WEBVTT

NOTE duration:"00:20:01"

NOTE recognizability:0.833

NOTE language:en-us

NOTE Confidence: 0.907784786666667

00:00:16.410 --> 00:00:17.938 Good afternoon, welcome back.

NOTE Confidence: 0.907784786666667

00:00:17.938 --> 00:00:20.340 This session is being recorded. Thank you.

NOTE Confidence: 0.859438012

00:00:23.720 --> 00:00:25.328 So our next speaker is going

NOTE Confidence: 0.859438012

00:00:25.328 --> 00:00:26.400 to be Gerald Schulman.

NOTE Confidence: 0.859438012

00:00:26.400 --> 00:00:28.040 He's professor of medicine as

NOTE Confidence: 0.859438012

00:00:28.040 --> 00:00:29.680 well as professor of cellular

NOTE Confidence: 0.859438012

00:00:29.739 --> 00:00:31.128 and molecular Physiology.

NOTE Confidence: 0.859438012

00:00:31.130 --> 00:00:33.056 Who's going to talk to us

NOTE Confidence: 0.859438012

00:00:33.056 --> 00:00:34.470 about the metabolism, Jerry?

NOTE Confidence: 0.772139626923077

00:00:40.440 --> 00:00:41.836 OK Rob, thank you.

NOTE Confidence: 0.772139626923077

00:00:41.836 --> 00:00:43.930 So I was asked to speak

NOTE Confidence: 0.772139626923077

00:00:44.017 --> 00:00:45.928 about liver metabolism.

NOTE Confidence: 0.772139626923077

00:00:45.930 --> 00:00:47.842 Here are my disclosures.

NOTE Confidence: 0.772139626923077

00:00:47.842 --> 00:00:51.264 I will be speaking about liver targeted

NOTE Confidence: 0.772139626923077

00:00:51.264 --> 00:00:52.800 mitochondrial coupling agents.

NOTE Confidence: 0.772139626923077

00:00:52.800 --> 00:00:54.140 This is a Yale patent.

NOTE Confidence: 0.772139626923077

00:00:54.140 --> 00:00:56.575 I'm an inventor and I'm

NOTE Confidence: 0.772139626923077

00:00:56.575 --> 00:00:58.036 a scientific co-founder,

NOTE Confidence: 0.772139626923077

00:00:58.040 --> 00:01:00.122 founder of a company that is

NOTE Confidence: 0.772139626923077

00:01:00.122 --> 00:01:01.510 promoting liver targeted uncoupling

NOTE Confidence: 0.772139626923077

00:01:01.565 --> 00:01:03.299 for treatment of Nathan and Ash.

NOTE Confidence: 0.772139626923077

00:01:03.300 --> 00:01:05.860 So I wanted to start with metabolic syndrome.

NOTE Confidence: 0.772139626923077

00:01:05.860 --> 00:01:07.430 This is something that's affecting.

NOTE Confidence: 0.772139626923077

00:01:07.430 --> 00:01:09.206 More than one in three Americans,

NOTE Confidence: 0.772139626923077

00:01:09.210 --> 00:01:11.470 this is from Jerry Reubens

NOTE Confidence: 0.772139626923077

00:01:11.470 --> 00:01:12.761 Banting Lecture 1988.

NOTE Confidence: 0.772139626923077

00:01:12.761 --> 00:01:14.666 It's a constellation of things

NOTE Confidence: 0.772139626923077

00:01:14.666 --> 00:01:16.190 associated with insulin resistance,

NOTE Confidence: 0.772139626923077

00:01:16.190 --> 00:01:17.426 of course, diabetes,

NOTE Confidence: 0.772139626923077

00:01:17.426 --> 00:01:19.898 but it's also leads to atherosclerosis,

NOTE Confidence: 0.772139626923077

00:01:19.900 --> 00:01:21.416 high triglycerides,

NOTE Confidence: 0.772139626923077

00:01:21.416 --> 00:01:23.690 alterations, and inflammation.

NOTE Confidence: 0.772139626923077

00:01:23.690 --> 00:01:27.230 Uric acid PCOS, hypertension,

NOTE Confidence: 0.772139626923077

00:01:27.230 --> 00:01:30.430 and moving to 2021.

NOTE Confidence: 0.772139626923077

00:01:30.430 --> 00:01:33.670 We can add not only cancer,

NOTE Confidence: 0.772139626923077

00:01:33.670 --> 00:01:35.770 but not alcoholic fatty

NOTE Confidence: 0.772139626923077

00:01:35.770 --> 00:01:37.870 liver disease and Nash.

NOTE Confidence: 0.772139626923077

00:01:37.870 --> 00:01:40.777 And what I'm going to do is try to

NOTE Confidence: 0.772139626923077

00:01:40.777 --> 00:01:43.989 show you how insulin resistance is

NOTE Confidence: 0.772139626923077

00:01:43.989 --> 00:01:46.124 actually promoting these abnormalities.

NOTE Confidence: 0.772139626923077

00:01:46.124 --> 00:01:49.302 We all know everyone on this zoom

NOTE Confidence: 0.772139626923077

00:01:49.302 --> 00:01:52.370 knows about the problem of NAFL and

NOTE Confidence: 0.772139626923077

00:01:52.370 --> 00:01:54.925 Nash also impacting probably at least

NOTE Confidence: 0.772139626923077

00:01:54.925 --> 00:01:57.283 one in three Americans that goes

NOTE Confidence: 0.772139626923077

00:01:57.283 --> 00:01:59.882 on to develop into inflammation,

NOTE Confidence: 0.772139626923077

00:01:59.882 --> 00:02:00.588 fibrosis,

NOTE Confidence: 0.772139626923077

00:02:00.588 --> 00:02:02.000 hepatocellular carcinoma

NOTE Confidence: 0.772139626923077

00:02:02.000 --> 00:02:04.824 and stage liver disease.

NOTE Confidence: 0.772139626923077

00:02:04.830 --> 00:02:07.956 And it's probably even more common.

NOTE Confidence: 0.772139626923077

00:02:07.960 --> 00:02:09.096 Than what we think.

NOTE Confidence: 0.772139626923077

00:02:09.096 --> 00:02:11.259 And so this is a study that

NOTE Confidence: 0.772139626923077

00:02:11.259 --> 00:02:13.179 is impressed by Kit Peterson.

NOTE Confidence: 0.772139626923077

00:02:13.180 --> 00:02:15.460 The threshold for non alcoholic

NOTE Confidence: 0.772139626923077

00:02:15.460 --> 00:02:18.158 fatty liver disease was defined by

NOTE Confidence: 0.772139626923077

00:02:18.158 --> 00:02:20.654 the Dallas Heart Group as 5.5% and

NOTE Confidence: 0.772139626923077

00:02:20.654 --> 00:02:23.468 studies that kit has done with Doug

NOTE Confidence: 0.772139626923077

00:02:23.468 --> 00:02:26.034 Rothman on Sylvie Dufour at our

NOTE Confidence: 0.772139626923077

00:02:26.034 --> 00:02:28.736 four Tesla instrument in young lean

NOTE Confidence: 0.772139626923077

00:02:28.736 --> 00:02:30.868 healthy individuals actually finds

NOTE Confidence: 0.772139626923077

00:02:30.868 --> 00:02:34.080 the 95th percentile for liver fat

NOTE Confidence: 0.772139626923077

00:02:34.080 --> 00:02:36.690 and healthy individuals is 1.85%.

NOTE Confidence: 0.772139626923077

00:02:36.690 --> 00:02:38.490 So I think actually.

