HIV and Abdominal Fat- Interview with Dr Steven Grinspoon

Video: https://www.youtube.com/watch?v=EJI9rCHpfUk

Nelson Vergel: Hello, everybody. This is Nelson Vergel with Program for Wellness Restoration. We are honored today by having with us a pioneer of metabolic research in HIV. I've been following this doctor's research since the mid-90s when we found out that many of us were getting better but, unfortunately, our bodies and metabolism were changing. Dr. Grinspoon was one of the first ones that presented data on a syndrome that we later called HIV lipodystrophy. I'm very pleased to have him explain where we are. He's is currently a Professor at Harvard Medical School and the Director of a Program in Nutritional Metabolism at Massachusetts General Hospital.

Welcome, Dr. Grinspoon. It's an honor and a pleasure to have you here. What don't we quickly start because we have close to 19 questions that have been posting them on different social medial sites. This is a topic that has not been discussed much in the past few years, and patients like me (33 years into my HIV infection), are a little frustrated as we think that HIV lipodystrophy research has been abandoned. A lot of us are concerned because, especially long term survivors, are still living with this issue.

Why don't we start by your providing a background to the audience about what HIV lipodystrophy syndrome is.

Dr Grinspoon: Thank you very much, Nelson. It's a pleasure to be here and to talk with you. You do really important work. Thank you. Lipodystrophy refers to a constellation of signs and symptoms in HIV infected patients. It really is a combination, in my mind, of increasing abdominal adiposity (fat) and at the same time loss of subcutaneous (under the skin) fat.

It's not one particular syndrome. There's different degrees of gaining abdominal fat and loss of subcutaneous fat. They don't always occur simultaneously, but in general the gain of abdominal fat is visceral (inside organ cavity) in nature so people gain abdominal visceral fat and lose subcutaneous fat both in the abdomen and extremities. We really refer to patients primarily as having lipohypertrophic or more of the abdominal type, or lipoatrophic more the fat loss type, or a combined type.

There's been no great agreement on terminology here, which is part of the problem in the field, but I think there is no doubt that lipodystrophy exists and it continues to exist. Some of the new studies show even with the new antiretroviral therapies there are disproportionate gains in visceral fat and loss of subcutaneous fat. Probably it is less common than it used to be because the drugs, particularly protease inhibitors like Crixivan, clearly contributed to it and are now hardly used. Some of the nucleoside transcriptase inhibitors like d4T and AZT contributed conversely to lipoatrophy and are hardly used now.

Some of the worst players are not there anymore, but that's how I would consider calling it both lipohypertrophy and lipoatrophy and I think each one has its own set of metabolic consequences, and both are bad. That's really the key point. The loss of subcutaneous fat is loss of a good depot (storage), and that's important. That's where we buffer our calories, we buffer our substrate. When you lose that, you get gain of fat in other ectopic (unusual) places like the liver, visceral area, etc. That's one hit, the loss of subcutaneous fat. The other one is the gain of visceral fat. Accompanying that would be ectopic fat, like fat in the muscle, fat in the heart, fat in other places.

Nelson Vergel: Do we know what actually causes this? Is this HIV infection itself? HIV treatment?

Dr Grinspoon: That's a good question, and unfortunately we still don't know. There's a couple of theories out there. One of the theories is that it may be inflammation caused by the virus itself. For example, even when AIDS was at its worst and we observed wasting syndrome and we did waist-hip ratios., there was an increase in the waist-hip ratio even in people with wasting. There were some hints that there was some disproportionate gain and loss even when people were in overall losing weight. I think those are amplified in the current era where patients are eating more healthy and having less calories and some of them are gaining weight even with that. It can be difficult to tease out this syndrome from generalized obesity, but I think it is possible to do it. Compared to patients with generalized obesity, there is relatively more visceral fat and less subcutaneous fat in patients with HIV.

