## LDL on LCHF - Dr. Sarah Hallberg

We are here tending to be talking

about what for many people is an incredibly controversial topic - Low-carb.

Well, within this controversial topic, I get to talk about the controversial topic.

Yes! Okay.

So, but, I'm not here to pronounce that, okay,

I'm here to say this is the answer

or that is the answer, or that anybody has the answer.

What I'm actually here today to talk about is the questions that we have,

because a lot of people would consider low-carb high-fat maybe even a fringe topic.

And what I do is not fringy,

what I practice is science.

I have a science-based practice.

And when you have a science-based practice,

you have to not only understand what's known,

you also have to be constantly asking questions,

understanding those questions,

about what isn't yet known and looking for answers for those questions.

And I'm going to kind of try to cover that in a very brief bit here.

But really quick first, kind of a quick background on me and how I got here,

talking about this today.

So, I actually started out as an exercise physiologist.

Didn't want to go to med school from age 5,

actually did it once I got accepted to get my PhD.

I always joke around that I was the only person who disappointed their parents,

when I said I was going to med school,

because my parents were both PhD's and that was supposed to be my path

and then I changed my mind halfway.

But, anyway, then I became an internist and I practiced primary care for a while,

actually almost 10 years,

but always obviously based on my background as an exercise physiologist,

had this interest in weight loss.

So, when any University health wanted to open weight loss program,

they came to me and I was glad to do it.

And people always say "How did you come upon low-carb for your practice?"

and I said "Because when they asked me to do this, I wanted to do a good job

and I went to the science and that's what was working.

That's where we had evidence, really helped."

So, my practice from day one has been only low-carb-based, that's what I do,

I run a low-carb practice.

And yes, my practice is called medically supervised weight loss,

but one of my goals this year is to convince IU

that we want to change the name, because weight-loss is secondary to me.

I run a metabolic health practice and that's really important to me.

And within this, when I realized some of these changes

that we were seeing in cholesterol on our patients,

I said "Okay, I need to understand this even more."

And so, I'd already had my obesity certification,

but I went back and got board-certified as a clinical lipidologist too,

because I wanted to really understand this,

I wanted to be able to understand the questions.

So I have our goals here and I put this here more than anything for me,

because I will tell you right now,

that I could talk about this topic for three hours, maybe six.

So I got to keep myself on track and I'm going to try my best

to keep us out of the weeds on a lot of this stuff.

But, number one I want to review some of the known and unknown

about LDL on a low-carb diet

and we're going to review a little bit on LDL-C, LDL-P, and small dense LDL,

just a little bit of the physiology.

What does the current literature tell us?

What are some of the possible mechanisms for rise in LDL?

Understand the questions that remain.

And again, I think that's the most important part.

And then I want to tell you about a research project

that we have going on in my clinic right now,

to try to get to the bottom of some of those questions.

So, what do we know about LDL on a low-carb high-fat diet?

Well, we know that saturated fats cause a rise in LDL-C and LDL-P in some people.

And we also know that there are many studies

that show us that low-carb high-fat will decrease small dense LDL.

Okay? So, those are both pretty well-established.

What do we not know?

Well, actually this list is pretty long.

What is the exact percentage of patients who have a rise in their LDL?

I mean, those of us who do this, who practice this clinically,

absolutely understand that most people do not have any problem with their LDL,

whether you are talking about LDL-C or LDL-P.

They do a low-carb high-fat diet and their LDL doesn't change,

or, just a surprise to many in the mainstream,

eating a lot of fat makes your LDL better.

But we all know also, that there's a subset of patients that that's not true on.

How many exactly and not only that, but how many in different demographics?

What if you are insulin resistants, what's the percentage there?

What if you're insulin sensitive?

And can we identify patients who are going to have a rise ahead of time?

Is that possible?

How much does LDL-C rise in if we correlate it with LDL-P?

And does rapid weight loss temporarily increase LDL in some patients?

And we will talk about that a little bit.

And how much improvement in small dense LDL?

And again, the demographic difference in this area, as well over time.

And how about the amount of carb restriction?

And then, I'm going to cover a little bit about residence time of LDL particles.

But ultimately here is the big question.

Does a rise in LDL-C or LDL-P represent

increased risk in that percentage of patients?

Where we see this? I don't know, I don't know.

I don't think anybody knows that for sure.