NOTE Confidence: 0.772139626923077

00:02:38.490 --> 00:02:40.236 We're significantly underestimating

NOTE Confidence: 0.772139626923077

00:02:40.236 --> 00:02:43.728 the degree of fatty liver and

NOTE Confidence: 0.772139626923077

00:02:43.728 --> 00:02:46.441 what kid Peterson has shown in

NOTE Confidence: 0.772139626923077

00:02:46.441 --> 00:02:48.897 this study is even when you

NOTE Confidence: 0.772139626923077

00:02:48.897 --> 00:02:51.010 have 1.85% liver fat or higher,

NOTE Confidence: 0.772139626923077

00:02:51.010 --> 00:02:53.360 it's associated with alterations in

NOTE Confidence: 0.772139626923077

00:02:53.360 --> 00:02:55.710 insulin resistance and plasma like

NOTE Confidence: 0.772139626923077

00:02:55.780 --> 00:02:57.928 proteins and high triglycerides,

NOTE Confidence: 0.772139626923077

00:02:57.930 --> 00:02:59.960 high cholesterol.

NOTE Confidence: 0.772139626923077

00:02:59.960 --> 00:03:02.088 So what I first want to the first

NOTE Confidence: 0.772139626923077

00:03:02.088 --> 00:03:04.936 piece of my talk is about how muscle

NOTE Confidence: 0.772139626923077

00:03:04.936 --> 00:03:06.758 insulin resistance actually can lead

NOTE Confidence: 0.772139626923077

00:03:06.758 --> 00:03:08.936 to not only dyslipidemia and atherogenesis,

NOTE Confidence: 0.772139626923077

00:03:08.936 --> 00:03:12.665 but a fatty liver simply by changing how

NOTE Confidence: 0.772139626923077

00:03:12.665 --> 00:03:15.094 the energy that we ingest is stored.

NOTE Confidence: 0.772139626923077

00:03:15.100 --> 00:03:16.828 When you're just carbohydrate,

NOTE Confidence: 0.772139626923077

00:03:16.828 --> 00:03:19.905 how is it then stored in liver

NOTE Confidence: 0.772139626923077

00:03:19.905 --> 00:03:22.329 and muscle as glycogen or fat?

NOTE Confidence: 0.772139626923077

00:03:22.330 --> 00:03:23.830 This is what we do.

NOTE Confidence: 0.772139626923077

00:03:23.830 --> 00:03:25.810 We screen healthy young individuals.

NOTE Confidence: 0.772139626923077

00:03:25.810 --> 00:03:27.508 Most of these are Yale undergraduates.

NOTE Confidence: 0.772139626923077

00:03:27.510 --> 00:03:29.508 They come in for our studies.

NOTE Confidence: 0.772139626923077

00:03:29.510 --> 00:03:31.029 We give them a drink of glucose.

NOTE Confidence: 0.772139626923077

00:03:31.030 --> 00:03:32.083 We measure insulin.

NOTE Confidence: 0.772139626923077

00:03:32.083 --> 00:03:34.189 We can assess insulin sensitivity index,

NOTE Confidence: 0.772139626923077

00:03:34.190 --> 00:03:35.650 and by definition we have.

NOTE Confidence: 0.772139626923077

00:03:35.650 --> 00:03:37.684 You have a nice bell shaped

NOTE Confidence: 0.772139626923077

00:03:37.684 --> 00:03:39.467 distribution as bottom quartile or

NOTE Confidence: 0.772139626923077

00:03:39.467 --> 00:03:41.287 resistant top world tile sensitive.

NOTE Confidence: 0.772139626923077

00:03:41.290 --> 00:03:43.426 We asked the very simple question

NOTE Confidence: 0.772139626923077

00:03:43.426 --> 00:03:44.850 when they ingest carbohydrate.

NOTE Confidence: 0.772139626923077

00:03:44.850 --> 00:03:47.058 Do these folks here who are

NOTE Confidence: 0.772139626923077

00:03:47.058 --> 00:03:48.530 resistant store the ingested

NOTE Confidence: 0.772139626923077

00:03:48.596 --> 00:03:50.172 carbohydrate differently from the

NOTE Confidence: 0.772139626923077

00:03:50.172 --> 00:03:52.536 ones in the top four tile?

NOTE Confidence: 0.772139626923077

00:03:52.540 --> 00:03:54.175 We bring them into the

NOTE Confidence: 0.772139626923077

00:03:54.175 --> 00:03:55.156 hospital research unit,

NOTE Confidence: 0.772139626923077

00:03:55.160 --> 00:03:57.872 measure plasma glucoses in both the

NOTE Confidence: 0.772139626923077

00:03:57.872 --> 00:04:01.118 resistant and yellow and sensitive in blue.

NOTE Confidence: 0.772139626923077

00:04:01.120 --> 00:04:02.878 No perceptible differences

NOTE Confidence: 0.772139626923077

00:04:02.878 --> 00:04:04.636 in glucose concentrations,

NOTE Confidence: 0.772139626923077

00:04:04.640 --> 00:04:06.908 but This is why it's at the

NOTE Confidence: 0.772139626923077

00:04:06.908 --> 00:04:07.880 expense of hyperinsulinemia,

NOTE Confidence: 0.772139626923077

00:04:07.880 --> 00:04:09.404 so the resistant individuals

NOTE Confidence: 0.772139626923077

00:04:09.404 --> 00:04:11.690 have to pump out twice the

NOTE Confidence: 0.895631421764706

00:04:11.762 --> 00:04:13.582 amount of insulin to

NOTE Confidence: 0.895631421764706

00:04:13.582 --> 00:04:14.947 maintain normal glycemia.

NOTE Confidence: 0.895631421764706

00:04:14.950 --> 00:04:16.442 Using carbon NMR methods,

NOTE Confidence: 0.895631421764706

00:04:16.442 --> 00:04:19.188 we have developed over the years we

NOTE Confidence: 0.895631421764706

00:04:19.188 --> 00:04:20.940 cannon invasively measure glycogen

NOTE Confidence: 0.895631421764706

00:04:20.940 --> 00:04:23.130 synthesis in muscle and liver.

NOTE Confidence: 0.895631421764706

00:04:23.130 --> 00:04:25.692 We find a profound defect in glucose

NOTE Confidence: 0.895631421764706

00:04:25.692 --> 00:04:27.794 getting into muscle glycogen no

NOTE Confidence: 0.895631421764706

00:04:27.794 --> 00:04:29.666 difference in glucose ingested,

NOTE Confidence: 0.895631421764706

00:04:29.670 --> 00:04:32.022 glucose getting into liver

NOTE Confidence: 0.895631421764706

00:04:32.022 --> 00:04:33.774 glycogen using proton annamar,

NOTE Confidence: 0.895631421764706

00:04:33.774 --> 00:04:36.102 we can actually quantify fat both

NOTE Confidence: 0.895631421764706

00:04:36.102 --> 00:04:38.367 inside the liver cell is probably

NOTE Confidence: 0.895631421764706

00:04:38.367 --> 00:04:40.182 the gold standard for assessing

NOTE Confidence: 0.895631421764706

00:04:40.245 --> 00:04:42.555 liver fat in noninvasively in humans,

NOTE Confidence: 0.895631421764706

00:04:42.560 --> 00:04:44.408 and we see this over 2 fold

NOTE Confidence: 0.895631421764706

00:04:44.408 --> 00:04:45.500 increase in liver fat.

NOTE Confidence: 0.895631421764706

00:04:45.500 --> 00:04:47.558 In the resistant individuals falling again,

NOTE Confidence: 0.895631421764706

00:04:47.560 --> 00:04:49.132 identical carbohydrate ingestion,

NOTE Confidence: 0.895631421764706

00:04:49.132 --> 00:04:52.800 and this is due to denovo lipogenesis.

NOTE Confidence: 0.895631421764706

00:04:52.800 --> 00:04:55.914 We have some deuterated heavy water

NOTE Confidence: 0.895631421764706

00:04:55.914 --> 00:04:59.159 in this milkshake that they ingest,

NOTE Confidence: 0.895631421764706

00:04:59.160 --> 00:05:01.536 and we can track the deuterium

NOTE Confidence: 0.895631421764706

00:05:01.536 --> 00:05:03.120 into the plasma triglyceride

NOTE Confidence: 0.895631421764706

00:05:03.190 --> 00:05:05.338 and quantify denovo lipogenesis.