I'm not going to say which particular drugs cause it because it's not really clear which ones really do, but I will say that the nucleoside transcriptase inhibitors that were mitochondrial toxins such as d4T clearly caused lipoatrophy, and in that context there was ectopic adipose tissue in the visceral and behind the neck. That one is fairly clear, and there are effects on PPAR-gamma and stuff like that, but what's less clear is why patients get visceral hypertrophy. The question there is, is it connected to the loss of subcutaneous fat? Is it independent? I think that's still we not know.

I might add that even though there's confusion in the field about terminology, as a practicing physician as well as a researcher, I know lipodystrophy when I see it. I think there is too much reticism in the field about, oh, there's not lipodystrophy. You know lipodystrophic patients when you see them. Granted some are not very diseased at all, but there are a number of patient that have what I call toxic lipodystrophy with severe abdominal hypertrophy and severe loss of limb fat, etc. Those patients are fairly easy to identify.

Nelson Vergel: Can we predict just by looking at their blood work, like lipids, glucose, etc whether or not that person is more prone to lipodystrophy? We're going to focus, by the way, for the next 40 minutes on lipohypertrophy or the gain of visceral fat. By the way, for the audience that doesn't know what visceral is, visceral is the fat deep within the organ cavity. That fat is very hard to get rid of. It's almost like an additional organ, and obviously we cannot do liposuction on that fat because it's too close to the organ cavity. Anyways, we know what causes lipoatrophy and there are some FDA approved facial fillers but obviously there are only for the face. When it comes to lipohypertrophy, we have only one product, and we'll talk a little bit later about it.

Tell us why visceral fat is not just a cosmetic issue because that's what we are running into sometimes when it comes to insurance reimbursement.

Dr Grinspoon: This is a really important point you bring up, really important. In general, studies in the noncHIV population have basically related overall weight to cardiovascular events. The heavier you are, the more events, etc. If you look behind that sort of initial veneer of studies and you look at the epidemiological data, even in non HIV, it's not just overall weight that contributes, it's actually the visceral fat. As you say, it's a particular type of fat that's around your viscera, your GI organs. It can be around your heart, etc. It's really contributing to metabolic disarray. That's because some of that fat can drain directly into the liver, through the portal vein, and there's excess fat that associated with liver fat in that context of excess visceral fat.

It's associated with insulin resistance. It's associated with dislypidemia (high cholesterol), high triglycerides. In the non HIV population, even when you control for regular overall weight, it's the

visceral fat that contributes and is most associated with cardiovascular events. The problem is that those are epidemiological association studies, and there is yet to be a product that actually reduces visceral fat. The FDA has not really made this connection as much. They discourage people to measure visceral fat because it's in the realm of experimental therapeutics. There is a gap between all the epidemiological data which suggests visceral fat is the key depot which contributes to cardiovascular events, insulin resistance, dyslipidemia and other health issues.

Interestingly, HIV has led the way, if you will, because in our group, we have actually have done research on a product which actually selectively reduces visceral fat while being neutral to subcutaneous fat. That's really important because you want something that doesn't further decrease the subcutaneous depot which may already be relatively decreased in HIV+ people exposed to old nucleosides.

In this context, improving the visceral fat has led to significant improvements in liver fat, quality of life, other aspects. I think that it's really important for HIV patients to understand that visceral fat contributes specifically to metabolic problems. The problem is, and the disconnect is, how does a HIV patient know that they have extra visceral fat? This is the problem because I would know by getting a CT scan but that's not readily available to most patients and it's still a research test. You can do a tape measure, and you can look at your abdominal circumference. In levels higher than 100, 105 centimeters or so are pretty high levels. You can look at waist-hip ratio, the ratio of your abdominal area to your hip area. Those are two things you can get by waist and hip measurements , which could give you a clue because they do relate very linearly to the amount of visceral fat.

I would say that if patients have a disproportionate high waist circumference compared to their hips, or just a generalized increased waist circumference in the context of not being generally obese, the odds are that they do have excess visceral fat. It's probably contributing to their metabolic situation. In the non HIV world, there's a concept called hypertriglyceridemic (high triglycerides) waist, where they take the waist circumference and they associate it with the triglyceride level and those two things together are an index of the metabolic health of the patient. I think we have not done it in HIV but that could be something we do in that population as well.