Okay, so, real quick, LDL-C.

What does that mean?

This is the one we're used to looking at. Right?

This is what everybody always orders.

I don't. I don't order standard lipid panel in any of my patients anymore, I order NMRs,

because I think that LDL-C is not what we want to be looking at,

I don't think it tells us enough information.

What does it exactly mean?

It just tells us how much cholesterol is in our particles.

Just the cholesterol - it doesn't tell us anything about the particle itself.

So, really quick again, without getting too much in the weeds here.

And this goes back to our insulin resistant patient, okay,

those with high triglycerides.

Patients who have insulin resistance, who have this high triglyceride levels,

they are secreting these big triglyceride rich VLDL particles. Okay?

And these are problematic all by themselves,

because these big particles here, increase viscosity,

they cause endothelial dysfunction,

increase in hyper coagulable state.

So, all by themselves are problems.

But then they become even bigger problems.

Because, what happens is,

number one - we get this broken down, these big VLDL particles,

the triglycerides get pulled out from them

and we get this very cholesterol rich remnants, okay,

which are probably problematic.

Then, we get this exchange.

Cholesterol ester transfer protein right here, okay,

is constantly exchanging the core of these particles

with other LDL and HDL particles.

And when that happens, and the hepatic lipase comes along

what happens is we form this small LDL particles.

So this is why when someone does a well formulated low-carb high-fat diet,

we get improvements in the triglycerides.

But then, what that leads to,

and it's probably incredibly important here,

is that, that leads to less of these small LDL particles.

So then we get to this LDL-P number, which is what I'm much more interested in.

And we can see from-- because of that physiology that we just on the last slide,

what we can have is two very different situations,

with the exact same LDL-C number.

So, you're carrying around the same cargo, your LDL-C number is the same,

but the number of particles that that LDL-C is being carried in,

is very different.

So, if we have those small dense particles

and you're carrying around a LDL-C of, let's just throw it out and say 70,

well, if they are all small,

it's going to take a lot more of those particles to carry that cargo, that 70.

Where is if we have the larger ones?

Again, this is what we tend to see in a low-carb high-fat diet,

it's going to take a lot fewer of those. Okay?

So, our particle number is going to be important and we missed this, totally,

if we just look at the standard lipid panel.

All right, so then we've got the small dense

and because all heard it may pattern A, pattern B.

Again, pattern A big, pattern B is that small dense, right,

more problematic, lipoprotein particles.

Okay, so, let's go over some of the research.

So, this study first of all--

I'm not going to cover all the research first of all, that we have here,

I mean, there's just tons.

And the ones that I'm covering are only ones where they actually looked at NMR data.

So they didn't just look at the LDL-C.

So, here we go - in 2003 healthy normolipidemic women

on a very low-carb versus low-fat diet, for six weeks.

And what I have in each of these slides bolded is the demographic.

And I think that's important, because what we can see

is that we've covered a lot of demographics on this topic

and we we'll find here that the results are pretty consistent,

despite the difference in demographics.

So, we have an increase in LDL-C compared to low-fat for the low-carb group,

no change in relative percentage of concentration of LDL,

subclassed versus low-fat.

Three of the 10 who wound up with the more problematic pattern B

had an increase in their LDL size. Great!

And this was eucaloric.

Alright, so, here we go - look at the demographic different.

Now, from normal women, we went to overweight men.

Low-carb, very low-carb again, versus low-fat for six weeks.

LDL-C not significantly changed in the low-carb group here.

Increase in a large, decrease in a small.

Fantastic. Right?

All looks good.

75% of pattern B switched to pattern A.

No change in oxidized LDL.

Urine ketones and food diaries were used to make sure that these people were following.

One pattern A switched to pattern B.

Oops!

Okay, so what do we say? Sucks to be you. Right?

I mean, but, wait a minute... we can't say that!

We can't say that! Right?

Because, I'm a doctor running a clinical practice

and just because our averages are good,

doesn't mean I can ignore this guy. Right?

I care about him, too! And what happens to him matters.

And I will tell you that I see this, I see this all the time.

I see this in patients who are following a ketogenic diet,

who are clearly listening to me, their ketones are high,

They are having dramatic improvements in their A1c,

yet, their triglycerides are up,

their small dense rise significantly,

their LDL-P is way high.

It's not the norm, it's definitely not the norm, but it happens.

Alright, so, next one.