NOTE Confidence: 0.895631421764706

00:05:05.340 --> 00:05:08.847 So this is the conversion of ingestive

NOTE Confidence: 0.895631421764706

00:05:08.847 --> 00:05:11.220 carbohydrate to fat in liver.

NOTE Confidence: 0.895631421764706

00:05:11.220 --> 00:05:15.112 And when you make more fat in the liver,

NOTE Confidence: 0.895631421764706

00:05:15.112 --> 00:05:18.088 it's exported and this results in

NOTE Confidence: 0.895631421764706

00:05:18.088 --> 00:05:19.732 increased plasma triglycerides

NOTE Confidence: 0.895631421764706

00:05:19.732 --> 00:05:22.008 and reduction in HDL.

NOTE Confidence: 0.895631421764706

00:05:22.010 --> 00:05:24.194 So conceptually, this is what we have here,

NOTE Confidence: 0.895631421764706

00:05:24.200 --> 00:05:26.816 so this is where you want to be.

NOTE Confidence: 0.895631421764706

00:05:26.820 --> 00:05:28.128 If you're in the top quartile,

NOTE Confidence: 0.895631421764706

00:05:28.130 --> 00:05:30.142 you ingest your carbohydrate.

NOTE Confidence: 0.895631421764706

00:05:30.142 --> 00:05:34.039 It's stored as glycogen in muscle and liver,

NOTE Confidence: 0.895631421764706

00:05:34.040 --> 00:05:35.958 and if you're in that bottom quartile

NOTE Confidence: 0.895631421764706

00:05:35.958 --> 00:05:38.078 and this is one in four Americans,

NOTE Confidence: 0.895631421764706

00:05:38.080 --> 00:05:39.448 and if you're overweight or obese,

NOTE Confidence: 0.895631421764706

00:05:39.450 --> 00:05:40.914 you're almost certainly already

NOTE Confidence: 0.895631421764706

00:05:40.914 --> 00:05:43.110 instantly resist since you have instant

NOTE Confidence: 0.895631421764706

00:05:43.170 --> 00:05:45.340 resistance to to ectopic lipid and muscle,

NOTE Confidence: 0.895631421764706

00:05:45.340 --> 00:05:47.960 you can't store that ingested

NOTE Confidence: 0.895631421764706

00:05:47.960 --> 00:05:49.864 carbohydrate as muscle glycogen,

NOTE Confidence: 0.895631421764706

00:05:49.864 --> 00:05:52.720 it's diverted to the liver hyperinsulinemia.

NOTE Confidence: 0.895631421764706

00:05:52.720 --> 00:05:54.813 Gives up the all the enzymes that

NOTE Confidence: 0.895631421764706

00:05:54.813 --> 00:05:56.529 are involved in conversion of

NOTE Confidence: 0.895631421764706

00:05:56.529 --> 00:05:58.404 glucose to fats with denoble.

NOTE Confidence: 0.895631421764706

00:05:58.410 --> 00:06:00.960 Lipogenesis is upregulated and this

NOTE Confidence: 0.895631421764706

00:06:00.960 --> 00:06:03.510 results in the high triglycerides

NOTE Confidence: 0.895631421764706

00:06:03.590 --> 00:06:06.548 and the reduction HGL this is

NOTE Confidence: 0.895631421764706

00:06:06.548 --> 00:06:08.027 your atherogenic dyslipidemia.

NOTE Confidence: 0.895631421764706

00:06:08.030 --> 00:06:10.100 That's going to lead to premature

NOTE Confidence: 0.895631421764706

00:06:10.100 --> 00:06:12.190 cardiovascular disease in your 50s and 60s,

NOTE Confidence: 0.895631421764706

00:06:12.190 --> 00:06:14.503 and with time this is what now is now.

NOTE Confidence: 0.895631421764706

00:06:14.510 --> 00:06:16.514 The most common cause of of

NOTE Confidence: 0.895631421764706

00:06:16.514 --> 00:06:17.850 of chronic liver disease.

NOTE Confidence: 0.895631421764706

00:06:17.850 --> 00:06:19.630 Non alcoholic fatty liver disease.

NOTE Confidence: 0.895631421764706

00:06:19.630 --> 00:06:21.730 So starting in muscle leading

NOTE Confidence: 0.895631421764706

00:06:21.730 --> 00:06:23.410 to fat and liver.

NOTE Confidence: 0.895631421764706

00:06:23.410 --> 00:06:25.082 And then now Phil,

NOTE Confidence: 0.895631421764706

00:06:25.082 --> 00:06:27.172 leading to Nash and potentially

NOTE Confidence: 0.895631421764706

00:06:27.172 --> 00:06:28.420 liver cirrhosis.

NOTE Confidence: 0.895631421764706

00:06:28.420 --> 00:06:29.950 Can we do anything about this?

NOTE Confidence: 0.895631421764706

00:06:29.950 --> 00:06:32.730 Well, to test this hypothesis,

NOTE Confidence: 0.895631421764706

00:06:32.730 --> 00:06:34.310 if we're right muscle and

NOTE Confidence: 0.895631421764706

00:06:34.310 --> 00:06:35.574 some resistance drives liver,

NOTE Confidence: 0.895631421764706

00:06:35.580 --> 00:06:36.364 fat generation,

NOTE Confidence: 0.895631421764706

00:06:36.364 --> 00:06:38.716 a study we've done many years

NOTE Confidence: 0.895631421764706

00:06:38.716 --> 00:06:40.738 ago looking at the same lean,

NOTE Confidence: 0.895631421764706

00:06:40.740 --> 00:06:41.928 instant resistant individuals,

NOTE Confidence: 0.895631421764706

00:06:41.928 --> 00:06:44.700 these are with two parents with diabetes.

NOTE Confidence: 0.895631421764706

00:06:44.700 --> 00:06:45.642 If you're resistant,

NOTE Confidence: 0.895631421764706

00:06:45.642 --> 00:06:47.526 you're young and you're young and

NOTE Confidence: 0.895631421764706

00:06:47.526 --> 00:06:49.357 you have parents with diabetes.

NOTE Confidence: 0.895631421764706

00:06:49.360 --> 00:06:50.670 Insulin resistance is the best

NOTE Confidence: 0.895631421764706

00:06:50.670 --> 00:06:52.264 predictor for whether or not you're

NOTE Confidence: 0.895631421764706

00:06:52.264 --> 00:06:53.895 going to go on to develop diabetes.

NOTE Confidence: 0.895631421764706

00:06:53.900 --> 00:06:56.004 And a study we did some years ago.

NOTE Confidence: 0.895631421764706

00:06:56.010 --> 00:06:58.120 Jean Luca Persaingan exercised these

NOTE Confidence: 0.895631421764706

00:06:58.120 --> 00:07:00.230 young healthy individuals and showed

NOTE Confidence: 0.895631421764706

00:07:00.289 --> 00:07:02.139 that we could normalize insulin,

NOTE Confidence: 0.895631421764706

00:07:02.140 --> 00:07:04.208 stimulated muscle glycogen synthesis

NOTE Confidence: 0.895631421764706

00:07:04.208 --> 00:07:08.230 so we can fix this defect in muscle.

NOTE Confidence: 0.895631421764706

00:07:08.230 --> 00:07:09.352 Insulin resistance,

NOTE Confidence: 0.895631421764706

00:07:09.352 --> 00:07:13.279 and so Rasmus Rubal was a fellow

NOTE Confidence: 0.895631421764706

00:07:13.279 --> 00:07:14.730 from Denmark,

NOTE Confidence: 0.895631421764706

00:07:14.730 --> 00:07:16.746 basically took the same insulin resistance.

NOTE Confidence: 0.895631421764706

00:07:16.750 --> 00:07:19.390 Individuals put them on a Stairmaster,

NOTE Confidence: 0.895631421764706

00:07:19.390 --> 00:07:21.610 exercise them for 45 minutes.