Nelson Vergel: What really puzzles me, the connection between high tryglycerides and lipohypertrophy is that so far, and I don't know if anybody researched this deeply, managing and modulating lipids with statins ahead starting antiretrovirals decreases the chance of accumulation of visceral fat. As a long term activist, that has always been my question. If it's related to lipids and glucose, why modulating lipids and glucose doesn't seem to help?

Dr Grinspoon: That's a good point. The changes in lipids may be directly related to antiretrovirals. There are certain protease inhibitors which really do increase the triglyceride levels. Also anyone who has excess visceral fat will tend to have high triglyceride. They run together because there might be insulin resistance and trouble clearly triglycerides. I think in the sequence of things, the visceral fat may occur first, and the triglycerides are either later or due to another factor. It does make sense that treating the triglyceride would probably not so much treat the visceral fat or vice versa.

You have to be careful because we don't want to say that treating lipids is not good for patients because it may be very good. In fact, we have a study as you know called the REPRIEVE trial which is a very large, randomized trial of a new statin which has particularly good effects in HIV patients that doesn't interact with antiretroviral meds. It's good for inflammation. The statins have that dual advantage of decreasing lipids and decreasing inflammation. What they don't do, and this is why we need other strategies for visceral fat, is that they don't really improve visceral fat per se.

You can attack this constellation of symptoms and signs by different therapeutics. For example, to decrease visceral fat, you wouldn't use a statin, you would use tesamorelin (Egrifta). If someone had a very high cholesterol, you'd pick a statin. Meanwhile, I might add to that tesamorelin, which reduces visceral fat, does reduce triglycerides by about 40 points, so it's a fairly good drug, in combination, to reduce visceral fat and triglycerides.

If you want to reduce overall weight and insulin resistance, you might pick metformin. There's different therapeutics you could use, and if we can convince, or teach, HIV clinicians how to use these more effectively we would have a better outcome for our patients.

Nelson Vergel: That is definitely a problem. Some clinicians even believe lipodystrophy is a thing of the past, which as you well stated is not really true. At the same time, on a different note, I'm concerned because I see some newly diagnosed HIV patients that try to postpone HIV antiretrovirals because of their fear of getting visceral fat accumulation. What can we tell those patients, especially in a new era of integrase inhibitors and all the new fancy drugs that we have now? Are they any better or have they shown to have more or less the same body effects? As you say, we have older drugs, Crixivan, that definitely caused huge problems with insulin resistance. How do you make the newly infected patient feel more reassured?

Dr Grinspoon: As you say, starting antiretrovirals really is very important, and that will save lives, and that is really, really important. You can't defer therapy for body composition purposes. You're losing the forest from the trees. The earlier you start, probably the better in terms of your overall health. You reset the immune set point earlier. It's much better for overall health and inflammation. HIV patients should be encouraged to start as soon as possible. I think the new drugs may, in a more moderate way but not zero effect, contribute to this. As I mentioned there's some recent ACTG studies which suggest that even newer sets of drugs can contribute to increases in fat mass even if it is at a lower incidence.

I think we don't understand who's at risk, which is a big issue. My guess is that there's some interaction between the biology of the person and the drugs. For example, maybe those patients who are prone to get abdominal hypertrophy anyway as they get older are more prone to these effects. That's a really important understanding. Maybe patients who have a family history of these things might be, I don't know. It hasn't really been very well looked at.

What I would tell HIV patients who go on HIV medicines for the first time is to maybe do a waist circumference or have your doctor do one, or so you understand where you're at, not to delay therapy but just have some baseline data. That's what I do with my patients. I say, here's where you were before, and let's see where you're going with this. Now it's true that I'm not doing a CT scan in every patient, where I could prove what would happen with initiation, but at least you could reassure the patient that your waist circumference is not getting larger.

