

# Paradigm Shifts in Obesity Research and Treatment: Roundtable Discussion

Jesse Roth,\*† Jeffrey S. Volek,‡ Marc Jacobson,‡‡§§ Joseph Hickey,\*\* Daniel T. Stein,†† Samuel Klein,§ Richard Feinman,¶ Gary J. Schwartz,|| and CJ Segal-Isaacson‡‡

*Audience Member.* I'm a reproductive endocrinologist, and I'm here because there are some striking differences that can be seen in female hormones based on weight. Some of you have looked at some hormones and have observed an increase in testosterone in men. Was that total testosterone and was that because of sex hormone binding globulin rising or was there an independent change in testosterone that you noticed?

*Dr. Volek.* In response to a low-carbohydrate diet, we have not shown a change in testosterone. The changes in testosterone occur more with a change in percentage fat of 10% to 40%. There are several studies of a higher-fat diet in that range that show an association with higher testosterone in women as well (1–5). But we did not see that in the low-carbohydrate diets when we went up to 60% to 65% fat.

*Audience Member.* So you didn't see any change in total testosterone, but did you see any change in free testosterone or free estrogen index?

*Dr. Volek.* We did measure free testosterone and sex hormone binding globulin. They were fasting levels, and we did not see changes there. We did not look at those in women though, just in men.

*Audience Member.* I suspect it's different. Sex hormone binding globulin is not going to be a big player. One of the striking differences we see in women is changes in progesterone, and that's not going to be carried by sex hormone

binding globulin. It may be a different mechanism; it just triggered the same sort of thoughts.

*Dr. Volek.* We have not measured reproductive hormones, so we don't have any data there.

*Dr. Roth.* Are you worried about fertility or just about well-being or . . .

*Audience Member.* What's interesting is that the pattern that you see in the larger women seems to favor less progesterone, a little bit less estrogen, and longer overall cycles. If this is, in fact, a chronic pattern and can be changed with weight loss, that may explain some of the reproductive diseases that we see in women that are overweight: decreases in fertility, perhaps increases in breast cancer risk, things like that.

*Dr. Jacobson.* And also may be related to polycystic ovarian syndrome as a form of insulin resistance.

*Audience Member.* Polycystic ovarian syndrome is a trigger, but clearly we see this in so many women, and only 5% to 7% can really be defined as polycystic ovarian syndrome. They're the tip of the iceberg. But there are also regularly cycling women where you see these changes in hormones. It's just a striking observation that I'm just trying to make sense of.

*Dr. Hickey.* I know in men I have studied testosterone, dihydrogen testosterone, and estrogen levels. The thought about prostate cancer is now that it is related to testosterone-estrogen ratio. As you get fatter, as you increase abdominal fat, you increase aromatase and  $\alpha$ -reductase. As you get more metabolically unstable and you get fatter, you increase the breakdown of testosterone into those two substances. Both of these substances increase prostatic stimulation ~10 times more than testosterone does. That leads to benign prostatic hyperplasia or enlarged prostate, and eventually, we think, prostate cancer. When these people lose weight, they reduce the breakdown of testosterone into dihydrotestosterone and estradiol and that's very favorable. We're trying to follow that and see whether we can shrink prostate sizes. I'm sure it works with women the same way.

*Audience Member.* This is probably a very basic question, but I've never been able to understand this. Insulin prevents

\*Office of the Geriatrician-in-Chief, North Shore-Long Island Jewish Health System, Great Neck, New York; †Department of Medicine, Albert Einstein College of Medicine, Bronx, New York; ‡Human Performance Laboratory, Department of Kinesiology, University of Connecticut, Storrs, Connecticut; §§Center for Human Nutrition, Washington University School of Medicine, St. Louis, Missouri; ¶Downstate Medical Center, Brooklyn, New York; ||Weill Medical College of Cornell University, New York, New York; \*\*Heritage Medical Partners, Hilton Head Island, South Carolina; ††Department of Medicine (Endocrinology), Albert Einstein College of Medicine, Bronx, New York; ‡‡Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York; and §§Department of Pediatrics, North Shore-Long Island Jewish Health System, Great Neck, New York. Address correspondence to CJ Segal-Isaacson, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Belfer 1308C, Bronx, NY 10461. E-mail: isaacson@aecom.yu.edu Copyright © 2004 NAASO

fat oxidation, and everyone wants to increase insulin sensitivity. If you increase insulin sensitivity, you're going to be getting more insulin into the cells. I would think this would not prevent fat oxidation but would increase the storage of fat. That's why when I see patients who have medications that improve insulin sensitivity, they gain weight.