NOTE Confidence: 0.895631421764706

00:07:21.610 --> 00:07:23.779 A single bout is able to open up the

NOTE Confidence: 0.895631421764706

00:07:23.779 --> 00:07:25.970 door to glucose transport and muscle,

NOTE Confidence: 0.895631421764706

00:07:25.970 --> 00:07:28.016 and what Rasmus found in this

NOTE Confidence: 0.895631421764706

00:07:28.016 --> 00:07:29.380 study is these resistant

NOTE Confidence: 0.82312862

00:07:29.445 --> 00:07:32.364 individuals were able to take the ingested

NOTE Confidence: 0.82312862

00:07:32.364 --> 00:07:34.689 carbohydrates stored as muscle glycogen,

NOTE Confidence: 0.82312862

00:07:34.690 --> 00:07:36.875 and that resulted in reduction

NOTE Confidence: 0.82312862

00:07:36.875 --> 00:07:38.186 and denovo lipogenesis.

NOTE Confidence: 0.82312862

00:07:38.190 --> 00:07:39.542 Pain reduction liver fat.

NOTE Confidence: 0.82312862

00:07:39.542 --> 00:07:42.015 So this is proof of the hypothesis

NOTE Confidence: 0.82312862

00:07:42.015 --> 00:07:44.619 that if we fix muscle and resistance

NOTE Confidence: 0.82312862

00:07:44.619 --> 00:07:47.648 we can reduce DNA and reduce liver fat.

NOTE Confidence: 0.82312862

00:07:47.650 --> 00:07:50.530 Vine carbohydrate ingestion?

NOTE Confidence: 0.82312862

00:07:50.530 --> 00:07:52.330 So what about fatty liver

NOTE Confidence: 0.82312862

00:07:52.330 --> 00:07:53.770 and type 2 diabetes?

NOTE Confidence: 0.82312862

00:07:53.770 --> 00:07:55.426 And so we've spent a lot of time

NOTE Confidence: 0.82312862

00:07:55.426 --> 00:07:56.980 trying to understand mechanisms.

NOTE Confidence: 0.82312862

00:07:56.980 --> 00:07:59.068 Why is it that a lot of our patients,

NOTE Confidence: 0.82312862

00:07:59.070 --> 00:08:00.897 not all, but most of them with fatty liver,

NOTE Confidence: 0.82312862

00:08:00.900 --> 00:08:02.764 have diabetes and dyslipidemia,

NOTE Confidence: 0.82312862

00:08:02.764 --> 00:08:06.312 and this is kind of the molecular

NOTE Confidence: 0.82312862

00:08:06.312 --> 00:08:08.956 basis for insulin resistance.

NOTE Confidence: 0.82312862

00:08:08.960 --> 00:08:12.187 So insulin binds the receptor and it

NOTE Confidence: 0.82312862

00:08:12.187 --> 00:08:14.260 causes autophosphorylation the receptor.

NOTE Confidence: 0.82312862

00:08:14.260 --> 00:08:15.780 The substrate for this receptor

NOTE Confidence: 0.82312862

00:08:15.780 --> 00:08:17.300 is instant receptor substrate 2,

NOTE Confidence: 0.82312862

00:08:17.300 --> 00:08:18.959 which undergoes tyrosine

NOTE Confidence: 0.82312862

00:08:18.959 --> 00:08:20.618 phosphorylation binds .

NOTE Confidence: 0.82312862

00:08:20.620 --> 00:08:22.912 The kinase and through a cascade

NOTE Confidence: 0.82312862

00:08:22.912 --> 00:08:24.982 activates glycogen synthesis and through

NOTE Confidence: 0.82312862

00:08:24.982 --> 00:08:26.910 transcription regulation of FOXO,

NOTE Confidence: 0.82312862

00:08:26.910 --> 00:08:29.208 it puts the brake on gluconeogenesis

NOTE Confidence: 0.82312862

00:08:29.208 --> 00:08:31.778 and work starting with ARM and Samuel,

NOTE Confidence: 0.82312862

00:08:31.780 --> 00:08:34.018 who was in the Investigational medicine

NOTE Confidence: 0.82312862

00:08:34.018 --> 00:08:36.588 program with me and received his pH.

NOTE Confidence: 0.82312862

00:08:36.590 --> 00:08:38.768 D on top of his MD.

NOTE Confidence: 0.82312862

00:08:38.770 --> 00:08:40.915 He was a trained endocrinologist

NOTE Confidence: 0.82312862

00:08:40.915 --> 00:08:43.790 when he came to work with me,

NOTE Confidence: 0.82312862

00:08:43.790 --> 00:08:45.700 found that it was specifically

NOTE Confidence: 0.82312862

00:08:45.700 --> 00:08:48.149 how fat and liver causes instant

NOTE Confidence: 0.82312862

00:08:48.149 --> 00:08:50.945 resistance was its accumulation of the.

NOTE Confidence: 0.82312862

00:08:50.950 --> 00:08:53.340 This product I asoli scroll.

NOTE Confidence: 0.82312862

00:08:53.340 --> 00:08:55.632 This is the penultimate step in

NOTE Confidence: 0.82312862

00:08:55.632 --> 00:08:57.160 triglyceride synthesis and what

NOTE Confidence: 0.82312862

00:08:57.224 --> 00:08:59.379 environment showed it activates protein

NOTE Confidence: 0.82312862

00:08:59.379 --> 00:09:02.080 kinase epsilon protein kinase C epsilon,

NOTE Confidence: 0.82312862

00:09:02.080 --> 00:09:03.990 which binds the receptor and

NOTE Confidence: 0.82312862

00:09:03.990 --> 00:09:05.518 inhibits the receptor kinase.

NOTE Confidence: 0.82312862

00:09:05.520 --> 00:09:07.736 And what Garmin did was to prove this.

NOTE Confidence: 0.82312862

00:09:07.740 --> 00:09:10.332 He knocked down PKC Epsilon and

NOTE Confidence: 0.82312862

00:09:10.332 --> 00:09:12.807 got protection from lipid induced

NOTE Confidence: 0.82312862

00:09:12.807 --> 00:09:14.799 hepatic insulin resistance.

NOTE Confidence: 0.82312862

00:09:14.800 --> 00:09:18.008 The last question in this was how is

NOTE Confidence: 0.82312862

00:09:18.008 --> 00:09:20.051 epsilon inhibiting the receptor kinase

NOTE Confidence: 0.82312862

00:09:20.051 --> 00:09:22.760 and this is where another MD PhD.

NOTE Confidence: 0.82312862

00:09:22.760 --> 00:09:26.870 Student Max Peterson working with Jesse

NOTE Confidence: 0.82312862

00:09:26.870 --> 00:09:29.610 Reinhardt doing untargeted phosphoproteomics,

NOTE Confidence: 0.82312862

00:09:29.610 --> 00:09:32.352 we discovered that PKC epsilon directly

NOTE Confidence: 0.82312862

00:09:32.352 --> 00:09:35.690 binds to the receptor and phosphorylates.

NOTE Confidence: 0.82312862

00:09:35.690 --> 00:09:38.578 This green loop is the instant receptor the

NOTE Confidence: 0.82312862

00:09:38.578 --> 00:09:40.808 catalytic domain of the instant receptor.

NOTE Confidence: 0.82312862

00:09:40.810 --> 00:09:43.180 These three tyrosines are required

NOTE Confidence: 0.82312862

00:09:43.180 --> 00:09:45.550 for insulin activation of the

NOTE Confidence: 0.82312862

00:09:45.630 --> 00:09:48.674 receptor and what Jesse and and Max

NOTE Confidence: 0.82312862

00:09:48.674 --> 00:09:50.904 and Brandon Gassaway found that

NOTE Confidence: 0.82312862

00:09:50.904 --> 00:09:52.769 Epsilon purified Epsilon.