When I start someone on new antiretroviral therapy, I have a baseline glucose level, a baseline lipid levels, baseline anthropometrics (body measurements), and then I would track those every six months or so on the therapy. Many patients will do just fine. For those that don't you can pick up a signal early. You can talk to your doctor about dietary strategies, other strategies, perhaps going on tesamorelin if you meet the criteria for it early, if you have insulin resistance considering metformin. Being proactive in those cases. I think the worst thing HIV patients can do is wait until this gets to be a real problem and there's severe lipodystrophy. The horse is out of the barn, if you will, and then it may get harder to fix. I think if you can be proactive, it will be very important. I agree with you

Nelson Vergel: What I see is that patients when they do have increased visceral fat, the approach the doctors, not all of them obviously, and the doctors say, "just watch what you are eating and exercise". Then it becomes a restrained thing because they don't bring it up again. The patients just say, well, I'm am doing both things. You have to bring it up. It's not a conversation item anymore because they know their doctor obviously is not well-versed in the hormonal treatment of this. By the way, before we jump into more details about treating lipodystrophy, what have you seen in general when it comes to hormone issues in HIV?

Dr Grinspoon: I think insulin resistance is an issue, and there's a higher preponderance of diabetes in HIV patients. We don't have great data from the real current era, but from five or ten years past, there was an increase of prevalence compared to the national prevalence by a few percentage points. That's something to really be careful about. People with severe insulin resistance can develop diabetes. The problem with insulin resistance is that it's not that easy to measure by glucose alone. You'd have to look at the insulin level, and it tend to run with visceral hypertrophy and high triglycerides. People with visceral hypertrophy, high waist circumference, high triglycerides are at risk for insulin resistance, and they should absolutely have their glucose monitored carefully. If they do become diabetic, they should be treated and consider use of metformin or other agents.

Insulin resistance is one thing. Low testosterone is another big one. In men, HIV patients have a higher prevalence of hypogonadism. There haven't been so many good studies in the real modern era, but in the years past there was a high prevalence. The problem with that is that you need to measure it correctly, you need to measure it in the morning, you can use a free testosterone level as a better level. People don't measure it correctly. They use the wrong testosterone at the wrong time of day and they misdiagnose people. You really want to do it right because you don't want to put someone with normal testosterone on testosterone because you could actually suppress the person's own natural testosterone with the exogenous testosterone.

The other one is lipid levels. Dyslipidemia is very common in HIV patients. They tend not to have high total cholesterol so much as high triglycerides. There are a number of strategies to reduce triglycerides. Diet, exercise and fenofibrates are important. If you treat insulin resistance, triglyerides can improve. If you treat the visceral fat with tesamorelin, as we'll talk about, that could improve. That's another big one.

The other one is growth hormone, which we're going to talk about. HIV patients and patients in general who have excess visceral fat have perturbed growth hormone patterns. Growth hormone is made in pulsatile packets in the pituitary based on signals from the hypothalamus, and it's not constantly but it's made in bursts, particularly overnight. The frequency of those bursts is adequate in HIV but the height of each burst or the area under the curve is abnormal. You have a decreased peak area under the curve or peak height, with the same number of pulses. We see a very significant pattern among HIV patients with visceral hypertrophy of perturbed growth hormone. I'll get back to how that leads into the therapeutic we developed.

To round out the other endocrine problems, women are an important group of HIV patients and they can have problems with hormones as well. They can have amenorrhea, problems with their periods. Women with HIV do have low testosterone even for women. We have done studies to show that testosterone replacement can be somewhat helpful, but there is no FDA approved product for women. It's a little risky because if you overreplace testosterone in a woman, you can get all sorts of problems that you don't want to get into, and it's particularly dangerous in pregnant women. That's an issue.

I do want to make one point that anabolic steroids are really a hard thing to think about and talk

about in HIV because yes, they have the potential to improve muscle mass, but they also have the potential to do harm in terms of problems with liver and suppression of someone's own indigenous testosterone. They are hard to use. In my own practice when I assess someone for hypogonadism I assess using the methods I spoke about, and I replace with natural testosterone. By natural, I mean not an anabolic steroid and a prescription but testosterone that's not an alkylated agent or anything like. I can stop there if you want or I can go into tesamorelin.

