

# WHAT IS THE BIOCHEMICAL ANSWER TO THE RIDDLE OF OBESITY?

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## INTRODUCTION

Conventional wisdom suggests that humans become obese by eating more calories than they expend. The cure should be to do the opposite: eat less and exercise more. But for those of us who take care of people struggling to maintain a healthy weight, the results have been generally disappointing and it has been difficult to achieve durable success with this strategy in more than occasional patients.

The purpose of this article is to argue that obesity is not caused by the twin sins of over-eating and under-exercising, but by a disorder of fat regulation and accumulation. After such an assertion, the question naturally arises: what regulates fat accumulation?

## FUNDAMENTALS OF ENERGY METABOLISM

The calories-in/calories-out hypothesis stems from the First Law of Thermodynamics: energy can change form, but it can't be created or destroyed. The energy of a closed system must remain constant. There are two problems with this principle as it applies to human obesity. First, it says nothing about causality, so though it is true that the obese consume more calories than their lean counterparts, the First Law does not tell us *why* they consume more calories. Second, the seemingly simple formula: Weight = calories in – calories out, has many interdependent variables. For example, if an animal's caloric intake is restricted, both its physical activity and cellular metabolism will fall. Thus, the First Law applies to physics, not to complex biological systems with dependent variables.

Second, we fully understand and accept that vertical human growth during childhood is influenced by growth hormone, and pubertal development is influenced by estrogen and testosterone. Is it possible that horizontal human growth is also influenced by hormonal action?

## REGULATION OF FAT METABOLISM IN THE FAT CELL (ADIPOCYTE)

Adipocyte metabolism is highly regulated. Whether the adipocyte (and the host) becomes bigger or smaller is tightly controlled by the cell membrane's

expression of lipoprotein lipase (LPL). When the *outer* adipocyte membrane is heavily laden with LPL, large circulating triglyceride particles, which are too big to pass into the cell, are taken up by LPL, are dismantled, and are passed into the adipocyte where they are reconstructed into the triglyceride particle. Once inside the adipocyte, the triglycerides will remain there as stored energy, awaiting the signal for lipolysis, a reverse scenario in which triglycerides are dismantled and passed out through the cellular membrane into circulation as free fatty acids available for cellular metabolism. This process of disassembling triglycerides into fatty acids is governed by the concentration of hormone-sensitive lipase (HSL) on the surface of the *inner* cell membrane of adipocytes.

Concentrations of LPL on the *external* cell membrane and concentrations of HSL on the *internal* cell membrane are highly dynamic, and can change rapidly in mere moments as they respond to hormonal signals. Insulin is the single most powerful mediator of these changes.<sup>1</sup> High levels of circulating insulin produce a rapid expression of LPL concentration on the external membrane and simultaneously lower HSL on the internal membrane. These processes enhance storage of energy in adipocytes as triglycerides, and make the adipocytes grow (along with the entire organism). Low concentrations of circulating insulin induce the opposite effects: HSL levels rise and LPL levels fall, which cause the adipocytes (and the entire organism) to become smaller.

Different parts of the human body vary greatly in their LPL expression and their subsequent expression of associated adiposity. LPL is rarely expressed on the back of the hand or the forehead. Even in your most obese patient, have you seen adiposity in these areas? A rapid rise in estrogen with pregnancy induces LPL expression in the posterior thighs and buttocks, which is thought to aid in weight distribution with the enlarging uterus. Falling levels of estrogen at menopause promotes a nearly global somatic increase in LPL levels, similarly, falling levels of testosterone induces

increased LPL expression in the lower abdomen accounting for the ‘paunch of andropause.’

#### HOW DIET INFLUENCES ENERGY METABOLISM

Although dietary protein produces some insulin response, the greatest insulin response is produced by carbohydrates, especially the highly refined forms. Anything that produces an insulin response promotes weight gain; anything that lowers insulin levels promotes weight loss. This explains the robust weight loss that accompanies restriction of dietary carbohydrate.

In the early 1970s, in order to promote reduced caloric intake, government agencies told us to eat less fat. This initiated the growth of the low-fat and non-fat food industry, which virtually always used carbohydrates as a substitute for fat. National BMI charts available on the CDC website<sup>2</sup> indicate a remarkable increase in our national weight beginning in the mid 1970s, which occurred in parallel with increased carbohydrate consumption.<sup>3</sup>

Man is one of the few animals born “prematurely” (courtesy of our large prefrontal cortex and the restrictive birth canal), and we thus remain dependent on others for our early survival. During feedings we are often loved unconditionally, which creates associations that—in later life—can make food consumption a surrogate for that same unconditional love. Carbohydrates are powerful stimulants of reward circuits in the brain that are close to the same area stimulated by cocaine. Carbohydrates are readily available in our environment, they taste good, and they are inexpensive. Is it any wonder they make up a large portion of our modern diet?