NOTE Confidence: 0.82312862

00:09:52.770 --> 00:09:55.185 Cost 4 relates the streaming 1160 which

NOTE Confidence: 0.82312862

00:09:55.185 --> 00:09:57.886 got us very excited because it's in

NOTE Confidence: 0.82312862

00:09:57.886 --> 00:10:00.960 the catalytic domain of the instant receptor.

NOTE Confidence: 0.82312862

00:10:00.960 --> 00:10:02.829 The other thing that got us excited

NOTE Confidence: 0.82312862

00:10:02.829 --> 00:10:05.199 is this 3 inning is conserved all the

NOTE Confidence: 0.82312862

00:10:05.199 --> 00:10:07.662 way from humans down to fruit flies as

NOTE Confidence: 0.82312862

00:10:07.662 --> 00:10:09.734 well as the three tyrosines in that

NOTE Confidence: 0.82312862

00:10:09.740 --> 00:10:11.925 are required for insulin activation

NOTE Confidence: 0.82312862

00:10:11.925 --> 00:10:14.752 of the kinase and the receptor.

NOTE Confidence: 0.82312862

00:10:14.752 --> 00:10:16.216 To prove this,

NOTE Confidence: 0.82312862

00:10:16.220 --> 00:10:18.677 Max knocked the the three nine to

NOTE Confidence: 0.82312862

00:10:18.677 --> 00:10:21.039 glutamic acid to mimic a phosphorylation

NOTE Confidence: 0.82312862

00:10:21.039 --> 00:10:23.517 event and showed that it was.

NOTE Confidence: 0.82312862

00:10:23.520 --> 00:10:24.963 Receptor kinase dead.

NOTE Confidence: 0.82312862

00:10:24.963 --> 00:10:27.368 He did the reverse experiment,

NOTE Confidence: 0.82312862

00:10:27.370 --> 00:10:29.806 mutated the three inch when alanine and

NOTE Confidence: 0.82312862

00:10:29.806 --> 00:10:31.990 she got protection from PKC epsilon

NOTE Confidence: 0.82312862

00:10:31.990 --> 00:10:33.806 induced reduction in receptor kinase

NOTE Confidence: 0.82312862

00:10:33.806 --> 00:10:36.386 activity and then we made the mouse

NOTE Confidence: 0.82312862

00:10:36.386 --> 00:10:38.994 and this is the three inning to the

NOTE Confidence: 0.82312862

00:10:38.994 --> 00:10:41.527 homologous site the 11:50 site to an alanine.

NOTE Confidence: 0.82312862

00:10:41.530 --> 00:10:44.018 I won't show you the date it's published

NOTE Confidence: 0.82312862

00:10:44.018 --> 00:10:45.929 regular child fed mice are perfectly

NOTE Confidence: 0.82312862

00:10:45.929 --> 00:10:48.059 normal but when you feed these mice

NOTE Confidence: 0.82312862

00:10:48.059 --> 00:10:50.183 a high fat diet this is what we see.

NOTE Confidence: 0.78363198014

00:10:50.190 --> 00:10:52.548 This is doing a hyperinsulinemic uyemura

NOTE Confidence: 0.78363198014

00:10:52.548 --> 00:10:55.077 clamp we give insulin. To these mice.

NOTE Confidence: 0.78363198014

00:10:55.077 --> 00:10:56.672 Normally it should suppress glucose

NOTE Confidence: 0.78363198014

00:10:56.672 --> 00:10:58.323 production and this is what we

NOTE Confidence: 0.78363198014

00:10:58.323 --> 00:10:59.763 always see with high fat feeding,

NOTE Confidence: 0.78363198014

00:10:59.770 --> 00:11:02.304 fat accumulation, fatty liver and the mice.

NOTE Confidence: 0.78363198014

00:11:02.310 --> 00:11:04.200 Insulin resistant as defined by inability

NOTE Confidence: 0.78363198014

00:11:04.200 --> 00:11:06.208 of insulin to put the brake on,

NOTE Confidence: 0.78363198014

00:11:06.210 --> 00:11:07.930 have had a glucose production.

NOTE Confidence: 0.78363198014

00:11:07.930 --> 00:11:11.066 In contrast, same amount of liver fat.

NOTE Confidence: 0.78363198014

00:11:11.070 --> 00:11:12.550 These these single mutation

NOTE Confidence: 0.78363198014

00:11:12.550 --> 00:11:14.400 in three to an alanine.

NOTE Confidence: 0.78363198014

00:11:14.400 --> 00:11:17.250 Normal suppression of the paddock glucose

NOTE Confidence: 0.78363198014

00:11:17.250 --> 00:11:19.647 production so they're protected from

NOTE Confidence: 0.78363198014

00:11:19.647 --> 00:11:21.762 fat induced hepatic insulin resistance

NOTE Confidence: 0.78363198014

00:11:21.762 --> 00:11:24.439 with the single amino acid mutation.

NOTE Confidence: 0.78363198014

00:11:24.440 --> 00:11:27.104 Follow up studies done by a graduate student.

NOTE Confidence: 0.78363198014

00:11:27.110 --> 00:11:29.846 Coonley you in the lab has shown working with

NOTE Confidence: 0.78363198014

00:11:29.846 --> 00:11:32.239 Jonathan Bogan to do Compartmentation to see.

NOTE Confidence: 0.78363198014

00:11:32.240 --> 00:11:33.540 OK, there's different isoforms

NOTE Confidence: 0.78363198014

00:11:33.540 --> 00:11:35.165 of these types of literals.

NOTE Confidence: 0.78363198014

00:11:35.170 --> 00:11:36.835 What is the compartment that's

NOTE Confidence: 0.78363198014

00:11:36.835 --> 00:11:38.500 actually triggering the fatty acid?

NOTE Confidence: 0.78363198014

00:11:38.500 --> 00:11:41.100 The lipid induced insulin resistance?

NOTE Confidence: 0.78363198014

00:11:41.100 --> 00:11:43.293 We found that it was the SN12

NOTE Confidence: 0.78363198014

00:11:43.293 --> 00:11:44.382 dice of glycerols,

NOTE Confidence: 0.78363198014

00:11:44.382 --> 00:11:46.560 as opposed to the 2-3 or

NOTE Confidence: 0.78363198014

00:11:46.639 --> 00:11:48.379 the 1/3 stereo isomers,

NOTE Confidence: 0.78363198014

00:11:48.380 --> 00:11:50.088 and it was specifically

NOTE Confidence: 0.78363198014

00:11:50.088 --> 00:11:51.796 in the plasma membrane.

NOTE Confidence: 0.78363198014

00:11:51.800 --> 00:11:54.284 The yes and 1/2 Dags accumulating

NOTE Confidence: 0.78363198014

00:11:54.284 --> 00:11:55.526 the plasma membrane.

NOTE Confidence: 0.78363198014

00:11:55.530 --> 00:11:58.477 This is what leads the PKC epsilon

NOTE Confidence: 0.78363198014

00:11:58.477 --> 00:12:01.020 translocation and that leads to the

NOTE Confidence: 0.78363198014

00:12:01.020 --> 00:12:03.015 phosphorylation of the three enine

NOTE Confidence: 0.78363198014

00:12:03.015 --> 00:12:06.073 and in defects in receptor kinase

NOTE Confidence: 0.78363198014

00:12:06.073 --> 00:12:08.253 activity and insulin resistance.

NOTE Confidence: 0.78363198014

00:12:08.260 --> 00:12:10.900 This concept is very important.

NOTE Confidence: 0.78363198014

00:12:10.900 --> 00:12:11.432 Very important.

NOTE Confidence: 0.78363198014

00:12:11.432 --> 00:12:13.028 I'll make a couple points here.

NOTE Confidence: 0.78363198014

00:12:13.030 --> 00:12:14.358 It's all about location.