Nelson Vergel: On the subject of anabolics, I've written a book on anabolics in HIV so I have a different opinion. Some of us started using anabolics for HIV wasting back in the horrible days, but now some of us are still working out and using these hormones with medical supervision with some good doctors monitoring us. We try to reshape our bodies so that our visceral fat is not as prominent. That's something that nobody talks about, but that's what we're doing in general for survivors.

Dr Grinspoon: I think the point you made about being under medical supervision is really important.

Nelson Vergel: It has to be. Let's move on to the actual treatment of lipohypertrophy and information on tesamorelin (Egrifta), the only product approved to decrease abdominal fat in HIV positive patients. You did a lot of work on that. Why don't we just start and get into the treatment, how it works, who it works for, how well it works, how we can predict if somebody's going to be a better responder.

Dr Grinspoon: The first thing is, this therapeutic was developed after a decade of research, and this research was published in good journals. This has led to the FDA approval of this product. When we talk about tesamorelin, we talk about what a very transparent process of research that is available for everyone to look at and for people to judge. That's really important. The ultimate approval was based on randomized placebo controlled trials in over 800 patients in US and Europe.

Just at the outset, there's a nice body of data regarding it, so it's easy to talk about. We first thought about this over ten years ago when we were noticing that the growth hormone patterns were off in HIV patients. We noticed, as I mentioned, that there were problems with the endogenous production of growth hormone and that overnight growth hormones were lower. By the way, you make most of your growth hormone at night. When your grandmother said, get sleep, you'll grow, she was right. Anyway, when you look at the nighttime levels, they're off in HIV patients, particularly those with abdominal fat. The higher the abdominal fat or visceral fat, the lower the growth hormone. That clearly has been shown now in a number of papers.

We asked ourselves at the beginning of this. We know that from non HIV populations that growth hormone can decrease fat and improve muscle mass and have other benefits. Would it be useful to augment growth hormone in this population? You can do that a couple of different ways. You could give growth hormone itself, or you can give the precursor hormone which is a growth hormone releasing peptide, GHRH, which will stimulate the pituitary to make its own growth hormone.

There's advantages and disadvantages of each particular strategy. The advantages of tesamorelin and the precursor is that feedback is intact, so it's very hard to overdose someone with tesamorelin. You should only use it at the prescribed doses. I'm not suggesting otherwise. There is some potential for overdose. It's harder because if you were to give too much, theoretically there would be feedback on the pituitary and it would be like a governor on the pituitary. When you give growth hormone, you're giving the end product and that's it. That's what gets injected, is what you put in. You can get a higher growth hormone level with growth hormone, per se. You don't get the nice pulsatile growth hormone that you get wit GHRH. These are really different strategies. Growth hormone itself does not give a pulsatile growth hormone pattern, whereas tesamorelin mimics the

endogenous (your body's natural) pulsatile growth hormone. I would say that tesamorelin is a much kinder, gentler way of giving growth hormone than giving actual growth hormone.

Having said that, there's something very interesting about giving a pulsatile paradigm, because it seems that for the level of increase in growth hormone, you get more of an effect to reduce visceral fat with the tesamorelin. It hasn't been tested head to head, but we've done similar studies where we've looked at tesamorelin achieving a certain dose of growth hormone, IGF-1, and then growth hormone per se achieving the same. Basically you get a bigger reduction in visceral fat for the same increase in IGF-1 with two different strategies. We think it has to do something with the pulsatile nature of this.

We proposed this pulsatile paradigm where you give the precursor hormone. We've seen in multiple studies now in HIV infected patients with abdominal hypertrophy even with low grade diabetes but not with severe diabetes that that group of patients will benefit from tesamorelin. What happens is the visceral fat goes down by an average of about 16-17% over about six months, and that continues with a little bit more of an increase, up to 18-19% or so over a year. That's the longest it's been tested, over one year. The results, you continue to see the effect even past six months. You tend not to lose subcutaneous fat. It tends to be neutral to subcutaneous fat. It reduces triglycerides about 40 mg/dl.

