

## **Lipidaholics Anonymous Case 291 Can losing weight worsen lipids?**

As a result of the epidemic of insulin resistance (IR) plaguing the world, and for sure the United States, the evils of carbohydrates are becoming realized. Large numbers of patients are now following any one of the many low carbohydrate, and even Paleo diets. The internet is ablaze with information (some great, most anecdotal and some nonsensical) on this topic. Most IR patients have significant metabolic abnormalities including dyslipidemia, or as it more aptly should be called, dyslipoproteinemia: they have too many atherogenic lipoproteins; which after age and smoking, are the biggest coronary heart disease risk factors. Other common IR-associated metabolic abnormalities are hyperuricemia, hyperhomocysteinemia, hyperglycemia, hyperinsulinemia, low adiponectin, rising fructosamine and HgbA1C levels, coagulation abnormalities, inflammatory abnormalities, etc. About 80% of the IR patients are overweight (but 20% are not) and many are also hypertensive.

My thoughts on the nutritional approach to IR-related dyslipoproteinemia changed radically after being exposed to the writings of famed author, Gary Taubes and then meeting his cofounder of the Nutrition Science Initiative (NuSI), Dr. Peter Attia. For those of you who have not done so please pick up and read “Why Do We Get Fat (and what to do about it)” and “Good Calories, Bad Calories”. You will soon realize how wrong conventional nutritional advice is when applied to IR patients and also learn that fat is the only food that does not raise insulin levels and much of the traditional anti-fat nutrition advice is dead wrong for some people.

The case to be discussed below is actually rather common and likely many providers have had similar such patients. I became involved in this case last year when I was still in practice when the patient, a menopausal, formerly overweight woman found me on Twitter. In her words: *“I went low-carb/higher fat paleo (with dairy) about 1.5 yrs ago. I've struggled with weight all my life. Even though I've exercised religiously since high school and tried to eat healthy foods--even eating vegetarian for a couple of years--I still couldn't get lean. I'm 5'4" and my teenage/adult weight was always around 145-160, though my body fat wasn't (and isn't) particularly high due to a lifetime of exercise. I have not had diabetes, metabolic syndrome or hypertension, and am very active. I've been interested in nutrition/fitness since my teens and try to keep up with the latest to do whatever I can to live a long and healthy life. I started reading about paleo, low-carb and the benefits of eating whole-foods in early 2011 and thought it made sense. I thought it might help me get lean and it did. Over the last year I started thyroid hormone (levothyroxine 50 mcg) to correct hypothyroidism and use MHT (menopausal hormone therapy: Estrogel 0.06% plus Prometrium brand of progesterone 100 mg). I take vitamin D3 (1 000 u daily) and get Omega-3 FA from dietary sources.”*

*“My family does have a tendency toward higher cholesterol--three brothers (maybe all four, but I couldn't confirm one) and my mother are on statins. My mother, who will be 76 in May, was recently diagnosed diabetic and has some indications of heart disease but I'm not clear on what heart tests she's had. No other family members with heart disease*

*that I'm aware of. Most in my family are not big exercisers or overly concerned with their diet."*

*"I started eating paleo/low-carb (with dairy) in Apr 2011. I should add that my diet has never been ultra low-carb -- just lower-carb than most people. My last blood test before going paleo was in Nov 2010 and my past numbers have always been similar:"*

Total cholesterol = 196, LDL-C = 105, HDL-C = 75, TG = 78 (all in mg/dL)  
TSH = 2.15

*"I lost 30 pounds in about 3 months and have kept it off ever since. Today I weigh 124 and maintain my weight easily eating this way, even though I am menopausal."* The lipid panel was repeated on the new diet:

**TC = 323, LDL-C = 230, HDL-C 83, TG 49** (all in mg/dL)  
**Total LDL-P = 2643 nmol/L** (99<sup>th</sup> percentile population cut point)  
TG/HDL-C = 0.59 (poor man's marker of insulin sensitivity) Under 2.0 is excellent

#### **DAYSRING DISCUSSION:**

My goodness! If a new healthy looking, normal weight patient showed up with an LDL-C ~ 230 mg/dL, we are all presuming that familial hypercholesterolemia is present. At the age of 54 we would be searching for arcus senilis, a sternotomy scar or xanthomata. Although there is no premature CHD, there are certainly cholesterol issues in her family. Although we do not have a baseline LDL-P or apoB, how can one go from a perfect lipid profile to a seeming very high risk one in a very short period of time? Can CV lipid/lipoprotein-related risk be worsened by the weight loss? Or perhaps the question is - does it matter what one consumes to lose weight? Is there a danger too low carbs/high fat in some people? Or how about this absurd question - can an LDL-P of ~2600 nmol/L not be associated with atherothrombotic risk? It has been reported for years that diets high in saturated fat raise TC and LDL-C and diets with reduced saturated fat lowers them (Evidence Level IA in NCEP ATP-III). MUFA and PUFA can be neutral or lower LDL-C. MUFA may raise HDL-C. Of course we now know what any therapy does to CV outcomes likely has little if any relationship to what that therapy does to HDL-C but the story that raising LDL-C is associated with or causal of atherosclerosis is widely accepted.