Again, look at the demographic.

Severely obese patients, 86% with diabetes or metabolic syndrome,

very low-carb versus low-fat, for six months.

LDL-P decreased the same in both groups... the same, a decrease.

Only the amount of weight actually correlated significantly

with the decrease in LDL-P.

Both diets increased large LDL, decrease small LDL.

They both worked in this case.

Diet recall was the method used.

Big drop out rate, big drop out rate in the study.

And some of these patients were on lipid lowering medication

and of course we all know that that matters.

Okay, so, here we go. Another different emographic.

Obese patients treated with statins who had pre-existing coronary artery disease.

This is a really interesting study.

So, basically they just told these guys, "Alright, eat bunch of meat."

I mean, "I want you to eat half of pound of beef at every meal."

I mean this was kind of the dietary instruction that these guys were given.

And they were checking ketones, but the interesting thing is,

they were checking ketones to try to try to make sure people were in ketosis.

And they were confounded by why some of these people were actually in ketosis,

given this instruction, "Eat only meat and cheese".

So, anyway, just very interesting, very interesting.

But, 10 out of 23 patients had metabolic syndrome at baseline

and of those, 8 out of 10 reduced or resolved.

One non-metabolic syndrome patient developed it.

It happens, it happens! Even on meat and cheese.

2009 abdominal obesity, at least one other metabolic syndrome risk factor,

very low-carb versus low-fat for 52 weeks.

Trend up in Apo B in the low-carb group, but it was not statistically significant.

Beta-hydroxybutyrate was higher in the low-carb group,

but, quite frankly it was still low, if you look at the numbers.

Isocaloric, food diary was used.

2005, overweight hyperlipidemic versus very low-carb versus low-fat six months.

No difference in LDL-P - both went down, they both went down.

Again, really great, wonderful!

Large LDL increases in 54% of the low-carb group,

unchanged in the low-fat group.

Decrease small dense. Okay.

So, alright, so we know that this happens in some people,

we know we just looked here.

We can see that even in this different demographic groups that I just pointed out,

the trend is the same.

When we look at the groups, things are better, they are just better.

But, individually, that's not always the case.

So, why do some people have a rise in LDL-P or LDL-C?

Well, there's a lot of different reasons that this may occur,

but one thing that is really interesting here because I pointed out specifically,

because I'll tell you what I see in a specific subgroup.

I see people who are insulin resistant

and they go on a low-carb high-fat diet,

everything gets better across-the-board.

Oh my gosh!

You know, their LDL is better, their diabetes has been resolved,

their triglycerides are way down - they are better.

And a year later, they've maintained their weight loss, all that stuff looks good,

except for all the sudden their LDL is up.

It wasn't before, initially, it was later.

It's like an insulin sensitive problem that they've developed.

And I think that there may be a mechanism as to why that occurs.

Because if we see here and we talk about insulin and Apo B,

what we see here is, insulin is supposed to come and bind to the receptor,

and it activates insulin receptor substrate,

which activates phosphatidylinositol... I'm going to probably botch this,

phosphatidylinositol 3-kinase, which then activates Akt,

which is a huge branch point here, a really important one.

Because Akt does two things, it blocks Fox 01.

And why is that significant here?

Fox 01 will then shutdown gluconeogenesis,

the blockade of that will turn off gluconeogenesis

and it will also down regulate something called MTP,

microsomal transfer protein, which is what lipidates VLDL.

So, this action of insulin coming in, if this all functions properly,

will actually decrease Apo B.

That would be good.

But what if we are really low now on our insulin,

because now we are not insulin resistant anymore,

we are insulin sensitive, we are following a low-carb diet properly,

we are doing a great job with it.

Now our insulin levels are really low.

Could we have just introduced a problem in some people with this mechanism?

It possible, it's possible.

Now, again, and I'm going to try to not get here too into the woods,

but, mTOR also plays a role in here. Okay?

And big thing to understand, really basics,

Insulin - growth factor, mTOR - growth factor...

They can be problematic.

And what we see with insulin resistance,

is that the blocking Fox 01 does not occur,

however mTOR still gets activated.

So we still have our growth going, but this time we are blocking the Fox 01,

which essentially, if we can get that blockade would shut down the Apo B.

So, we can kind of see here, how this could run into a problem.

Okay, so then, the other thing too, and I just want to--

again, I won't get too much into this, but I want to point out one thing.