NOTE Confidence: 0.78363198014

00:12:14.358 --> 00:12:16.780 So if the S1 Dags build up

NOTE Confidence: 0.78363198014

00:12:16.780 --> 00:12:18.565 in a lipid droplet fraction,

NOTE Confidence: 0.78363198014

00:12:18.570 --> 00:12:19.940 they do not cause insulin

NOTE Confidence: 0.78363198014

00:12:19.940 --> 00:12:21.310 resistance and we see this.

NOTE Confidence: 0.78363198014

00:12:21.310 --> 00:12:23.214 We see this in some of our fatty

NOTE Confidence: 0.78363198014

00:12:23.214 --> 00:12:24.905 liver patients that do not have

NOTE Confidence: 0.78363198014

00:12:24.905 --> 00:12:26.069 a paddock instant resistance,

NOTE Confidence: 0.78363198014

00:12:26.070 --> 00:12:28.177 and that's because the fact and even

NOTE Confidence: 0.78363198014

00:12:28.177 --> 00:12:30.745 the Dags are in are in a lipid droplet.

NOTE Confidence: 0.78363198014

00:12:30.750 --> 00:12:32.205 It's only the plasma membrane

NOTE Confidence: 0.78363198014

00:12:32.205 --> 00:12:33.369 Dyson Glycerols that trigger

NOTE Confidence: 0.78363198014

00:12:33.369 --> 00:12:34.610 the insulin resistance.

NOTE Confidence: 0.78363198014

00:12:34.610 --> 00:12:36.734 And this explains many of the

NOTE Confidence: 0.78363198014

00:12:36.734 --> 00:12:38.330 confusion literature the HDAC 3.

NOTE Confidence: 0.78363198014

00:12:38.330 --> 00:12:40.436 Lock down which Lazar made huge

NOTE Confidence: 0.78363198014

00:12:40.436 --> 00:12:41.840 fatty liver insulin resistance.

NOTE Confidence: 0.78363198014

00:12:41.840 --> 00:12:44.138 We've shown CGI 58 knocked down.

NOTE Confidence: 0.78363198014

00:12:44.140 --> 00:12:46.408 This is a cofactor for AGL,

NOTE Confidence: 0.78363198014

00:12:46.410 --> 00:12:49.098 the light base and the huge fat accumulation.

NOTE Confidence: 0.78363198014

00:12:49.100 --> 00:12:50.670 Knowing some resistance and most

NOTE Confidence: 0.78363198014

00:12:50.670 --> 00:12:53.034 recently we showed when you have knockout

NOTE Confidence: 0.78363198014

00:12:53.034 --> 00:12:54.869 of the microsomal transfer protein.

NOTE Confidence: 0.78363198014

00:12:54.870 --> 00:12:58.262 This is involved when the Assembly of the

NOTE Confidence: 0.78363198014

00:12:58.262 --> 00:13:01.460 lipid particle again huge lipid accumulation,

NOTE Confidence: 0.78363198014

00:13:01.460 --> 00:13:02.908 no insulin resistance because

NOTE Confidence: 0.78363198014

00:13:02.908 --> 00:13:05.080 it's all in the lipid droplet.

NOTE Confidence: 0.78363198014

00:13:05.080 --> 00:13:05.443 OK,

NOTE Confidence: 0.78363198014

00:13:05.443 --> 00:13:08.347 so we've gone on to basically establish this.

NOTE Confidence: 0.78363198014

00:13:08.350 --> 00:13:11.040 In liver.

NOTE Confidence: 0.78363198014

00:13:11.040 --> 00:13:13.266 **** Liu, shown in the same thing,

NOTE Confidence: 0.78363198014

00:13:13.270 --> 00:13:14.632 is happening with short term high

NOTE Confidence: 0.78363198014

00:13:14.632 --> 00:13:15.970 fat feeding and the fat cell.

NOTE Confidence: 0.78363198014

00:13:15.970 --> 00:13:17.056 Same mechanism.

NOTE Confidence: 0.78363198014

00:13:17.056 --> 00:13:19.771 712 PKC epsilon transportation another

NOTE Confidence: 0.78363198014

00:13:19.771 --> 00:13:22.753 graduate student showed that this is

NOTE Confidence: 0.78363198014

00:13:22.753 --> 00:13:24.883 what's happening in skeletal muscle.

NOTE Confidence: 0.78363198014

00:13:24.890 --> 00:13:25.804 Same mechanism.

NOTE Confidence: 0.78363198014

00:13:25.804 --> 00:13:26.261 SM12,

NOTE Confidence: 0.78363198014

00:13:26.261 --> 00:13:29.003 PKC hitting the receptor and another

NOTE Confidence: 0.78363198014

00:13:29.003 --> 00:13:31.962 MD PhD student has found that the

NOTE Confidence: 0.78363198014

00:13:31.962 --> 00:13:34.708 same thing is happening in the kidney.

NOTE Confidence: 0.78363198014

00:13:34.710 --> 00:13:36.162 We don't think about the kidney

NOTE Confidence: 0.78363198014

00:13:36.162 --> 00:13:37.130 as being instant responsive.

NOTE Confidence: 0.78363198014

00:13:37.130 --> 00:13:39.730 It is and it gets instant resistant and

NOTE Confidence: 0.78363198014

00:13:39.730 --> 00:13:42.036 Brandon has shown that it's the same.

NOTE Confidence: 0.78363198014

00:13:42.040 --> 00:13:44.668 Mechanism SM12 daggs in the membrane.

NOTE Confidence: 0.78363198014

00:13:44.670 --> 00:13:46.239 Activating PKC epsilon.

NOTE Confidence: 0.8256661445

00:13:49.120 --> 00:13:51.731 Activation of Epsilon does many other things

NOTE Confidence: 0.8256661445

00:13:51.731 --> 00:13:54.227 besides the receptors to work by Jesse

NOTE Confidence: 0.8256661445

00:13:54.227 --> 00:13:56.195 Reinhard and his graduates from Gassaway.

NOTE Confidence: 0.8256661445

00:13:56.200 --> 00:13:58.664 Working with us showed that epsilon hits

NOTE Confidence: 0.8256661445

00:13:58.664 --> 00:14:01.384 many other targets besides receptors, so it

NOTE Confidence: 0.8256661445

00:14:01.384 --> 00:14:02.956 could actually explain many other things.

NOTE Confidence: 0.8256661445

00:14:02.960 --> 00:14:05.550 Going on post receptor defects

NOTE Confidence: 0.8256661445

00:14:05.550 --> 00:14:07.104 and insulin action.

NOTE Confidence: 0.8256661445

00:14:07.110 --> 00:14:08.614 I just wanted to share this with you

NOTE Confidence: 0.8256661445

00:14:08.614 --> 00:14:10.010 because you have to ask the question,

NOTE Confidence: 0.8256661445

00:14:10.010 --> 00:14:13.150 why has insulin resistance exists?

NOTE Confidence: 0.8256661445

00:14:13.150 --> 00:14:15.054 Why has it? Why does it exist?

NOTE Confidence: 0.8256661445

00:14:15.060 --> 00:14:16.817 Why is that three name being conserved

NOTE Confidence: 0.8256661445

00:14:16.817 --> 00:14:18.990 all the way from humans to fruit flies?

NOTE Confidence: 0.8256661445

00:14:18.990 --> 00:14:20.579 And so here is a hypothesis I

NOTE Confidence: 0.8256661445

00:14:20.579 --> 00:14:21.789 want to share with you.

NOTE Confidence: 0.8256661445

00:14:21.790 --> 00:14:25.305 Where with starvation this pathways

NOTE Confidence: 0.8256661445

00:14:25.305 --> 00:14:28.820 activated every model you starve,

NOTE Confidence: 0.8256661445

00:14:28.820 --> 00:14:31.326 gets fatty liver that goes from mice,

NOTE Confidence: 0.8256661445

00:14:31.330 --> 00:14:32.401 rats to humans.

NOTE Confidence: 0.8256661445

00:14:32.401 --> 00:14:34.543 During starvation you get fatty liver.

