Case # 281 Giving the jejunum its due!

I was asked by nutritionist about a patient who she believed was a good candidate for cholesterol/ noncholesterol sterol absorption testing. She is a post-menopausal (TD note: postmenopausal women are dead – I prefer the term menopausal women) 60 year old hypertensive female, whose height is 5'3" and weight is 133 pounds giving her a BMI of 23.5. She did gain 5-7 pounds through the perimenopause/menopause transition. Her BP is well controlled on lisinopril.

She had been started on simvastatin over a year ago because of an LDL-P, but the lowest it got was 1720 nmol/L. She now uses rosuvastatin (Crestor) 20 mg daily and her total LDL-P dropped to 1542 nmol/L. Current lab testing showed her TGs were mildly at elevated at 168 mg/dL but other recent testing showed a value of 106 mg/dL. Her Lp(a)-C & apo(a) mass are elevated and increasing. Her sdLDL-C remains high despite statin monotherapy.

The patient was following husband's vegan diet but more recently has reintroduced heart healthy animal proteins and decreased processed plant protein (veggie/faux meats, etc.), and grains. She has lost a few pounds in the last month. She maintains 150 minutes vigorous exercise/week regularly. She was using Caltrate with Vitamin D. but because of a low Vitamin D, an additional 5000 IU Vitamin D was added. Interestingly the nutritionist suggested Benecol (sitostanol) Chews.

The nutritionist then asked:

1) If she is a hyperabsorber and taking Benecol Chews (1.4g plant stanol esters/day), will her non-cholesterol sterols lab be affected by this? My guess is yes.
2) If she is a hyperabsorber, we should also see a decrease in LDL-P from when she was on statin monotherapy…Yes? And if so, by how much? I imagine adding ezetimibe should also be considered among therapeutic options – Do we monitor/treat absorption & synthesis markers along with LDL-P to goal? Anything else I need to know?

3) Other than the obvious (avoiding foods fortified with plant sterols), are there sterol-rich foods (i.e. nuts, corn, rice bran, flax, etc.) that we should be counseling hyperabsorbers to avoid?

DAYSPRING DISCUSSION

Those interested in cutting edge, aggressive CV risk assessment and treatment are staring to order markers of cholesterol absorption and synthesis. Although there is a learning curve, mastering this topic can elevate one's CV skills significantly. Cholesterol homeostasis ideally would be normal in everyone, but if it were we would not really need a specialty called lipidology. Although such homeostasis is regulated by each and every cell in the body, the two major organs that ultimately are the regulators are the liver and

intestine and both are equal partners. What one organ does to cholesterol is recognized by the other using complex signaling via nuclear transcription factors. Clinicians need to ask in persons with lipid and lipoprotein disorders, does the patient have hyper or hypo synthesis and absorption, both or neither. Having those facts at baseline will enhance risk assessment and guide both initial and subsequent treatment decisions.

What follows is a quick summary of sterol absorption and for additional info please go to http://www.lipidcenter.com/pdf/Understanding_Sterols_Stanols.pdf Sterols are steranes with an –OH group on one of the aromatic rings. Some refer to them as steroid alcohols. Again please see slid3 # one at http://www.lipidcenter.com/pdf/Noncholesterol_Sterols.pdf

Sterols are grouped into Zoosterols (only one and it is cholesterol) and phytosterols of which there are many, the most abundant in the human diet being sitosterol and campesterol. Cholesterol is a 27 carbon molecule with a hydrophilic –OH group at the # 3 position and an aliphatic lipophilic tail. There is a double bond between carbons 6 and seven. Molecules that have very similar sterol structures to cholesterol are collectively called noncholesterol sterols. A stanol is simply a saturated sterol (the double bind at C6-7 is gone. Both zoosterols and phytosterols are very prevalent in the modern diet. Even if one is a vegan, there is considerable cholesterol (of endogenous origin delivered in the bile) in the gut after a meal. On average humans absorb about 55% of the cholesterol and noncholesterol sterols that present to the jejunum. Only unesterified or free cholesterol (UC) can be absorbed, meaning cholesteryl ester (CE) cannot. Any CE that is eaten must be de-esterified by intestinal esterolases before in absorbed. All biliary cholesterol is unesterified (meaning it is readily available for reabsorption once it enters the jejunum. Stanols are not absorbed to any appreciable extent. Sterol entry into the intestine (from the gut lumen) or the hepatocyte (back flux from the bile) records a sterol influx transporter called the Niemann Pick C1L1 protein which surprise can be expressed at the gut lumen/enterocyte or hepatobiliary interface. However just because a sterol enters the enterocyte, it is only considered absorbed if it makes it into the plasma as a passenger inside a lipoprotein. Although some unesterified will make it into the surface of a chylomicron, the vast majority of the cholesterol within a chylomicron core is CE. The UC must be esterified to a long chain fatty acid by an esterification enzyme (ACAT) creating CE. Any nonesterified sterol is returned to the gut lumen by sterol efflux proteins called ABCG5 and ABCG8 (ATP binding cassette transporters). Phytosterols cannot be esterified so they are normally pretty much all returned to the gut lumen and do not get into chylomicrons and therefore do not gain systemic entrance. If you follow the above it is the balance of NPC1L1 (influx) and ABCG5, G8 (efflux) proteins that regulate absorption. And they are at play in both the jejunum and the hepatobiliary interface. Since phytosterols are not normally absorbed and only can be when there is more NPC1L1 expression than ABCG5, G expression they can be measured and used as a marker of sterol absorption. Boston Heart Lab uses sitosterol and campesterol and HD Labs uses both of them plus cholestanol (a stanol that reflects intestinal absorption). Lastly hyperabsorbers not only over lipidate chylomicrons but also HDL particles: excess UC in the gut can be effluxed via enterocyte ABCA1 sterol efflux transporters to unlipidated or prebeta HDLs.