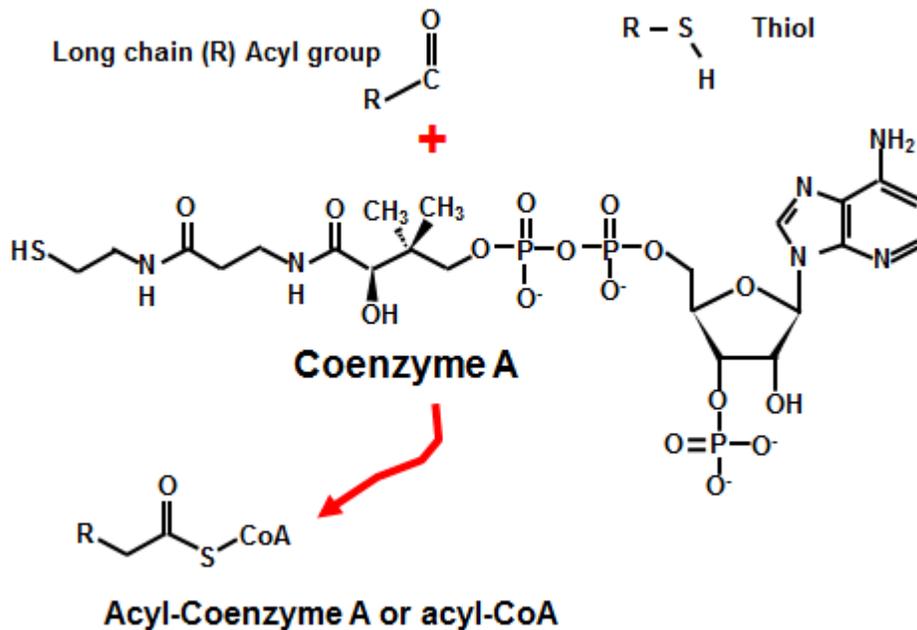
I and other lipidologists and many patients themselves are starting to see that the above lipid response to a high fat diet as not being very rare response in people who abandon carbs and replace it with saturated fat, especially so in those doing extreme carb restriction to achieve nutritional ketosis. Many of the patients who pursue this lifestyle did so because they were overweight and exhibited many phenotypic and metabolic markers of insulin resistance and were at risk for the associated morbidities. Carbohydrate intake reduction or avoidance in IR patients, regardless of how much fat is consumed, tends to tremendously improve insulin sensitivity: as measured by weight,

waist size, IR-related lipid parameters (TG, HDL-C), IR-related lipoprotein parameters (large VLDL-P, reduced large HDL-P, HDL size, LDL size, VLDL size, LP-IR score) inflammation biomarkers, metabolic (UA, homocysteine) and platelet coagulation biomarkers (urine 11-dehydrothromboxane B2). In many (including the patient being discussed) but certainly not all (the true incidence remains to be determined but experienced colleagues who have a lot of patients on low carb diets advise it is about 1/3 of patients) despite all of the above biomarker and waist size and BMI improvements there is a drastic worsening of TC, LDL-C and most worrisome of all apoB and LDL-P. There is little doubt after a review of the literature that the most important CHD risk factor apart from age and smoking is having too many atherogenic lipoproteins as measured by elevated apoB (LDL-P). In the US there are now 5 major CV subspecialty organizations that have signed on to use of apoB and LDL-P (via NMR) specifically the ADA, ACC, AACC, AACE, and NLA in appropriate patients (mostly the IR patients who are typically at high cardiometabolic risk). Of course for years nutritionists have been, and still are telling us, to avoid dietary fat and cholesterol or else LDL-C will go up and we all know how bad that is with respect to CHD risk – right? As always in medicine, there is more to the story.