NOTE Confidence: 0.8256661445

00:14:34.550 --> 00:14:35.850 This pathway gets activated,

NOTE Confidence: 0.8256661445

00:14:35.850 --> 00:14:37.150 you get instant resistance.

NOTE Confidence: 0.8256661445

00:14:37.150 --> 00:14:40.450 The starvation and this maintains glucose

NOTE Confidence: 0.8256661445

00:14:40.450 --> 00:14:44.730 in the bloodstream for the for the CNS,

NOTE Confidence: 0.8256661445

00:14:44.730 --> 00:14:46.277 the brain and the red blood cells.

NOTE Confidence: 0.8256661445

00:14:46.280 --> 00:14:50.459 And this is starvation induced in some

NOTE Confidence: 0.8256661445

00:14:50.459 --> 00:14:53.539 resistances and protective for survival.

NOTE Confidence: 0.8256661445

00:14:53.540 --> 00:14:53.892 OK.

NOTE Confidence: 0.8256661445

00:14:53.892 --> 00:14:56.356 And then finally I just want to

NOTE Confidence: 0.8256661445

00:14:56.356 --> 00:14:59.420 end up here by sharing with you 2.

NOTE Confidence: 0.8256661445

00:14:59.420 --> 00:15:00.880 How do we fix this?

NOTE Confidence: 0.8256661445

00:15:00.880 --> 00:15:03.800 And if we're right, the two bad actors,

NOTE Confidence: 0.8256661445

00:15:03.800 --> 00:15:06.579 one of them diacylglycerol in the plasma

NOTE Confidence: 0.8256661445

00:15:06.579 --> 00:15:07.960 membrane, the other is acetyl Co.

NOTE Confidence: 0.8256661445

00:15:07.960 --> 00:15:09.560 Way which directly activates

NOTE Confidence: 0.8256661445

00:15:09.560 --> 00:15:10.360 perfect carboxylase.

NOTE Confidence: 0.8256661445

00:15:10.360 --> 00:15:11.252 They don't have much.

NOTE Confidence: 0.8256661445

00:15:11.252 --> 00:15:13.369 I don't have enough time to talk about that,

NOTE Confidence: 0.8256661445

00:15:13.370 --> 00:15:14.802 and if we're right,

NOTE Confidence: 0.8256661445

00:15:14.802 --> 00:15:16.950 if we can reduce these moieties

NOTE Confidence: 0.8256661445

00:15:17.025 --> 00:15:18.150 in the parasite,

NOTE Confidence: 0.8256661445

00:15:18.150 --> 00:15:20.852 we can fix all the metabolic dysfunction

NOTE Confidence: 0.8256661445

00:15:20.852 --> 00:15:23.330 of metabolic syndrome and type 2 diabetes.

NOTE Confidence: 0.8256661445

00:15:23.330 --> 00:15:25.913 One way to do that is reduce energy intake.

NOTE Confidence: 0.8256661445

00:15:25.920 --> 00:15:28.768 The other is revving up the TCA cycle.

NOTE Confidence: 0.8256661445

00:15:28.770 --> 00:15:32.930 So here as a study that we did years ago,

NOTE Confidence: 0.8256661445

00:15:32.930 --> 00:15:33.554 Kit Peterson,

NOTE Confidence: 0.8256661445

00:15:33.554 --> 00:15:35.426 we took patients with fatty liver,

NOTE Confidence: 0.8256661445

00:15:35.430 --> 00:15:38.190 put them on a 1200 calorie diet in.

NOTE Confidence: 0.8256661445

00:15:38.190 --> 00:15:40.050 These are type 2 diabetics,

NOTE Confidence: 0.8256661445

00:15:40.050 --> 00:15:41.127 fast and hyperglycemia.

NOTE Confidence: 0.8256661445

00:15:41.127 --> 00:15:43.281 This is due to increased hepatic

NOTE Confidence: 0.8256661445

00:15:43.281 --> 00:15:45.454 glucose production due to increased

NOTE Confidence: 0.8256661445

00:15:45.454 --> 00:15:47.206 gluconeogenesis and insulin resistance

NOTE Confidence: 0.8256661445

00:15:47.206 --> 00:15:49.712 and ability to insulin suppress glucose

NOTE Confidence: 0.8256661445

00:15:49.712 --> 00:15:51.622 production and 1200 calorie diet.

NOTE Confidence: 0.8256661445

00:15:51.622 --> 00:15:54.253 They only had to lose 10% of

NOTE Confidence: 0.8256661445

00:15:54.253 --> 00:15:56.168 their body weight, sometimes 8%.

NOTE Confidence: 0.8256661445

00:15:56.170 --> 00:15:57.634 We fix fasting hyperglycemia,

NOTE Confidence: 0.8256661445

00:15:57.634 --> 00:16:00.385 we it's due to reduction in patient

NOTE Confidence: 0.8256661445

00:16:00.385 --> 00:16:02.825 glucose production due to decreased

NOTE Confidence: 0.8256661445

00:16:02.825 --> 00:16:05.295 gluconeogenesis and we normalize insulin's

NOTE Confidence: 0.8256661445

00:16:05.295 --> 00:16:07.870 ability to suppress glucose production.

NOTE Confidence: 0.8256661445

00:16:07.870 --> 00:16:08.680 So again,

NOTE Confidence: 0.8256661445

00:16:08.680 --> 00:16:11.110 three points here for the clinicians,

NOTE Confidence: 0.8256661445

00:16:11.110 --> 00:16:13.085 10% weight reduction was sufficient

NOTE Confidence: 0.8256661445

00:16:13.085 --> 00:16:16.180 to get rid of all the liver fat,

NOTE Confidence: 0.8256661445

00:16:16.180 --> 00:16:17.710 and this is now, I think,

NOTE Confidence: 0.8256661445

00:16:17.710 --> 00:16:18.694 been replicated many,

NOTE Confidence: 0.8256661445

00:16:18.694 --> 00:16:19.350 many times.

NOTE Confidence: 0.8256661445

00:16:19.350 --> 00:16:22.342 It's in the textbooks and the second thing

NOTE Confidence: 0.8256661445

00:16:22.342 --> 00:16:24.950 this again 2005 to almost 20 years ago.

NOTE Confidence: 0.8256661445

00:16:24.950 --> 00:16:27.038 Every patient with type poorly controlled

NOTE Confidence: 0.8256661445

00:16:27.038 --> 00:16:29.810 type 2 diabetes has too much fat and liver.

NOTE Confidence: 0.8256661445

00:16:29.810 --> 00:16:32.450 Normal as I showed you one point 8%,

NOTE Confidence: 0.8256661445

00:16:32.450 --> 00:16:34.772 it's about 10 times normal and

NOTE Confidence: 0.8256661445

00:16:34.772 --> 00:16:36.642 again 10% rate reduction is able

NOTE Confidence: 0.8256661445

00:16:36.642 --> 00:16:38.580 to get rid of that liver fat.

NOTE Confidence: 0.8256661445

00:16:38.580 --> 00:16:39.805 You get rid of the liver fat.

NOTE Confidence: 0.8256661445

00:16:39.810 --> 00:16:41.340 You fix diabetes.

NOTE Confidence: 0.8256661445

00:16:41.340 --> 00:16:44.400 Finally, how do we fix it?

NOTE Confidence: 0.8256661445

00:16:44.400 --> 00:16:45.116 It's again,

NOTE Confidence: 0.8256661445

00:16:45.116 --> 00:16:47.264 unfortunately we all know weight loss

NOTE Confidence: 0.8256661445

00:16:47.264 --> 00:16:49.935 is very hard to achieve in the clinic.

NOTE Confidence: 0.8256661445

00:16:49.940 --> 00:16:50.784 Are there other ways?

NOTE Confidence: 0.8256661445

00:16:50.784 --> 00:16:52.050 And this is what I'll share

NOTE Confidence: 0.89793599

00:16:52.093 --> 00:16:53.725 with you in the last two minutes here.