And that is that, when carbs are low, glucose is low, okay,

we need to oxidize fat for energy.

I mean, we all accept that, we understand that.

And when fat gets oxidized, we make Acetyl-CoA.

And one thing I want to point out is,

Acetyl-CoA is the beginning of ketone bodies,

but it's also the beginning in making cholesterol.

So, it can go both ways, it can go both ways.

There's many reasons why it would do one over the other,

but the other thing is there's going to be individual variance in this, very much so.

Okay, so, LDL residence time.

And I think this is really important. Okay?

So, this could be a big protective mechanism

even in these people who have higher LDL-P's.

Because, maybe their LDL-P is high, but we've got this constant circulation,

so any LDL-P particle is not in the circulation for long.

Small dense, LDL lasts four about 5 days.

Large, 2 days.

That's a big difference.

So, even in this people who have a rise in LDL-P.

Is it possibly not problematic, because they are just constantly circulating this?

That's possible.

There's more oxidative damage in these "aged" small dense LDL particles.

Okay, so, here is an interesting thing.

I mean, a lot of people who will criticize low-carb high-fat,

will point to the Scott M. Grundy trials, from a while ago,

that showed that saturated fat will decrease our LDL receptors.

And if you go back and look at that, the problem is that, yes,

they were on a high saturated fat-diet,

but they were also one a high-carb diet, it was a high both.

So, I think it's very difficult to then move that and say

"We are comparing apples to apples here,

when we are talking about a low carbohydrate diet", very difficult.

And one of the big reasons may actually be PCSK9's,

because anyone heard of the PCSK9 inhibitors the other, the big things. Right?

Okay, so, I'm kind of horrified by these medications,

because my big fear is if they are becoming widespread use,

that we are going to all of a sudden have a society

where everybody has an LDL cholesterol of 20

and Lord knows in 10 years what's going to happen as a consequence of that.

Makes me really nervous.

But the fact to the matter is the deal with PCSK9 is,

if you can inhibit PCSK9, more LDL receptors stay up. Okay?

We can get that circulation, we can speed up the circulation,

because we are able to take in more of the LDL particles.

And insulin increases PCSK9.

So, in essence if we can decrease insulin,

we are actually up regulating those receptors.

Why does studies then, who are high-carb and high saturated fat

may not be applicable at all, in a carb restricted state?

So, residence time, I think is going to be a big part of the answer,

to our many questions here.

Okay, and then just really quick, again I don't want to get into this too much,

but I, like I said before earlier, I don't order standard lipid panels,

especially because I run a weight loss clinic.

And so most of my patients, if not all of them really, are insulin resistant

and a regular lipid panel is so unhelpful in an insulin resistant person,

I get NMR's on everybody.

And it's interesting in the cholesterol world right now,

we kind of have developed two camps. Right?

A camp that says LDL-P is really important

and that's the big thing we need to be following,

a camp that says small dense is really important.

And I think there's evidence for both.

But I can kind of firmly plant one foot on each side of this,

because I can say what I do tends to improve both. Okay?

So, studies for a while have suggested that LDL-P was the most important thing

and the small dense really doesn't matter that much,

if you're looking at total particle numbers.

But, I think newer studies are bringing this into question,

so, I think again, what we are going to find at the end of the day,

is that both play a role.

Okay, so, what about rapid weight loss in its impact?

So, Steve Phinney did a study of this a while ago

and does mobilization of fat, because our biggest cholesterol stores... where are they?

Our biggest cholesterol stores are in our fat,

so if I've got someone who's lost 30 pounds in two months

and then cholesterol goes up,

is that maybe part of the answer, that they just mobilized all this stuff?

And I think we don't have big data set on this yet,

but anecdotally in my clinic, I think I'm going to say, for a lot of people,

the answer to this is, yes,

that, if we wait until they get weight stabilized, we'll see that LDL come down.

So, are these people who have a rise in LDL over absorbing cholesterol in their diet?

No, no.

I mean, we only absorb 50% of the cholesterol in our gut

and of that 50%, 85% of it, is endogenous, okay, is not what we're eating.

So, you just have to be in such massive amounts of this stuff,

to really have absorption be a problem here.

Okay, so, case closed. Right?

What have I just presented you? All these things that sound great.

Case is closed, LDL-P doesn't matter, because everything else is better.