Unlike growth hormone, per se, it does not aggravate glucose to a significant degree, and that's a really, really important distinction. I think that's because it's pulsatile and it's gentler. The glucose levels tend not to go up over six months or one year, the hemoglobin A1C remains pretty steady. You can see an initial slight increase in glucose but it tends not to be clinically very significant. That's not true with growth hormone. You have to be really careful how you use growth hormone. If you give too much, your glucose will really go up. I might add that the FDA also had a package presented to it of growth hormone for the treatment of abdominal fat, not tesamorelin but growth hormone per se, and the FDA rejected that application due to side effects. They accepted tesamorelin and rejected growth hormone, and I think it's because you can achieve a nice reduction on visceral fat, triglyceride, with gentle effects on glucose compared to growth hormones.

If I was talking to a patient and I wanted to talk about the only FDA approved therapy, I would talk about tesamorelin. I can talk more about it but this suggests that if I tell the patient it works in about two-thirds to 70% of patients, so 70% will have an effect, 30% won't. That was twice as high as the placebo. That's what you see in most drugs in America pharmacopoeia now. It doesn't work in everybody but it works in the majority of people, which is why it was FDA approved.

I tell people it may not work on you but it will work in most people. The best person to put on that is someone with clear evidence of visceral hypertrophy, increased waist circumference. I would avoid anyone with a history of cancer or active cancer. There is no evidence that this contributes to cancer, but it a theoretical concern. I would avoid out of control diabetics. Perhaps when they get under control they might be a good candidate, but I would not do it when they are out of control. I would look to make sure the growth hormone levels and IGF-1 don't go too high. The vast majority of tesamorelin patients will not go too high because of the mechanisms I mentioned.

Side effects, about 3% of patients will have a kind of rash at the injection site. Some people have antibodies but they're not interfering antibodies so they don't tend to get in the way of the product. Overall, it's been well received. It's used by a number of patients. It's a nice option to have. I don't understand why all insurance companies don't approve it. It's FDA approved. It's FDA tested. It's clearly efficacious. It works. I also am very careful not to give it to the wrong person. I

don’t give it to someone without any evidence of lipodystrophy just to make them feel good. I do not do that. You don’t give it to non HIV patients because it wasn’t developed and approved for that population. If it wasn’t working after six months, I would probably stop it.

I’m careful how I prescribe it but I think within those confines, if you use it according to the label, what the FDA tested, you will in most cases have a positive benefit. Some ID practitioners are afraid of patients using an injection. It is in the form of an injection once a day, but it’s like a little needle that looks like a diabetic needle. It’s tiny. It’s very well tolerated. Patients tend not to mind it that are on it. There’s some fear about it but I think largely ungrounded. No drug is perfectly safe in the United States. Every drug has some side effects. This, too, but in general the benefits outweigh the risks.

Nelson Vergel: Something that always puzzled me is nobody has really looked, maybe I haven't done the proper research, on the synergy between exercise and dietary modifications and the use of tesamorelin. By the way, for the audience, it is spelled t-e-s-a-m-o-r-e-l-i-n. Tesamorelin. We say it so quickly sometimes. It may be their first time, the audience has never heard of it.

There are patients that are exercising or driven to exercise, watching their diet and increasing fiber intake, decreasing sugar intake, no bad fats, more protein… Is anybody looking at whether or not those patients tend to have a better response to tesamorelin?

Dr Grinspoon: No. Unfortunately that's a really good point that hasn't been very well researched. That's a great idea, to give it in combination with exercise. It seems quite logical. Even giving it in combination with other drugs might seem logical, for example if you have severe insulin resistance and giving it in combination with metformin. There's no contraindication to that. Be careful but if there's insulin resistance then you can do that. It might increase the effects.

