

Obesity is a Complex Disease: Scope and Pathophysiology

The following is from a question-and-answer session that followed the live presentation between the participants and the presenter. The questions and answers have been edited for length and clarity.

Question: Should we be doing genetic testing for patients with obesity, and will it benefit in a better understanding to individualize care?

Answer: We're able to assay a lot of genes, alleles, and variants but there are so many that we don't understand their clinical significance. Some people have many of the strong genotypes for obesity but don't express it in their phenotypes: they don't have obesity and we don't understand why this is the case. They might have other genes that mitigate what those other genes are saying. Obesity is difficult because it's multi-factorial, unlike a single gene disorder such as Prader-Willi syndrome that causes obesity in children. Those single gene disorders, we can do genetic testing. The indications for the genetic testing are in patients who meet one of the following criteria:

- ≤ 18 years of age, BMI ≥ 97 th percentile or
- ≥ 19 years of age, BMI ≥ 40 , and a history of childhood obesity

Question: If the energy intake exceeds expenditure and you gain weight, then how is that not just calories in/calories out equals obesity?

Answer: We have learned that obesity is more than calories in and calories out, they are just part of the story. We have discussed genetics already, beyond that may be changes in the microbiome, and environmental influences through endocrine disrupting chemicals. The bio-signaling of energy homeostasis is dysregulated. Obesity is a disorder related to energy expenditure in the brain and dysfunction in peripheral areas such as the gut that influence how we absorb energy from food.

Question: Can you tell us a little bit more about GIP versus GLP1?

Answer: GIP is a hormone released in the gut in response to food. GLP-1, NPY responds strongly to macronutrients but particularly with protein and fat. GIP is released in response to carbohydrate consumption. You don't get a strong satiety response when you eat primarily carbs. And when you eat a lot of protein or fat, you feel full longer. GIP is a big player with glucose metabolism, it plays a role in the peripheral cells. It has recently been discovered that there are GIP receptors in the hypothalamus near the receptors for GLP-1. It apparently works with and stimulates or synergizes GLP-1 and probably other receptors. GLP-1 doesn't just work in the brain for satiety and energy expenditure. GLP-1 also works in the periphery. The two work synergistically.

Question: Are there any studies that show that people will lose weight if they have improved sleep, or is it just that improved sleep prevents weight regain?

Answer: It was the infectious disease researchers who were the first to establish importance of sleep when it comes to immune function and overall health over 30 years ago and this has been widely accepted. Sleep keeps things in balance, it keeps things regulated. Disordered sleep is associated with multiple negative health outcomes including weight gain. We know shift workers have many problems and some people are genetically more predisposed. If you decrease sleep apnea, the

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inflammatory cytokines reduce. I have seen weight stabilize and drop. I have not seen anything but preventing a progression of the metabolic sequela from it.

Question: Can you change, alter, or improve chronotype, can you cause a response on weight gain or weight loss?

Answer: You can't change your chronotype. It is genetically encoded. If you are a night person or a morning person, we believe this is encoded in your genes. There are things that you can do to improve your sleep schedule, such as getting the television out of the room.

Question: Are there studies that address biracial people? We're getting a lot of studies on ethnic groups or racial groups – Asians, Blacks, Mexican, Hispanic. But I've not seen any studies in the obesity literature that address biracial groups.

Answer: Not specifically.

Question: How do we overcome metabolic adaptation, that can make metabolic adaptation makes it sound fruitless.

Answer: We now understand the bio-physiology of metabolic adaptation. Due to the drop-in metabolic rate with weight loss during obesity treatment, patients find they must increase physical activity to overcome this. With weight loss there is a down regulation of satiety hormones and up regulation of hunger hormones. This can be overcome by giving medications to help overcome this change in hormones of eating.