My sweet heart was broken: Fat metabolism and diabetes in the heart

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Abstract

Production of triglycerides is how we evolved to circulate calories from the gut, to the liver, to the tissues. Triglyceride supplies our heart and skeletal muscles with fuel, and allows our adipose to efficiently store fat. Each triglyceride molecule supplies more than ten times the energy of a molecular of glucose; failure to transport, acquire and use triglyceride leads to energy deficiency and often death. But as is often the case, we can have too much of a good thing. In the blood excess triglyceride leads to pancreatitis, a clinical condition most often seen with poorly control Type 2 diabetes. In the heart excess triglyceride causes cardiomyopathy. My laboratory has focused on the transport, uptake, storage and pathological consequences of too much fat in the wrong places. 1) In the circulation, triglyceride is transported in lipoproteins and cleared via the actions of lipoprotein lipase (LpL) and hepatic triglyceride lipase. By inhibiting these enzymes we showed that triglyceride metabolism regulates LDL and HDL; hepatic lipase inhibition shifts LDL to larger, more buoyant particles and LpL inhibition reduces HDL cholesterol by >50%. 2) Genetic variations that regulate the activity of LpL correlate with cardiovascular risk, as do circulating triglyceride levels. LpL is expressed by macrophages within the arterial wall and, in contrast to its anti-atherosclerotic effects when expressed in muscle, macrophage LpL deficiency reduces macrophage function and atherosclerosis. 3) In the heart, oxidation of fatty acids from triglyceride produces to majority of ATP. Cardiomyocyte-specific LpL deletion leads heart failure with aging and with increased afterload. However, excess lipid accumulation can cause lipotoxic heart failure and ventricular fibrillation. Another source of heart lipids, non-esterified fatty acids, are also used by the heart and their efficient uptake requires endothelial cell expression of CD36. By defining the pathways mediating heart lipid uptake, we will test whether these forms of heart failure can be prevented. Heart disease(s) are about more lipids than cholesterol.