That research is lacking, and there hasn't been a lot of federal funds to do subsequent follow up research to tesamorelin. Ironically once a product get approved, sometimes the pipeline for research diminishes because it's already approved. I will say that there are a number of secondary benefits. We are researching with federal dollars. One of them is on the liver. Tesamorelin has an important effect to significant reduce liver fat in HIV infected patients. We published that in JAMA in 2014. It was a very nice effect in a randomized single control trial. Liver inflammation improved, so they improved with the use of tesamorelin. What we are now looking at is liver biopsies, and we're actually doing an interesting study in collaboration with the National Institute of Health, taking patients with biopsy proven liver fat and inflammation and randomizing tesamorelin or not.

That's an interesting study because if we can prove that this drug really reduces liver inflammation by biopsy, liver fat, visceral fat and looking at these other metabolic indices, that's a really significant effect if we show that. There is some federal research going on. We are doing some. There is also some work that I'm aware of linking effects of tesamorelin and maybe perhaps improving cognition and there are some studies on that. There are some studies considering looking at it with sleep apnea and other conditions which can occur. There's a handful of studies going on but there's not hundreds of studies with it.

Nelson Vergel: You mentioned some ID physicians are not either prescribing or not even discussing the use of this option for their patients with lipohypertrophy. This is probably related to barriers not only to education but the fact that some physicians think that if a patient has no insurance or very limited insurance policy he or she may not get approved for reimbursement. But the makers of the drug actually have patient assistance programs to cover that and copay assistance also.

Dr Grinspoon: Many insurance companies do pay for it. Most do but some don't.

Nelson Vergel: When they don't the company can actually even help that process or provide some assistance if patients visit Egrifta.com. That's something I really think the community does not know and is a good thing to know. Finances are always the main driving force for adherence. The fact that it is a daily injection can also be an issue to some.

Just really quickly I was wondering, and we only have 5, 10 minutes left. It is an injection. There is no oral growth hormone enhancer, right? There is a lot of that in the supplement market. That's basically bogus, right?

Dr Grinspoon: It has to do with the absorption and how you can get the peptide in through the GI system. There is one form of growth hormone, called Ghrelin, which they're developing for oral use. The problem with Ghrelin is it's not pure GHRH. It's a different hormone. It's actually made in the stomach, and it's actually a hunger hormone. It's a hormone that goes up after having eaten to tell you to eat. GHRH tesamorelin doesn't stimulate hunger, whereas Ghrelin does. In fact, Ghrelin is being tested for wasting and metabolism, so I don't think it's a good therapeutic for lipodystrophy per se.

Yes, it may become available and if it does, I'd be very surprised if the FDA approved it for HIV lipodystrophy.

Nelson Vergel: No, they would prefer uses for low appetite related to. On another topic, why is liver fat damaging to anybody, HIV or not?

Dr Grinspoon: It's not entirely clear, but I think some of the theories are that when you have significant liver fat, you have insulin resistance at the liver, so you have increased hepatic glucose output and decreased action of insulin. You can have inflammation that is associated with liver fat. Of course, the most obvious answer is that liver fat can … there's a sequence and liver fat of severe can progress to steatohepatitis or inflammation which can progress ultimately to liver cancer. There is a sequence. A certain fraction of patients with liver fat alone progressed to the inflammation of steatohepatitis and a certain fraction of those progressed on to hepatocellular carcinoma and end stage liver disease. There's metabolic effects and then there's local effects. It's extremely important to try and reduce liver fat and not just liver fat but liver inflammation. As I mentioned, were going one step further with our new study to see if we can actually reduce liver inflammation.

Nelson Vergel:

Last but not least, because I'm very interested in your new research on this thing called Dicer. I read your paper. I think I'm an educated patient and an activist but never heard of this. There seems to be dicer deficiency in HIV lipodystrophy. Can I use the word deficiency?