Right?

Not so fast,

because I think we've been down this road before. Right?

And I think we all as a community have highly criticized this road, justifiably.

Let's go back and draw a parallel.

Low-fat. How could it be wrong?

Right? Come on!

You cut the fat out of your diet; you're going to cut the fat out of you.

It's going to be perfect.

We all are going to be healthy and happy because of it.

The road of unintended consequences.

We have to be asking,

"Is there any chance we do the same thing?"

I don't know, I don't know the answer.

And for most people I would say "Absolutely not."

Because we just saw that everything is better.

Everything is better.

But, what about those poor guys, what about those one whose LDL P went up,

whose small dense even went up and stayed up?

Is there any unintended consequence there?

We have to be asking these questions, we have to,

because the fact to the matter is nobody knows the answer.

I want to know the answer. I want to know the answer.

So, we've got a current study going on,

that I don't by any stretch of the imagination claim,

is going to solve every question.

But it's going to go away to helping us understand this better.

Okay, so what is our study?

500 patients with type 2 diabetes or prediabetes are enrolled,

we've just finally closed enrollment.

Okay, so, and defined by a hemoglobyne A1c of 5.7 or higher,

who meets the criteria for metabolic syndrome.

So these are insulin resistant patients. Okay?

So we got to, of course, understand,

we are just following that one demographic here.

Okay, so, 400 of these patients are treatment patients,

all treated with ketogenic diet.

So, these people are eating a lot of saturated fat, a lot of saturated fat.

Blood ketones are obtained

so that we can make sure that they're actually doing what they're saying they're doing.

200 of these patients are treated "live" in our clinic.

We see them initially on a weekly basis,

then they go to every other week,

then, some of our patients are already on just monthly visits

and they taper off after that.

And it's over two years,

so, this is going to be some longer-term data.

200 of these patients are going to be treated with a ketogenic diet,

but they're all being treated virtually, online.

They get all their education-- all their medical care being done via computer.

Now, we have 100 control patients, treated with the good old ADA.

Who do you think is going to do better?

So, can I tell you a funny story on this?

So, we had a patient called at our clinic,

who was in our control group,

just throwing a fit at the staff,

"Well, I've got a bunch of my friends who are in the treatment group

"and they are all getting better! They are off of their medicine!

"I don't want to be a control patient!

This is a totally raw deal here!"

Okay, so, anyway, I mean we explained all this to every patient, but anyway.

Once the reality hit in, then he could see it was pretty interesting.

Okay, so, primary outcome.

Body weight, metabolic syndrome criteria, type 2 diabetes status.

Okay, but, we are also looking at some secondary outcomes.

Again, that relate to this LDL question.

So, we're looking at carotid intima media thickness

measured by ultrasound,

over 2 years, we're getting baseline 1 year and 2 year data on these people.

And we'll be able to see obviously,

we are getting NMR data on these on a regular basis.

So, in these people whose LDL-P goes up,

is it associated with progression of disease?

Then the other question is, you know...

How is it the disease progressing

in association with the people who are treated with the ADA plan?

So I think this will be a really important and interesting information.

We are also getting DEXA Full Body, so we can get body fat percentage.

And we've got a lot of bank samples too, so that we can kind of decide

that there are other parameters we want to look at, in the future.

And believe me, there will be plenty, I'm sure, that we're going to come up with,

so we can get some questions answered.

So, the ultimate questions here.

Does the rise in LDL-P in minority...?

It's a minority of patients! Okay?

I think a lot of people in the mainstream don't appreciate that,

but, the minority of patients still count.

On a low-carb high-fat diet represent an increased risk of vascular disease

and does LDL-P resident rise at the time go down,

thereby making a high particle number, less relevant?

Can we predict who these people are, who are going to have this rise in LDL-P?

Do all patients eventually have a decrease in small dense,

who follow a low-carb high-fat diet?

Will they get there at some point?

How long after dietary changes should we be checking lipids?

Or should we wait for weight stability,

so we don't freak anybody out? Right?

Because some of those people may have that rise from weight loss itself.

And is insulin-- I mean here's a crazy question...

potentially a double edge sword for some?

Possible.

Alright, so, thank you again.

Like I said, I think the big question is, if we want to be science-based,

science driven, we have to constantly be asking the questions

and sometimes that means acknowledging the things we don't 100% know.

Thank you very much.