Cholesterol synthesis is a complex synthetic process of 37 steps. The rate limiting enzyme is of course HMGCoA reductase: at the end of the chain just before cholesterol are the two precursor sterols, lathosterol and desmosterol. They serve as markers of cholesterol absorption. Boston Heart uses lathosterol and HD Labs desmosterol.

So high/low desmosterol or lathosterol levels signify hyper/hypo synthesis of cholesterol and high/low sitosterol, campesterol, cholestanol signify hyper/hypo absorption of cholesterol. In several clinical trials, but not all, hyperabsorption of sterols is a CV risk factor and hypoabsorption is associated with good CV outcomes. Hypersynthesis is usually associated with CV risk. Interestingly since there is an inverse relationship between synthesis and absorption, hyperabsorbers tend to be hyposynthesizers and vice versa. If you think about it a hyperabsorber of cholesterol will have lots of chylomicron delivery of cholesterol to the liver. If the liver is receiving extra cholesterol, the synthetic process is down regulated and there will be little production of HMGCoA reductase: such patients will have high sitosterol/campesterol/cholestanol levels and reduced desmosterol or lathosterol levels. If a patient's cell are overproducing cholesterol there will be a down regulation of NPC1L1 and upregulation of ABCG5,G8 in the gut and hepatobiliary interface and there will often be hypoabsorption of cholesterol. It is not uncommon for a drug that inhibits synthesis to cause an increase in absorption and vice versa, an absorption inhibitor will often increase synthesis. A potent way to restore abnormal cholesterol absorption/synthesis abnormalities in at risk patients is to use a statin with an absorption blocker. So back to the case and the questions posed:

Question 1. If she is a hyperabsorber and taking Benecol Chews (1.4g plant stanol esters/day), will her non-cholesterol sterols lab be affected by this? The answer is indeed yes: absorptive sterol measurements should go down in someone taking Benecol. The stanol (Benecol is sitostanol) displaces sterols from biliary micelles and those displaced sterols are then excreted in the stool. Once the micelle attaches to the microvilli of the jejunal enterocyte stanols unlike sterols cannot be absorbed to any appreciable degree and they are also excreted in the stool: thus the previously high markers of absorption, namely levels of sitosterol, campesterol and cholestanol should drop. If they do not a more potent sterol absorption inhibitor like ezetimibe (Zetia) will be needed.

Question 2. If she is a hyperabsorber, we should also see a decrease in LDL-P from when she was on statin monotherapy…Yes? And if so, by how much? The answer is yes but instead of the usual 30-35% LDL-P reduction typical of a statin, it would be a hypo-response - typically 10-15%; When statins do not lower LDL-P as much as one would suspect you have to think hyperabsorption is present.

Question 3. I imagine adding ezetimibe should also be considered among therapeutic options – Do we monitor/treat absorption & synthesis markers along with LDL-P to goal? Yes, adding ezetimibe can help a statin achieve LDL-P goal, as well as lower phytosterol

levels, especially in a hyperabsorber. However, even in a person with normal absorption, ezetimibe will still work, as it makes a normal absorber a hypoabsorber. If less cholesterol is delivered to the liver, additional hepatic LDL receptors will be upregulated

Question 4. Other than the obvious (avoiding foods fortified with plant sterols or using sterol supplements), are there sterol-rich foods (i.e. nuts, corn, rice bran, flax, etc.) that we should be counseling hyperabsorbers to avoid? Answer: A hyperabsorber does not have to avoid vegetables per se: but they should not supplement with additional phytosterols or foods fortified with sterols. If LDL-P is high in someone with an increase in absorptive markers, then they need ezetimibe or if indicated for other reasons a fibrate (which also reduces intestinal absorption of sterols). Drastic reductions in absorption can occur when combining sitostanol (Benecol), ezetimibe and fenofibrate (never use gemfibrozil with ezetimibe).

Finally, if you see normal absorption and synthesis markers but high apoB and LDL-P: Suspect decreased clearance of LDL particles (defective apoB, LDL receptor issues, Familial hypercholesterolemia including PCSK9 gain of function mutations, and TG driven LDL-P, etc.

TAKE HOME POINTS: Please do not think there are no treatable risk factors remain when lipid concentrations and even apoB are at goal. If you get a hyporesponse to a statin: investigate absorption! Seek and ye might find! Baseline markers of absorption and synthesis which need to be repeated on therapy will take you to the next level of Therapeutic Lipidology. Here is why you need to utilize sterol testing:

1) Identify patients with homozygous or heterozygous phytosterolemia or patients with likely genetic variants in *ABCG5* or *ABCG8*, or over or under expression of NPC1L1.
2) Identify patients for whom ezetimibe or sitostanol should be part of the therapy. There would be little reason to prescribe statin monotherapy to a patient who hyperabsorbs cholesterol. However, since ezetimibe monotherapy induces over synthesis of cholesterol it should not be used as monotherapy (other than true phytosterolemia) but preferably with a statin to maximize LDL lowering.
3) Identify patients on ezetimibe monotherapy who might benefit from addition of a statin, fenofibrate or sitostanol.
4) Identify statin-treated patients who have drug-induced increased sterol absorption and who would therefore likely benefit by the addition of ezetimibe, sitostanol or fibrate, or statin-intolerant patients who might respond well to fenofibrate/ezetimibe.
5) Understand why certain patients have atherosclerotic events with unremarkable levels of standard lipid concentrations, i.e., phytosterolemia or variant thereof.
6) Part of the thorough investigation of anyone with xanthomas.

7) To diagnose cerebrotendinous xanthomatosis (CTX) with cholestanol measurement.