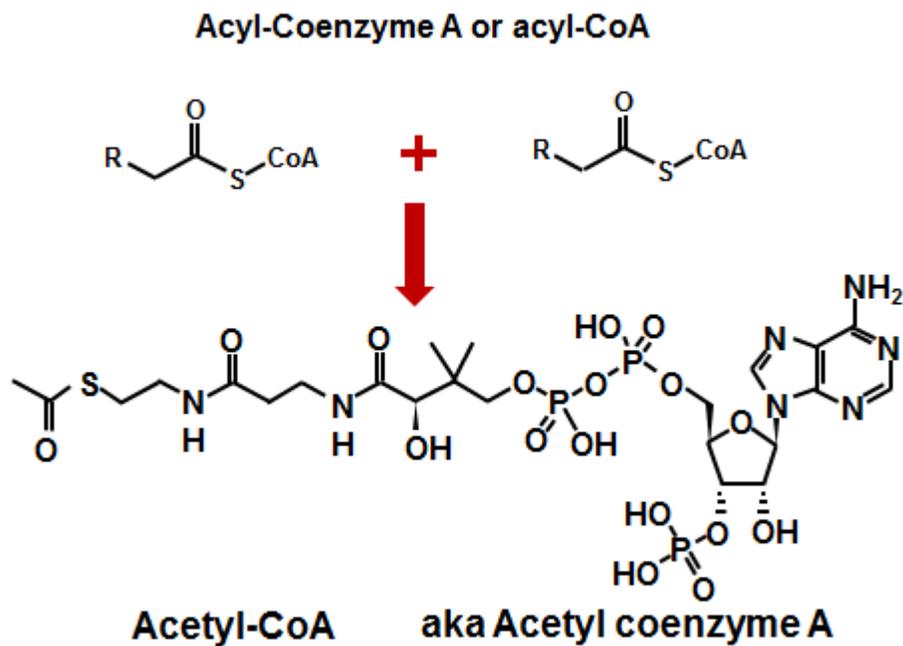
Let's get rid of the nonsense seen all over the internet that atherosclerosis is an inflammatory disease, not a cholesterol disease. That is baloney-with the reality being it is both. One cannot have atherosclerosis without sterols, predominantly cholesterol being in the artery wall: No cholesterol in arteries – no atherosclerosis. Plenty of folks have no systemic vascular inflammation and have atherosclerotic plaque. However clinicians have no test that measures cholesterol within the plaque – it is measured in the plasma. It is assumed that if total or LDL-C or non-HDL-C levels are elevated the odds are good that some of that cholesterol will find its way into the arteries and for sure there are many studies correlating those measurements with CHD risk. Yet we have lots of patients with very low TC and LDL-C who get horrific atherosclerosis. We now recognize that the cholesterol usually gains arterial entry as a passenger inside of an apoB-containing lipoprotein (the vast majority of which are LDLs) and the primary factor driving LDL entry into the artery is particle number (LDL-P), not particle cholesterol content (LDL-C). Because the core lipid content of each and every LDL differs (how many cholesterol molecules it traffics) it takes different numbers of LDLs to traffic a given number of cholesterol molecules: the more depleted an LDL is of cholesterol, the more particles (LDL-P) it will take to carry a given cholesterol mass (LDL-C). The usual causes of cholesterol depleted particles are that the particles are small or they are TG-rich and thus have less room to carry cholesterol molecules. Who has small LDLs or TG-rich LDLs – insulin resistant patients? After particle number endothelial integrity is certainly related to atherogenic particle entry: inflamed endothelia have inter-cellular gaps and express receptors that facilitate apoB-particle entry. So the worse scenario is to have both high apoB and an inflamed dysfunctional endothelium. Is it better to have no inflammation in the endothelium – of course! **But make no mistake** the driving force of atherogenesis is entry of apoB particles and that force is driven primarily by particle number not arterial wall inflammation: please see Ira Tabas, Kevin Jon Williams, Jan Borén. Subendothelial Lipoprotein Retention as the Initiating Process in Atherosclerosis Update and Therapeutic Implications *Circulation*. 2007;116:1832-1844.

So next let's review dietary fats and cholesterol as they relate to lipid measurements. Ingestion and small intestinal absorption of saturated fatty acids in some patients can lead to a hypersynthesis of cholesterol. Fatty acids are usually ingested as TG (triglycerides or more descriptive triacylglycerol) which are much too large a molecule to be absorbed. In the gut lumen a variety of pancreatic lipases hydrolyze the TG resulting into two fatty acids and MAG or monoacylglycerol (glycerol molecule with one FA attached) both of which can be absorbed. Once in the enterocyte long chain FA and MAG are reassembled into TG which are incorporated along with cholesterol, cholesteryl ester and phospholipids into apoB-48 wrapped lipoproteins called chylomicrons for systemic (lymphatic) entry. Note that TG carry mostly long chain FA as short and medium chain FA that are in the enterocyte can pass right into plasma and unlike long chain FA do not require a chylomicron to deliver them. Hence eating short and medium chain fatty acids (like the saturated fats in coconut oil predominantly lauric acid but also caproic, caprylic, and myristic acids in coconut oil) do not raise TG. But as you will see saturated fat in some can certainly drive cholesterol synthesis.

In those on low carb diets, fewer carbohydrates are available for energy, and that energy (adenosine triphosphate or ATP) must then come from fatty acids which are broken down by a catabolic (oxidative: oxidation = burning) process. Once in the cell, FA are "activated" utilizing a coenzyme A-derived enzyme called long chain fatty acyl-CoA synthetase resulting in the formation of fatty acyl-CoA or simply acyl-CoA. The cofactor coenzyme A is a thiol (a sulfhydryl or organosulfur compound – sort of a sulfur analogue of alcohols). CoA is made from cysteamine which is a metabolic product of the amino acid cysteine.