*Dr. Stein.* I agree that is something of a paradox. Certainly, there are studies showing that one of the major risk factors for gaining weight is insulin sensitivity. The converse is also true: the more weight you gain, the more insulin resistant you are. I think what this means is that there are genetic, probably polygenic, determinants of the level of sensitivity. With our modern Western lifestyle, if you're sedentary enough and eat just enough calories, and you're the kind of person who tends to be insulin sensitive, you will gain weight, and you'll gain it until such time as the body defends against further weight gain. There's a defense that is probably central, as Dr. Schwartz was telling us, but there is probably also a defense based on lipolysis. At a certain point, more fat cannot be loaded into the fat cells, and they release fat. The net result downstream of that is the metabolic syndrome, i.e., high circulating lipids and lipids where they don't belong: in muscles, in liver, in the endothelium, and probably contributing to atherosclerosis. I don't have a really good answer other than to say that each person's set-point is probably different and that one should ideally maintain a body weight that probably is on that edge of insulin sensitivity. In the old days, when we all starved as hunter-gatherers, this wasn't an issue because we were trying to avoid starving to death, but in our modern society, we all probably run up against that.

*Dr. Klein.* Insulin sensitivity is important in terms of the metabolic complications of obesity. From a metabolic and health perspective, the more insulin sensitive you are, the better, because insulin reduces the breakdown of fat from adipose tissue, thereby decreasing the release of fatty acids into the bloodstream, which can cause insulin resistance in liver and muscle. But body weight is regulated by energy balance, which may not have anything to do with insulin sensitivity. In general, if you eat more calories than you burn up, you gain weight, and if you eat fewer calories than you expend, you lose weight, whether you're insulin sensitive or insulin resistant. The oxidation of fat or preventing the oxidation of fat by being more sensitive to insulin does not affect overall energy balance, which determines body weight. The oxidation of fat and insulin sensitivity may be very important in the pathophysiology of obesity but probably is not important as a cause of obesity.

*Dr. Hickey.* You also have to think about what you're doing. If you put a diabetic on an insulin sensitizer, but you're not changing the nutrient profile or the glucose increase, you are going to help more glucose into the cell. You're not going to accomplish that much except lower the blood sugar. That's why carbohydrate restriction really goes

well with this sort of therapy. I don't really think we get more insulin sensitive, because as soon as I let my patients start eating carbohydrates again, everything deteriorates. I think what we do is just lower our need for insulin, that's why the insulin level drops. But if you put someone on an insulin sensitizer, which we often do, and then feed them carbohydrates, you are going to make them worse.

*Dr. Feinman.* I have a comment or maybe it's a question. I had the impression that insulin sensitivity is not uniform across all systems. The first target of insulin is really lipolysis, both kinetically and thermodynamically, even before insulin-responsive glucose transporter 4 (GLUT-4)<sup>1</sup> receptors are recruited. You may be insulin-resistant in terms of reduction of blood glucose, but I have a feeling that the lipolysis cycle is still inhibited in the direction of storing fat.

*Dr. Roth.* I was going to elaborate on that exact point, in that insulin sensitivity as we define it is a very convenient shorthand. The answers that were given were given in terms of insulin sensitivity relative to glucose use. Now we know that insulin receptors are widely distributed on almost all cells of the body. Each receptor affects the pathways that diverge within each cell very quickly, and there are multiple effects within each cell. To define insulin resistance, we picked one item to define the whole. I think your point is excellent, and we need to look at each of these pathways when we're talking about heightened or reduced insulin effect at a given insulin level. It's a convenient shorthand, but remember, it's a very simplified shorthand.