Dr Grinspoon: The reduction. It's a fascinating line of research. It actually stemmed from some animal studies with collaborators and dicer is an endoribonuclease which affects multiple metabolic pathways, some of which control brown fat, adipogenesis metabolism. Ron Conn discovered that when you knock dicer out of mice, they become very lipodystrophic, fat appear in the belly. Of course, their animals but they're not humans, but it was an interesting observation. They also became insulin resistant and have other metabolic problems.

He and I got together and we said this looks a lot like HIV lipodystrophy, of course one's an animal model and one's a human model. We should look to see what the situation of dicer is in humans. One thing that is interesting is the HIV virus is a really clever, deadly virus and it actually can affect

dicer and downregulate it to effectuate its immunological effect. There's actually a mechanism by which the HIV virus is known to affect dicer and is thought to help the virus infect us, if you will, affect HIV patients. It's very clever in that regard, and there's a mechanism by which you could postulate reduction in dicer.

That's sort of the background. Animal model, potential effects of HIV on this. We did subcutaneous fat biopsies in lipodystrophic patients and we saw a remarkably reduced dicer concentration in the subcutaneous fat. The lower the dicer, the lower the production of brown fat, the adipogenesis in those kind of precursors. Also, the lower the dicer, the more insulin resistant the patient was. Fascinatingly, the lower the dicer suppression, there was an increase in the subcutaneous depot around the neck, which we haven't talked about.

Nelson Vergel: Buffalo hump.

Dr Grinspoon: Buffalo hump. This was really interesting to us, and people can read these papers that we wrote. In a series of papers, we found out that the fat in this buffalo hump can be more sort of brown fat-like, a good fat. One theory, and it's only a theory, is that perhaps this buffalo hump is sprouting as a compensatory mechanism to improve metabolism in the context of reduced dicer and dysfunctional subcutaneous adipose tissue. This is really an interesting observation. This would be one of the initial mechanistic links about how HIV patients could be lipodystrophic. There's also other theories as well in which some of the viral proteins, VPR, can actually upregulate the glucocorticoid receptor and downregulate PPAR-gamma.

The point you made is really interesting. Everyone has been focusing on drugs' effect on fat, right? Maybe it's not the drugs alone. Maybe it's some direct effect of the HIV virus, either by capturing and corrupting dicer or affecting these other receptors, glucocorticoid or PPAR-gamma. I actually think that is probably true. That's why patients get it early on perhaps and have it even despite better drugs. I think that is probably true.

You could ask, what would one do about that, and that clinical question is not, the answer to that is just starting. We had to put in some grants to try to come up with strategies to upregulate dicer, if you will. Could you imagine that? HIV reduces it and even in well controlled people maybe we could upregulate dicer and improve the brown fat, energetic production of that type of fat, maybe this would decrease if the dicer goes up. Maybe the metabolic situation of the patient will improve. What we think we found is one potential sort of human analog of this mouse knockout model and I think it's quite interesting to be honest with you. I think so are other theories. We're in the genre of HIV direct effects on these different mechanisms.

Nelson Vergel: Yes, very exciting, and as I said, I was following the lipodystrophy field, whatever is left of it and saw this was a new piece of information.

I guess we are done. I think you are moving on to your next meeting. First of all I want to thank you. Thank you because you have not abandoned this field. We have seen people abandon this field because they are moving on to other fields that are getting funded better or because of the perception that lipodystrophy is no longer an issue.

From a community point of view I want to thank you because you are one of the pioneers but you are still looking into this issue. This dicer topic is fascinating and I am going to be following that very closely. Maybe we'll have another interview in a year or two when you get more funding to get more research on dicer. I appreciate your time. This is going to be posted everywhere, YouTube, social media. I will be managing questions. Obviously people will have questions (Ask here). I may

forward them to you and see if you have time to answer them. I appreciate your time. Thanks a lot, and thanks to everybody that watched this video. Please forward it to your friends and your doctors. This is also made for clinicians. Thank you so much. Until next time.

Dr Grinspoon: Thank you, Nelson, and thank you for the work you do, too. Thank you very much.