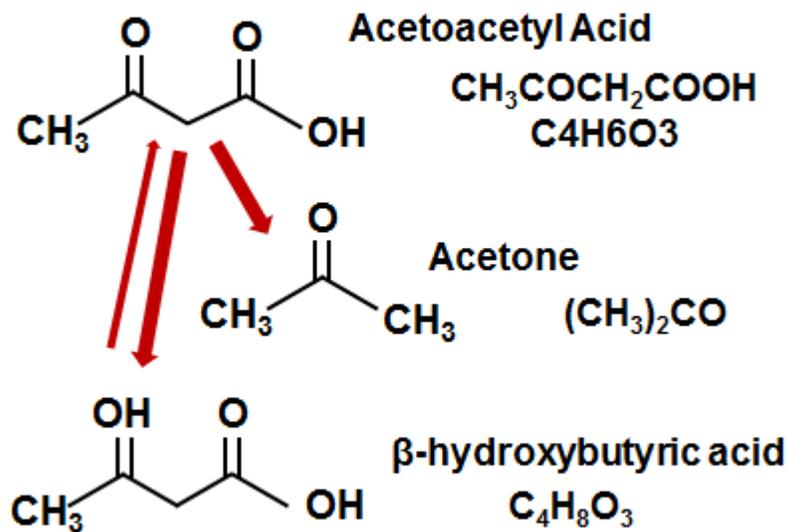


In mitochondria fatty acid acyl-CoA molecules are, via a multistep process, converted to two molecules of acetyl-coA, a thioester, whose function it is to convey the carbon atoms within the acetyl group to the citric acid cycle (Krebs cycle) where they can be oxidized for energy production. Thioesters are a product of esterification between a carboxylic acid (such as a fatty acid) and a thiol (e.g. Coenzyme A) and are compounds with the functional group C-S-CO-C where CO is the carbonyl group (carbon double bonded to oxygen).

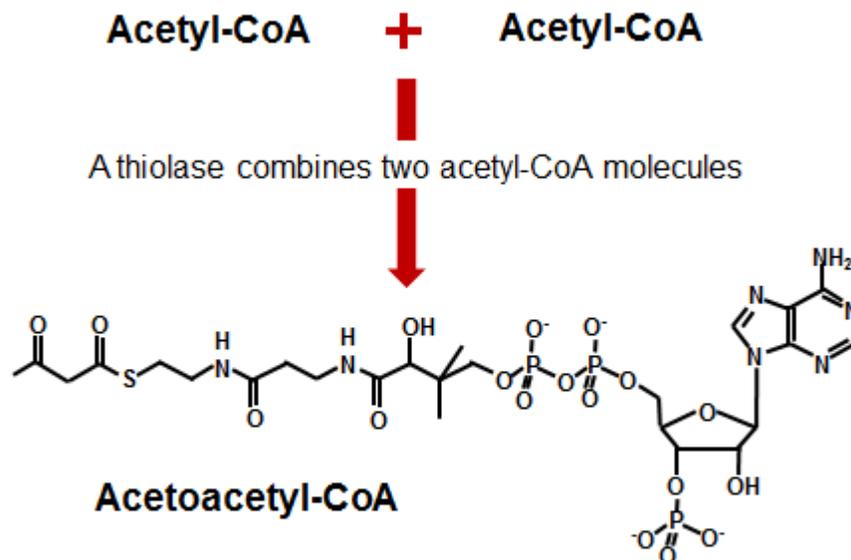


Acetyl-CoA is also available for various metabolic pathways including being converted to ketone bodies (which are actually not bodies or particles but simply water soluble molecules). The three classic ketone bodies are acetone, acetoacetic acid, and beta-hydroxybutyric acid.

