaling. However, obesity and insulin resistance diminishes that inhibitory signal, and more fatty acids are released from adipocytes than is healthy. (There is usually enough insulin signaling to prevent massive adipose triacylglycerol hydrolysis and decrease of adipose stores, unlike in untreated type 1 diabetics who rapidly lose fat stores as they enter keto-acidosis). Hepatocytes absorb many of the released fatty acids and convert them back for triacylglycerol for storage and VLDL synthesis (see Selective insulin resistance and VLDL synthesis.pdf for more information).

B. Cholesterol ester transfer protein (CETP) is an enzyme in the blood stream that catalyzes the exchange of cholesterol esters and triacylglycerol between lipoprotein particles. This enzyme is not regulated by insulin and is not directly involved with causing elevated blood triglycerides in people with insulin resistance.

C. Glucose 6-phosphatase is required for glucose release from the liver and it's activity is most likely insufficiently elevated in this patient (contributing to his hyperglycemia and likely hyper-insulinemia). However, increased activity of glucose 6-phosphatase does not directly contribute to his elevated triglycerides.

D. Lipoprotein lipase (LPL) in capillary beds lower blood triglyceride levels by releasing the fatty acids from triglyceride-rich lipoproteins (VLDLs and chylomicrons). Normally insulin signaling in adipocytes leads to activation of LPL activity in adipose capillaries, allowing the released fatty acids to be taken up into adipocytes and re-synthesized as triacylglycerol for storage. Insulin resistance leads to lower LPL activity, not higher.

E. Pancreatic lipase is a digestive enzyme that is secreted into the lumen of the small intestine after a meal. It's activity is not insulin regulated and is not directly relevant to fasting triglyceride levels.

F. Phospho(enol)pyruvate carboxykinase (PEPCK) is a gluconeogenic enzyme and similar to glucose 6-phosphatase is most likely inappropriately activated in this patient. This contributes to his hyperglycemia but not directly to his hypertriglyceridemia.

2. **Excessive activation of which enzyme in his hepatocytes is most likely contributing to his elevated triglycerides?**
   A. Fumarase
   B. Glycerol 3-phosphate Acyl Transferase (GPAT)
   C. Hydroxy-methylglutaryl (HMG)-CoA reductase
   D. HMG-CoA lyase
   E. Very long chain acyl-CoA dehydrogenase (VLCAD)

Choice B: Glycerol 3-phosphate Acyl Transferase (GPAT) is the rate-limiting and highly regulated step in triacylglycerol synthesis. It is one of the enzymes that is highly activated by insulin signaling, even in during insulin resistance (part of 'selective insulin resistance'); see Selective insulin resistance and VLDL synthesis.pdf for more information.

1. Fumarase is a TCA cycle enzyme. It is not insulin regulated and not directly related to blood triglycerides.

C. HMG-CoA Reductase catalyzes the rate-limiting step of cholesterol synthesis. This patient likely has excessive HMG-CoA Reductase activity, leading to elevated cholesterol but not directly to increased blood triglycerides.

D. HMG-CoA lyase is an enzyme in ketone body synthesis that is not directly relevant to this case.

E. Very long chain acyl-CoA dehydrogenase (VLCAD) is a fatty acid oxidation enzyme. Increased activity of this enzyme might decrease fatty acid levels (because they'd be oxidized) but wouldn't lead to increased triglyceride levels.

3. List at least 3 others enzymes that are also most likely to be excessively activated in his hepatocytes and directly contribute to his elevated blood triglycerides.

In addition to increased GPAT activity, the following enzymes would also likely be increased in this patient who appears to eats lots of carbohydrates:

1. ATP-citrate lyase (provides cytosolic acetyl-CoA for fatty acid synthesis)
2. Acetyl CoA carboxylase (creates malonyl CoA for fatty acid synthesis and inhibition of CPT1 to inhibit fatty acid oxidation)
3. Fatty acid synthase

Recommended study materials:

1. Boards & Beyond lipid metabolism video and quiz
2. Feed-fasting cycle video (9:43) http://www.youtube.com/watch?v=sLcffnvNF7A
3. Fatty acid synthesis video (review from MCC) (7:41) http://www.youtube.com/watch?v=0F9V_XJYaGI
4. Selective insulin resistance and VLDL synthesis.pdf