Diets rich in carbohydrates produce an intense insulin response which sequesters the bulk of consumed energy assets in the adipocyte and inhibits lipolysis. It is not until insulin is largely dismissed from the metabolic picture that the host can harvest the accumulated assets for use in cellular metabolism. Understanding this chemistry provides insight as to why the obese overeat. They do so because they must, as they cannot readily access their stored energy.

Insulin’s powerful inhibition of lipolysis causes a dearth of metabolic substrate for cellular metabolism. As long as insulin stands ‘on guard’ preventing the access to energy substrate stored in the adipocyte, it compels the host to feed again. And that meal is likely to be similar to the previous meal, rich in highly refined carbohydrates. Such a diet initiates a vicious cycle of adipocyte hypertrophy and proliferation.

And though we were taught in medical school that we are born with a certain number of adipocytes and we do not produce any more, new data indicates insulin effectively stimulates adipocytogenesis.<sup>4</sup> Furthermore, adipocytes produce inflammatory cytokines which initiate and accelerate atherosclerotic processes. And, unrelenting insulin spikes eventually render the host resistant to insulin, which explains our current epidemic of type 2 diabetes.

#### HOW CAN WE USE OUR UNDERSTANDING OF ENERGY METABOLISM?

Modern humans have been living on the earth for about 100,000 years.

We have had refined carbohydrates for a minority of that time. Our ancestors consumed fruit which, although rich in simple sugars, were ‘packaged’ in substantial fiber that limits rapid absorption and intense insulin response. Our avid consumption of refined carbohydrates has rapidly outpaced the evolution of our metabolism to effectively deal with them, as evidenced by our national epidemic of obesity and type 2 diabetes.

With the exception of humans and domesticated animals, obesity does not exist in nature. This is true in virtually all animals in the wild, even in those systems where food is always in abundance. The normal check and balance in nature doesn’t seem to apply to modern man, likely promulgated by insulin’s effect.

The principal of carbohydrate restriction for weight control is not new, and was most famously advocated by the late Robert Atkins. But Atkins did not advocate a life devoid of carbohydrates. True, for those struggling to lose weight, intense carbohydrate restriction facilitates rapid weight loss, but properly followed Atkins-type diets bring carbohydrates back into the diet as target weight is achieved. Non-starchy high-fiber vegetables play a prominent role in a healthy diet once the weight goal is achieved.

#### WHAT IS THE LANCASTER EXPERIENCE?

In March of 2012 we started a pilot program at Healthy Weight Management for patients with a BMI of at least 30. We provided 16 hours of group education and a medically supervised program of full or partial meal replacements comprised of protein and fat and very little carbohydrates. The 21 individuals who completed the program lost a total of 881 pounds. Diuretics, anti-hypertensives, and oral diabetic agents were stopped on the first day of the program.

There is no denying that striking restriction of caloric intake (800 cal/day) was the major component that resulted in their weight loss, but equally striking is that this group did not report hunger. This important benefit can be attributed to the liberation of adequate energy assets from adipocyte lipolysis. This group is now moving toward the incorporation of 'normal foods' and will participate in a 6-month maintenance phase of ongoing educational support.

Our recent practice at The Heart Group of Lancaster General Health Prevention Clinic is to offer counseling about carbohydrate restriction to those who struggle to maintain a healthy weight. One such patient, who lives at a prominent local retirement facility where food is available in abundance, was seen for

follow up 6 months after her initial evaluation. She had lost 76 pounds in just 6 months. As she approaches her target weight, she is introducing complex carbohydrates into her diet slowly so she may ascertain her individual carbohydrate tolerance.

#### CONCLUSIONS

Scientific studies tell us that relative concentrations of LPL and HSL in adipocyte cell membranes dictate the accumulation or depletion of fat, and thus the size of the host. In turn, the concentrations of LPL and HSL are determined by serum insulin levels, which are themselves determined by the levels of readily absorbed, refined dietary carbohydrates.

In sum, if we help our patients reduce their carbohydrate intake, we will help them achieve a healthier weight.

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#### REFERENCES

1. Arteriosclerosis, Thrombosis, and Vascular Biology. 1997;17:2287-2292.
2. [www.cdc.gov/nchs/data/hestat/overweight/overweight\\_adult.htm](http://www.cdc.gov/nchs/data/hestat/overweight/overweight_adult.htm)
3. MMWR Feb 6, 2004/53(04);80-82.
4. PLoS One. 2009;e6189.

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#### NOTE

LG Health's Healthy Weight Management is located at 2150 Harrisburg Pike, Lancaster, PA, 17604. Comprehensive healthy weight management services are provided in a team approach by a medical bariatrician, bariatric surgeons, registered dietitians, and exercise physiologists.

Referrals can be made by calling 1-717-544-2935.

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