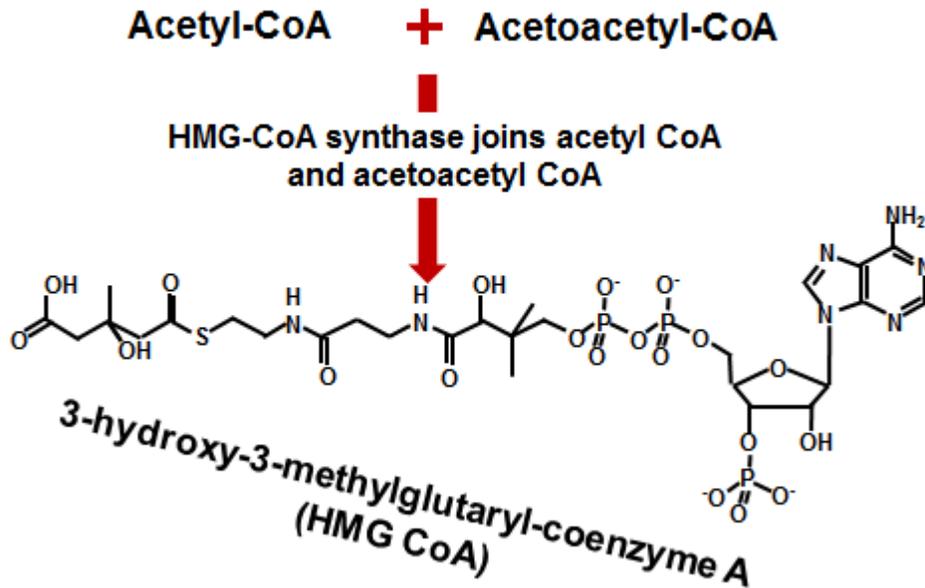
## Ketone Bodies



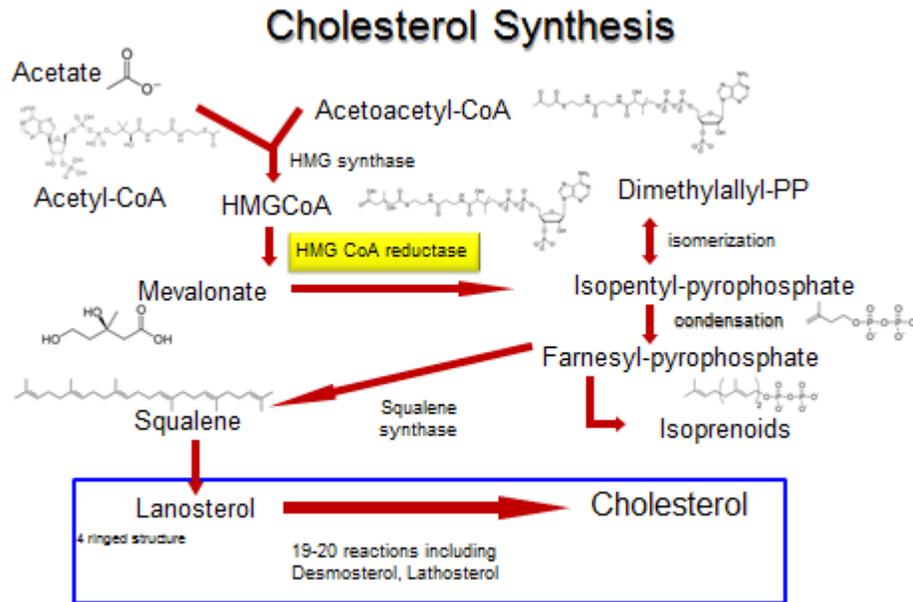
Those familiar with the multistep process of cholesterol synthesis (see my chapter in the textbook Therapeutic Lipidology) know that two acetyl-CoA molecules can be condensed to create acetoacetyl-CoA, the first step in the HMG-CoA/mevalonic acid pathway, leading to synthesis of isoprenoids like mevalonic acid and ultimately cholesterol.



The molecule 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) is formed from acetyl CoA and acetoacetyl CoA via the action of the enzyme HMG-CoA synthase.



The HMG-CoA molecule when acted upon by the enzyme HMG CoA synthase leads to mevalonic acid the major precursor to **cholesterol** synthesis. The multistep cholesterol synthesis pathway is illustrated in the following graphic.



Adapted from Dayspring T in Chap 14 Davidson, Toth, Maki Therapeutic Lipidology 2008

But the HMG-CoA molecule is also a precursor **ketone body** synthesis (especially when glucose is not around for energy): upon the action of HMG-CoA lyase it becomes the ketone body acetoacetate which if not utilized for energy can become acetate or  $\beta$ -hydroxybutyrate. A lyase is an enzyme that catalyzes the breaking of various chemical bonds by means other than hydrolysis and oxidation, often forming a new double bond or a new ring structure. Systematic names are formed as "*substrate group-lyase*" as in HMG-CoA lyase. Common names for lyases include decarboxylase, dehydratase, aldolase, etc. When the reverse reaction is more important, synthase may be used in the name.

So when ketone bodies are in excess,  $\beta$ -hydroxybutyric acid utilizes a dehydrogenase enzyme and converts to acetoacetate which can then enter the cholesterol synthesis pathway by joining with acetyl-CoA in reforming HMG-CoA which in turn then enters the cholesterol synthesis pathway. So no one should be shocked that substituting saturated fat for carbohydrates to improve insulin sensitivity can lead to cholesterol hypersynthesis. Some of the highest total and LDL-C levels I have ever seen were not in patients with FH but in persons with significant diabetic ketoacidosis (that has developed over several days) this process is in overdrive. Cure the dangerous ketoacidosis with aggressive glycemic therapy and the high cholesterol levels disappear virtually overnight. This likely also explains the severe lipid abnormalities seen in some Fredrickson Type V patients. It is well known that women with anorexia nervosa develop very high cholesterol concentrations in part through this same mechanism.