NOTE Confidence: 0.89793599

00:16:53.730 --> 00:16:55.380 If we Rev up the mitochondria,

NOTE Confidence: 0.89793599

00:16:55.380 --> 00:16:56.964 this is a way of burning the fat to

NOTE Confidence: 0.89793599

00:16:56.964 --> 00:16:58.692 get rid of it, and the first study

NOTE Confidence: 0.89793599

00:16:58.692 --> 00:17:00.270 was done actually by Varman Samuel,

NOTE Confidence: 0.89793599

00:17:00.270 --> 00:17:01.990 who already introduced you to,

NOTE Confidence: 0.89793599

00:17:01.990 --> 00:17:03.615 and we've known about Diane

NOTE Confidence: 0.89793599

00:17:03.615 --> 00:17:05.560 DNP for almost a century now.

NOTE Confidence: 0.89793599

00:17:05.560 --> 00:17:06.571 It's an uncoupler.

NOTE Confidence: 0.89793599

00:17:06.571 --> 00:17:08.593 It promotes dissipates the proton gradient,

NOTE Confidence: 0.89793599

00:17:08.600 --> 00:17:11.232 Revs up fat oxidation, and in this paper

NOTE Confidence: 0.89793599

00:17:11.232 --> 00:17:14.120 of Armin showed it reduced tags and dags.

NOTE Confidence: 0.89793599

00:17:14.120 --> 00:17:16.670 We prevented PKC epsilon activation and

NOTE Confidence: 0.89793599

00:17:16.670 --> 00:17:19.210 proved the paddock insulin sensitivity.

NOTE Confidence: 0.89793599

00:17:19.210 --> 00:17:21.958 DNP is a search with many talk.

NOTE Confidence: 0.89793599

00:17:21.958 --> 00:17:25.006 The main toxicity is on target.

NOTE Confidence: 0.89793599

00:17:25.010 --> 00:17:27.096 It promotes hyperthermia and so we came

NOTE Confidence: 0.89793599

00:17:27.096 --> 00:17:30.088 up with an idea of what if we liver targeted.

NOTE Confidence: 0.89793599

00:17:30.090 --> 00:17:32.190 Can we avoid the toxicity and

NOTE Confidence: 0.89793599

00:17:32.190 --> 00:17:34.950 so in a series of studies done,

NOTE Confidence: 0.89793599

00:17:34.950 --> 00:17:37.570 but we do need to kind of just wrap up

NOTE Confidence: 0.89793599

00:17:37.639 --> 00:17:40.183 so we have time for the next session.

NOTE Confidence: 0.89793599

00:17:40.190 --> 00:17:41.798 This is all published,

NOTE Confidence: 0.89793599

00:17:41.798 --> 00:17:43.808 but we deliver targeted DNP.

NOTE Confidence: 0.89793599

00:17:43.810 --> 00:17:46.828 We're able to prevent the hyperthermia,

NOTE Confidence: 0.89793599

00:17:46.830 --> 00:17:49.938 and it's 50 fold safer than the

NOTE Confidence: 0.89793599

00:17:49.938 --> 00:17:50.826 parent compound.

NOTE Confidence: 0.89793599

00:17:50.830 --> 00:17:52.606 We reverse insulin resistance.

NOTE Confidence: 0.89793599

00:17:52.606 --> 00:17:55.270 This is our second generation compound.

NOTE Confidence: 0.89793599

00:17:55.270 --> 00:17:56.798 It's even tenfold safer.

NOTE Confidence: 0.89793599

00:17:56.798 --> 00:17:58.326 We fix insulin resistance,

NOTE Confidence: 0.89793599

00:17:58.330 --> 00:17:59.923 and this is the key thing for the liver.

NOTE Confidence: 0.89793599

00:17:59.930 --> 00:18:00.330 People.

NOTE Confidence: 0.89793599

00:18:00.330 --> 00:18:02.330 We get rid of inflammation.

NOTE Confidence: 0.89793599

00:18:02.330 --> 00:18:03.978 We get rid of the liver fat and

NOTE Confidence: 0.89793599

00:18:03.978 --> 00:18:05.669 you get reduced liver fibrosis.

NOTE Confidence: 0.89793599

00:18:05.670 --> 00:18:08.256 And so we've developed methods to

NOTE Confidence: 0.89793599

00:18:08.256 --> 00:18:10.486 assess mitochondrial oxidation.

NOTE Confidence: 0.89793599

00:18:10.486 --> 00:18:13.180 Vivo using NMR.

NOTE Confidence: 0.89793599

00:18:13.180 --> 00:18:16.001 Spectroscopy we've shown it safe and non

NOTE Confidence: 0.89793599

00:18:16.001 --> 00:18:18.927 human primates and this paper is impressed.

NOTE Confidence: 0.89793599

00:18:18.930 --> 00:18:21.216 We've shown it actually reduces the

NOTE Confidence: 0.89793599

00:18:21.216 --> 00:18:23.630 how to cellular carcinoma in a aging

NOTE Confidence: 0.89793599

00:18:23.630 --> 00:18:25.956 mouse model and this is Rachel Perry's work.

NOTE Confidence: 0.89793599

00:18:25.960 --> 00:18:28.284 She's now also shown again obesity associated

NOTE Confidence: 0.89793599

00:18:28.284 --> 00:18:30.239 cancers are going through the roof.

NOTE Confidence: 0.89793599

00:18:30.240 --> 00:18:31.934 You get rid of insulin resistance and

NOTE Confidence: 0.89793599

00:18:31.934 --> 00:18:33.638 in two studies this is one of them.

NOTE Confidence: 0.89793599

00:18:33.640 --> 00:18:36.336 Racial has shown it slows down the growth

NOTE Confidence: 0.89793599

00:18:36.336 --> 00:18:39.235 of colon cancer as well as breast cancer.

NOTE Confidence: 0.89793599

00:18:39.240 --> 00:18:40.860 So this is my final slide.

NOTE Confidence: 0.89793599

00:18:40.860 --> 00:18:43.330 You Rev up mitochondrial and.

NOTE Confidence: 0.89793599

00:18:43.330 --> 00:18:45.605 Pulling and liver you reduce liver fat.

NOTE Confidence: 0.89793599

00:18:45.610 --> 00:18:46.960 It's going to be heart healthy.

NOTE Confidence: 0.89793599

00:18:46.960 --> 00:18:48.925 You reduce triglycerides and eldil

NOTE Confidence: 0.89793599

00:18:48.925 --> 00:18:50.890 cholesterol and you secondarily improve

NOTE Confidence: 0.89793599

00:18:50.952 --> 00:18:52.932 muscle and some resistance because you

NOTE Confidence: 0.89793599

00:18:52.932 --> 00:18:55.049 decrease export of that to the muscle.

NOTE Confidence: 0.89793599

00:18:55.050 --> 00:18:57.372 So this is my oh and many other groups

NOTE Confidence: 0.89793599

00:18:57.372 --> 00:18:59.677 are jumping on this now and it's actually

NOTE Confidence: 0.89793599

00:18:59.677 --> 00:19:02.893 it is in clinical trials and it's been

NOTE Confidence: 0.89793599

00:19:02.893 --> 00:19:06.120 shown to be safe and reduce liver

NOTE Confidence: 0.89793599

00:19:06.223 --> 00:19:09.024 fat in humans as a related compound.

NOTE Confidence: 0.89793599

00:19:09.024 --> 00:19:10.167 So most important,

NOTE Confidence: 0.89793599

00:19:10.170 --> 00:19:11.670 slide the collaborators.

NOTE Confidence: 0.89793599

00:19:11.670 --> 00:19:15.170 I was mostly able to acknowledge during

NOTE Confidence: 0.89793599

00:19:15.248 --> 00:19:18.263 my talk and this was that window a year

NOTE Confidence: 0.89793599

00:19:18.263 --> 00:19:21.024 ago when we go maskless before Omicron.

NOTE Confidence: 0.89793599

00:19:21.024 --> 00:19:24.013 Thank you very much for your attention.