*Dr. Feinman.* I think the point on obesity and insulin control is that in extremes of dietary balance you're not running on equilibrium thermodynamics, you're running on nonequilibrium thermodynamics, that is, you're running on kinetics: how fast the flux of, in this case, lipids is flowing through the system. If you want to lower insulin, you may have enough GLUT-4 receptors, but you get the benefit from lipolysis without being afraid of not supplying yourself with glucose.

*Audience Member.* I wanted to point out some papers by Bisschop. There are three papers that came out of a study very similar to the one that Dan is doing now. If you're worried that Dan's finding won't be replicated, it's very similar to these papers by Bisschop (6–9). If you really want more, this last summer I and several people tried to project what the metabolism would be like on a low-carbohydrate diet, and we published that in *Current Atherosclerosis Reports* (10) in November. I would really like feedback on that because it's a work in progress. We projected what it would be like, and we need data on what the actual physiology really is. After studying this all summer, it strikes me that insulin is a big factor here. Insulin goes down on a low-carbohydrate diet to a greater extent compared

---

<sup>1</sup> Nonstandard abbreviations: GLUT, insulin-responsive glucose transporter 4.

with other diets, even when you control for weight loss. Is it possible that insulin is doing more than we think or that there is some downstream effect? As a clinician, we've all had the experience of giving diabetic patients insulin and finding that they get very hungry and gain weight. There is an effect of insulin on appetite, so I'd like to shift gears. The anorectic effect of the diet is very strong, and I wonder if that's related to insulin.

*Dr. Klein.* Insulin administered to the brain has been shown to inhibit food intake (11). But we don't know what effect excess circulating plasma insulin might have on food intake. For example, although insulin in the brain suppresses appetite, patients with diabetes who are treated with insulin tend to gain weight. Some have suggested that the transient decreases in blood glucose that occur in diabetics treated with insulin stimulate food intake.

*Dr. Schwartz.* Another important aspect of insulin action that Woods and colleagues have investigated is that insulin has the possibility to interact with other gut satiety factors, e.g., cholecystokinin, to the extent that the central administration of cholecystokinin and insulin are more capable of reducing food intake than insulin alone. With respect to the dichotomy between central and peripheral actions, to the extent that meal-related insulin secretion and cholecystokinin release are affected during these diets, it's very likely that you're going to have different forms of synergistic interaction, because these two act together at the central nervous system level.

*Dr. Segal-Isaacson.* I don't have any data for the next statement, but I'll throw it out. If you are not shutting off fatty acid oxidation, it's possible that you're also experiencing greater satiety and less hunger and are less driven to eat at that point. Whereas, I think that if you are shuttling fat into adipose tissue, it may be that you are also triggering greater hunger and end up eating more calories that way. I'm wondering if that's one of the mechanisms; that by not shutting down carnitine palmitoyl transferase-1, you're essentially alleviating hunger longer.

*Audience Member.* The question that I have is directed toward Jeff to explore a little bit more on trying to feed a low-carbohydrate diet to normal weight individuals and actually have them maintain their weight. Our experience in the overweight population is that when you feed ad libitum a well-controlled very-low-carbohydrate diet, they reduce their caloric intake by ~30%. This is compared with what their actual caloric requirements are for weight loss. The range is actually between ~49% to 89% of their needs. So if you're trying to feed a low-carbohydrate diet to somebody to maintain their weight, I'm wondering if you're actually overfeeding them in terms of their hunger and in terms of what they would actually select. What was your experience with that; what was the response of participants to actually having to consume that type of diet and actually maintain

their weight? I would think it would be a hypercaloric diet with respect to what they would want to eat.

*Dr. Volek.* Thank you for the question. We've done three studies: two in men (12,13) and one in women (14). Our intentions were to minimize changes in body weight because we were looking at lipids and we didn't want to have to deal with confounding factors and people saying it's the weight loss that caused the lipid changes. We probably did overfeed them, and it was very, very challenging. People didn't want to eat more, and we would monitor body weight, and it would drop off, and we would intensively aggressively counsel them to eat more to try to bring the body weight up. But we weren't successful. Especially with the men, we saw small weight losses that we could not prevent. The women did a pretty good job, I think it was <1 kg they lost. Because we didn't know what their baseline energy requirements were precisely, we can't say for sure what the caloric excess was, but I would imagine that we were feeding them more. At least our food records indicate that. But it's challenging in a free-living environment to maintain body weight on that type of diet.