A liver synthesizing excess cholesterol (cholesterol synthesis biomarkers like lathosterol and desmosterol will be high) will attach it (along with TG) to newly formed apoB<sub>100</sub> creating increased numbers of small cholesterol-rich VLDLs or IDLs which after release

and peripheral lipolysis convert to LDLs, raising apoB and LDL-P and presumably CHD risk. Also since the liver cholesterol pool is increased there is decreased expression of LDL receptors and subsequent decreased clearance of apoB-containing LDL particles (further raising LDL-C and LDL-P).

Let's use this case to revisit the cholesterol synthesis pathway utilizing the ketone body acetone. With individual variability (likely related to genes) low carbohydrate or ketosis producing diets can lead to significant hepatic cholesterol synthesis. Conversion to cholesteryl ester (CE) leads to increased production and secretion of apoB containing lipoproteins which if TGs are not an issue are typically small, CE-rich VLDLs or IDLs (LDL precursors). The excess hepatic pool of cholesterol activates the nuclear transcription factor (NTF) called the Liver X receptor (LXR) which is the "sterol toxicity sensor." Despite its name LXR exists and regulates sterols in many tissues including but not limited to the liver. Excess cholesterol and xenosterols (sterols other than cholesterol) can cause cellular apoptosis and at times of increased cellular cholesterol concentrations the LXR activates gene response elements that lead to production of enzymes and receptors that facilitate a reduction in cellular cholesterol including:

- 1) Efflux of cholesterol from cells using sterol efflux proteins like ATP binding Cassette Transporters A1, G1 (ABCA1, ABCG1) which lipidate of HDL. This explains why some folks who have both high LDL-C and HDL-C. There is also increased efflux of hepatic cholesterol into the bile and enterocyte cholesterol into the gut lumen via upregulation of ABCG5 and ABCG8 (expressed at hepatobiliary interface and enterocyte/gut lumen interface).

- 2) Increased the conversion of cholesterol to bile acids via increased expression of enzyme 7-alpha-hydroxylase.

- 3) Down-regulation of sterol entry transporters like the Niemann Pick C1 Like 1 (NPC1L1) protein, which reduces entry of sterols into enterocytes and from bile back to liver. Thus typically hypersynthesis of cholesterol is associated with decreased absorption.

- 4) Decreased reabsorption of bile acids at the ileum via suppression of IBAT or ileal bile acid transporter. If bile acids are not reabsorbed, hepatic cholesterol will be utilized to synthesize new bile acids (see step 2 above).

For those advanced students seeking to better understand translational lipid biochemistry and the many NTFs, please see: [please click here to see the lecture on " Translational Lipoprotein Biochemistry](#)

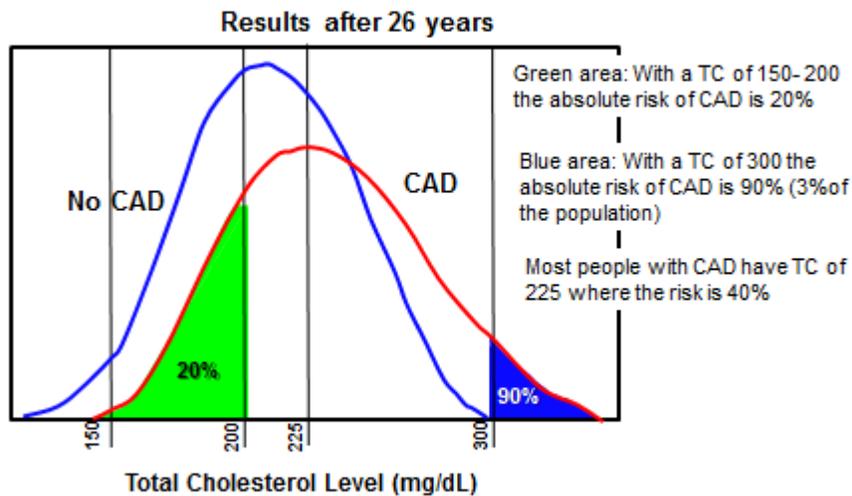
Many of the low carb and Paleo folks not only ingest increased saturated fat but also cholesterol (love their eggs and shellfish) – would one expect that to also contribute to the increased cholesterol levels seen in some? The answer is no:

The vast majority of cholesterol absorbed by the gut has an endogenous (produced by body cells) not exogenous (as in eaten) origin. Thus the proximal small intestinal unesterified cholesterol (the only type of cholesterol that can be absorbed) pool (which is

the pool subject to internalization into enterocytes) is on average 85% hepatobiliary derived cholesterol not of an oral/esophageal meaning eaten origin. In a typical human who absorbs ~50% of gut sterols, the majority of absorbed cholesterol will be of hepatobiliary origin (endogenously produced). Eating extra eggs or other cholesterol-laden foods (unless the intake is massive) will not change that. Also much of ingested cholesterol is in the non-absorbable form cholesteryl ester which must be de-esterified by intestinal lipases in order to be absorbed: no de-esterification, no absorption. In reality dietary cholesterol has little to do with CHD risk. Even NCEP ATP-III, 12 years ago stated dietary cholesterol causes marked hypercholesterolemia in many laboratory animals, including nonhuman primates but high intakes of cholesterol in humans, however, do not cause such a marked increase in serum cholesterol.

