Insulin resistance and hyperinsulinemia are probably the primary causes of CHD in obese patients with metabolic syndrome. To complement the research readings on the IPHY 3700 Web site, I will discuss below the effect of insulin on carbohydrates (CHO) and lipids, and how insulin resistance and hyperinsulinism contribute to hypercholesterolemia and hypertriglyceridemia. I will also discuss the proposed mechanisms by which atherosclerosis develops.

**Atherosclerosis**

Atherosclerosis usually begins with some form of damage to the vascular endothelium. This damage can result from oxidative stress, due either to inflammation (doesn’t have to be local) or smoking (or other toxic chemicals such as street grade meth), or from some physical source such as hypertension. Atherosclerosis usually begins to develop during middle age and really is apparent in later years, simply because when we are young, even if markers for CVD are poor,
we have pliable vessels and we heal much better. As we age our vessels become increasingly more inelastic, due to breakdowns in connective tissues such as collagen and elastin and a decreased ability to repair free radical damage, and become more susceptible to injury. Anyhow, this initial injury results in the formation of a lipid patch. LDL is essentially transported across the endothelium into the damaged area. This lipid patch then begins to oxidize due to cellular secretions in that matrix. As the lipids oxidize, the protein portion of the LDL modifies with degradation, resulting in nonrecognition of it by the LDL receptor and therefore an increased uptake of LDL to “fill” the patch. Ultimately, this leads to a chronic inflammatory state which essentially keeps piling up the LDL/triglycerides and forms a fatty plaque. As this plaque grows, it activates expression of genes that contribute to arterial calcification. Furthermore, the plaque may reach a critical level at which it ruptures, resulting in a “clotting cascade” and development of a thrombosis or blockage. (Atherosclerosis: Basic Mechanisms. http://www.circ.ahajournals.org/cgi/content/full/91/9/2488)

**Insulin Activity**

Insulin acts in the body to allow the cellular uptake of glucose, storage of fats, and utilization of lipids as substrate for ATP formation. Regarding CHOs, insulin acts to signal the migration, primarily, of GLUT-4 glucose transporters to the cellular membrane, where glucose can then be transported into the cell. This occurs in many cell types, including muscle and adipose cells. In muscle and liver cells, insulin also triggers the cell to store glucose in the form of glycogen, for use at a later time. Regarding lipids, insulin also acts on the liver to promote lipid formation and exportation. Once glycogen stores are at capacity, glycogen formation is strongly suppressed and glucose is readily shunted down the path of fatty-acid formation. These fatty-acids are then exported from the liver in the form of VLDL. Incidentally, these VLDLs contain a significantly greater quantity of apoB, resulting in smaller LDL particles which are more atherogenic (more likely to cause atherosclerosis) that larger LDL particles. In the periphery, insulin acts on adipose tissue to store the triglycerides derived from the VLDLs as fat, inhibiting the breakdown of fats for fuel by inhibiting adipose hormone sensitive lipase. From a homeostasis perspective, it is essentially like your body telling its cells “hey, there is a lot of glucose available, store this fat for later and burn CHOs right now.” In the absence of insulin, adipose cells freely metabolize
triglyceride into FFAs to provide substrate for ATP formation. (Physiologic Effects of Insulin
http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/pancreas/insulin_phys.html)

**Insulin Resistance**

For reasons not entirely understood, insulin resistance is particularly common in obese individuals. This condition causes the beta cells of the pancreas to release more insulin than is necessary, because blood glucose levels are not falling and the stimulus to keep producing insulin is still present. The result is hyperinsulinism.

**Hypercholesterolemia**

Insulin acts on the liver to convert glucose to glycogen. When glycogen stores reach capacity, insulin acts to convert glucose into triglyceride. This triglyceride is preferentially exported from the liver to adipose tissue in the form of VLDL. VLDL is the precursor to LDL-cholesterol. The greater the rate of VLDL exportation from the liver the higher the resultant circulating LDL cholesterol levels will be. Here's a possible effect of low-carb diets: Remove insulin, remove the increased exportation of VLDL, decrease LDL-cholesterol. Even though insulin doesn’t work on peripheral tissues, in this case, it still works on the liver. Insulin isn’t necessary for the liver to transport glucose into hepatocytes.

**Hypertriglyceridemia**

The peripheral role of insulin is to essentially allow for the uptake of glucose and allow for the storage of fat via the storage of triglycerides within a cell. With insulin resistance, cells (specifically adipose cells) are not signaled/activated/whatever to store fat. Therefore the active uptake and storage of triglyceride is not occurring and therefore you have greater circulating levels of blood triglyceride. However, adipose tissue breakdown is occurring, because the insulin isn’t recognized/is blocked/whatever, and because the body cannot use glucose for fuel, resulting in the formation of fat and ketones which build up in the blood.