*Dr. Roth.* There are two cosmic truths that we should take home that relate to all of our science. That it took so many years to get a low-carbohydrate diet accepted as a possible thing to experiment on and talk about was a shock to us. The scientific community absolutely stonewalled that for so long, and we allowed them to stonewall it. It is a shame, and in a way, we're both guilty, the stonewallers and the people who knew better but weren't able to put up enough opposition to force the issue. I think congratulations are due because finally this has broken out into the open, and it's talked about, and there are studies done, and people can get grants. It's a shame that it took so long. The second thing is another example of the way we accept that the naysayers have fixed their minds. When I was growing up, everybody knew that eating too much sugar was what caused diabetes. And then we went through the stage where eating glucose and sugar had absolutely nothing to do with diabetes and now suddenly we're coming back to that again. Maybe there's a middle position in here. But, again, the strength of the community, the *fixéte* of the milieu of the scientist's brain, is the biggest enemy of progress. Thank you.

#### References

1. **Reed MJ, Cheng RW, Simmonds M, Richmond W, James VHT.** Dietary lipids: an additional regulator of plasma levels of sex hormone binding globulin. *J Clin Endocrinol Metab.* 1987;64:1083-5.
2. **Hämäläinen E, Aldercreutz H, Puska P, Pietinen P.** Diet and serum sex hormones in healthy men. *J Steroid Biochem.* 1984;20:459-64.
3. **Dorgan JF, Judd JT, Longcope C, et al.** Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. *Am J Clin Nutr.* 1996;64:850-5.

4. **Goldin BR, Woods MN, Spiegelman DL, et al.** The effect of dietary fat and fiber on serum estrogen concentrations in premenopausal women under controlled dietary conditions. *Cancer*. 1984;74:1125–31.
5. **Ingram DM, Bennett FC, Wilcox D, de Klerk N.** Effect of low-fat diet on female sex hormone levels. *J Natl Cancer Inst*. 1987;79:1225–9.
6. **Bisschop PH, Pereira Arias AM, Ackermans MT, et al.** The effects of carbohydrate variation in isocaloric diets on glycolysis and gluconeogenesis in healthy men. *J Clin Endocrinol Metab*. 2000;85:1963–7.
7. **Bisschop PH, Bandsma RHJ, Stellaard F, et al.** Low-fat, high-carbohydrate and high-fat, low-carbohydrate diets decrease primary bile acid synthesis in humans. *Am J Clin Nutr*. 2004;79:570–6.
8. **Bisschop PH, de Metz J, Ackermans MT, et al.** Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *Am J Clin Nutr*. 2001;73:554–9.
9. **Bisschop PH, De Sain-Van Der Velden MGM, Stellaard F, et al.** Dietary carbohydrate deprivation increases 24-hour nitrogen excretion without affecting postabsorptive hepatic or whole body protein metabolism in healthy men. *J Clin Endocrinol Metab*. 2003;88:3801–5.
10. **Westman EC, Mavropoulos J, Yancy WS Jr, Volek JS.** A review of low-carbohydrate ketogenic diets. *Curr Atherosclerosis Rep*. 2003;5:476–83.
11. **Benoit SC, Clegg DJ, Seeley RJ, Woods SC.** Insulin and leptin as adiposity signals. *Recent Prog Horm Res*. 2004;59:267–85.
12. **Volek JS, Gómez AL, Kraemer WJ.** Fasting and postprandial lipoprotein responses to a low-carbohydrate diet supplemented with n-3 fatty acids. *J Am Coll Nutr*. 2000;19:383–91.
13. **Volek JS, Sharman MJ, Love DM, et al.** Body composition and hormonal responses to a carbohydrate-restricted diet. *Metab Clin Exp*. 2002;51:864–70.
14. **Volek JS, Sharman MJ, Gómez AL, Scheett TP, Kraemer WJ.** An isoenergetic very low-carbohydrate diet is associated with improved serum high-density lipoprotein cholesterol (HDL-C), total cholesterol to HDL-C ratio, triacylglycerols, and postprandial lipemic responses compared to a low-fat diet in normal weight, normolipidemic women. *J Nutr*. 2003;33:2756–61.