So with very high total cholesterol (TC) and LDL-C which are certainly classic risk factors for atherosclerotic risk, do we have to be very worried? If we go back to the Framingham Heart Study we would see in the population that the higher the TC and LDL-C the higher the CV risk. Yet if one looks at the distribution of TC levels and CHD risk what we see, depicted below is a bell shaped curve where some folks with high TC are at risk and others with the same level are not.

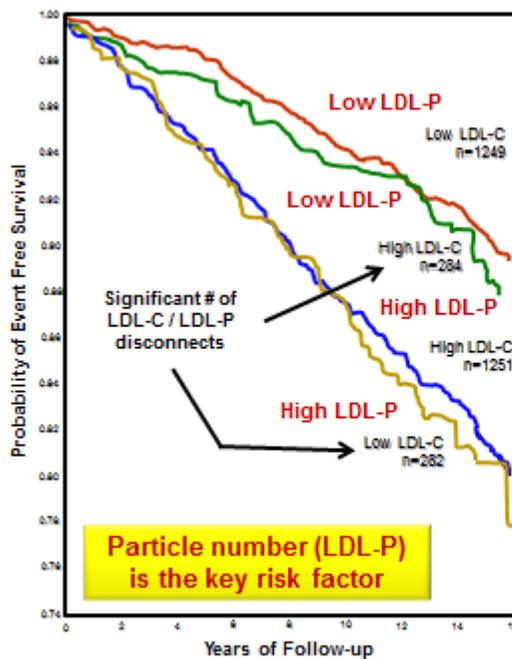
## Framingham Heart Study



Castelli, William. *The American Journal Of Cardiology*, 1998; 82: 60T-65T

Lipidologists, who see and follow patients with familial or nonfamilial hypercholesterolemia, have all seen the rare aged patient with horrific LDL-C as well as apoB who for whatever reason do not have atherosclerosis. So at least in that seemingly high-risk population there are exceptions to the LDL-C rule. We all know that in IR patients there are large numbers of high-risk cases with normal or low LDL-C levels who have horrific atherosclerosis, usually explained by their cholesterol depleted LDLs causing discordantly high apoB and LDL-P levels.

The classic study of the Framingham Offspring Study done by Bill Cromwell showed clearly that risk trafficked better with LDL-P, than LDL-C. In persons with elevated or reduced LDL-C, risk was pretty much related to LDL-P, meaning there are patients with high LDL-C who had excellent survival because their LDL-P was not elevated. Also those with lower levels of LDL-C but elevated levels of LDL-P did have CV risk.



### Framingham Heart Study Offspring Cohort

Event-free survival among participants with low-density lipoprotein cholesterol (LDL-C) and LDL particle number (LDL-P) above or below the median.

Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.

LDL-P was strongly associated with increased CVD risk in both men and women ( $p < 0.0001$ )

When data for men and women were combined, LDL-P was approximately twice as strongly related to CVD incidence as LDL-C

Cromwell W et al. J Clin Lipidol 2007;1:583-592

So is a low carb with high LDL-C and not high LDL-P is likely safe from CVD risk. But what about a low carb with both high LDL-P and LDL-C – check the Kaplan Meir survival plot above (blue line) in that group – Oh Oh lights out – dead men walking? The answer I often get from advocates of that lifestyle is that Framingham offspring is not a study of those on a low carb or paleo diet and thus does not necessarily apply to them and that is true and that is the dilemma.

Numerous studies have shown that high risk (80<sup>th</sup> percentile population cut points) LDL biomarker levels are:

- LDL-C > 160 mg/dL
- LDL-P > 1600 nmol/L
- ApoB > 120 mg/dl

For those new to that terminology- having a lab value at the 80<sup>th</sup> percentile cut point of a reference population means that 80% of the patients had a lower value and 20% had a higher value – With respect to LDL-C, LDL-P or apoB that would be associated with CHD high risk.

So, should the people who have this increased LDL-C and LDL-P response to a low carb or ketotic diet be worried? Have they simply gone from one type of CV risk to another. Usually the diet drives weight loss and improves many markers of insulin resistance (TG, glucose, insulin, etc). Some have proposed based on anecdotal experience that rise in LDL-P may be transient and take several months to return to normal theorizing there is confusion on the part of the body as to where and from what substrate to generate ATP. The big question right now really is: Are there persons who do not get atherosclerosis with apoB-cholesterol/lipoprotein levels greater than the above posted concentrations who do not get atherosclerosis? Can a human last long with atherogenic lipid concentrations above the 80<sup>th</sup> percentile population cut point? It seems for a small percentage of people that is true, but using existing trial evidence (which looked at folks on no specific diets or standard AHA low fat, low cholesterol type diets) they are rare exceptions, not the rule. Maybe one day someone will do a mega trial enrolling tens of thousands of low-carbers or paleo diet enthusiasts and follow them over many years to determine what happens to morbidity and mortality. But let's not hold our breath on that one? Could some sort of atherosclerosis trial utilizing imaging be done – i.e. carotid intimal thickening or coronary calcium? Before we use in them to advise a therapy is working or not working a trial relating positive or negative changes in those images to CV events has to be done. As of 2013, neither of those imaging techniques has shown in an empowered clinical trial that changes (good or bad) in response related to a given therapy are related to CV outcomes and no national CV guideline advises them to be used in that fashion. Right now CAC and IMT should only be used for risk assessment and even there coronary calcium is especially poor in risk assessment in women unless they are rather elderly and CIMT is only of value for screening when done by very competent professionals.

The patient was informed of all of the above and was given the option of altering the diet without returning to carbohydrates or using an LDL-P lowering medication, specifically a statin. The dietary advice was to cut back on saturated fat and use more MUFA and PUFA without increasing carbs. After doing just that for a few months the patient reports: *“The only modifications I've made because of my high lipids are eating steel cut oats regularly, adding chia seeds to my diet, and eating apples regularly (to increase fiber levels); cutting out most dairy; and watching my saturated fat intake a little more closely--all aimed at getting my high LDL-P down.”* Weight has remained stable.

Here are the follow up labs:

TC = 178, LDL-C = 92 (was 230), HDL-C = 82, TG = 21, Non-HDL-C = 96 (all in mg/dL)

Total LDL-P: 948 nmol/L (recall it was grossly elevated at 2643) < 1000 nmol/L (20<sup>th</sup> percentile population cut point) is desirable

Small LDL-P: < 90 nmol/L (normal)

LDL Size: 21.4 nm (quite large)

CRP was near 0.

Metabolic #s are all great.

Patient also notes: *“Testing confirmed I am a hyper absorber of cholesterol and plant sterols.”*

Synthesis marker: Lathosterol/TC: 31 (low)

Absorption marker: Campesterol/TC: 217 (normal)

Absorption marker: Beta-sitosterol/TC: 231 (high)

Couple of key points: Note those sterol markers are adjusted for cholesterol and are not absolute levels. Many believe especially in drug naïve patients, the absolute levels not adjusted for cholesterol are best suited to estimate risk in individual patients. In this case, I wish we had had absorption/synthesis markers prior to reducing the saturated fat as it is very likely in view of the very high LDL-C and LDL-P that the cholesterol synthesis was very high. The reduction of saturated fat certainly normalized cholesterol synthesis and elevated LDL-P. It is not at all unusual that when a person reduces cholesterol hypersynthesis that some increase in absorption occurs and that is what we are seeing here. However because the overall CV risk is now low, and the LDL-P is perfect the mild hyperabsorption likely has little if any consequences.

Another key point regarding absorption synthesis markers is that these change in response to nutrition, drugs, aging, other morbidities and they are not ever to be used as a onetime assessment. In at risk persons, like lipid and lipoprotein and other biomarkers, they need to be repeated with each and every blood draw.

So what conclusions do I have regarding patients on low-carb and paleo regimens who show the response of drastically aggravating LDL-C and LDL-P (apoB) together? Every trial, many of them quite large has associated those markers with atherogenesis and CV morbidity and mortality. But some folks are “outliers” and defy that rule. Could the low carb crowd be outliers and in them we can ignore LDL-C and LDL-P? The advocates of those diets say there is no study showing harm of elevated LDL-P and LDL-C in patients who have eliminated or drastically reduced their insulin resistance and inflammatory markers by low carb. That is true but what they want to ignore is that there is no data anywhere that shows they are an exception. Their belief is that by reducing all other atherosclerotic risk factors and normalizing their arterial wall and endothelial biology that, apoB-containing lipoproteins like LDL cannot enter the arterial wall. Although LDL-C and LDL-P in plasma are high none of the cholesterol content of the apoB-particles gains entry into the arterial wall. Is that plausible???? Sure! But is that also erroneous or wishful thinking? Sure? Does one want to bet their CV health or life on a plausible theory? Some do and some do not. Seems to me the first step is to do what this woman did: adjust the nutritional regimen. Now for those who want to live in a ketotic state – ketosis will not happen on this patients regimen, the options are then threefold – (1) stop repeating these measurements, keep your fingers crossed and go about life or (2) reduce saturated fat in the diet to whatever level does not cause cholesterol synthesis or (3) start apoB-lowering therapy, specifically statins or statin/ezetimibe depending on absorption/synthesis markers. Sometimes options (2) and (3) are needed together. Statins are not only among the most effective drugs ever created (have saved more lives than

anything but antibiotics and vaccines) but are also among the safest. I sometimes get a laugh out of those condemning drugs, especially statins, in favor of some therapy that has little outcome or safety evidence like supplements or various diets. Even diets may have adverse consequences!