Health Condition: Obesity & Inflammation

“Human beings have evolved in an environment in which they have had hundreds of thousands of years of consistency. The human body—the immune system—develops a sort of friendship with that consistency, such that there is no adverse reaction. In other words, if we are eating fruits and vegetables as we have been doing for the last hundred thousand years, the immune system perceives this is something that is quite natural. It’s like a bacterial virus that we’ve evolved over hundreds of thousands of years. And we have several of these. Of course, we call them our ‘little friends’; they are very friendly bacteria and microorganisms that we’ve grown with, and in fact we’ve come to depend on them.

The sudden change that occurred around the time of the industrial revolution—let’s say mid-19th century—has meant that our lifestyle has changed dramatically so that we’re eating processed foods that haven’t evolved with us over those hundreds of thousands of years. We’ve become much, much less active as a result of technology. The stress levels have changed dramatically. Our sleep levels have changed because we’ve got lights and electronics and so on. As a result, the body has reacted—the immune system has reacted—in this low grade, systemic, meta-inflammation response.”

—Garry Egger, MD, PhD
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The Obesity Epidemic

In 2004, an article was published in *The New England Journal of Medicine* titled "Obesity and Metabolic Syndrome in Children and Adolescents."[1] The prevalence of metabolic syndrome has increased significantly over the last decade and a half, and the prevalence of type 2 diabetes and cardiovascular disease has followed it, particularly in the adolescent population. In this article, the authors point out that the prevalence of the metabolic syndrome is high among obese children and adolescents and increases with worsening obesity. Biomarkers of an increased risk of adverse cardiovascular outcomes are already present in these youngsters, indicating that as they move into their 20s and 30s, they are likely to be high users of medical services because they will have complications of type 2 diabetes and cardiovascular disease at a much younger age than ever before.

We are witnessing an epidemic rise in the prevalence of obesity in our society. Morbid obesity has a very dramatic relationship to chronic health problems, metabolic disturbances, and virtually every chronic, age-related disease: coronary artery disease, stroke, hypertensive-related disorders, renal failure, diabetes, cancer, osteoporosis, arthritis, and spinal compression fractures. In 2005, a landmark paper was published in *The New England Journal of Medicine* from a group of collaborative investigators.[2] This paper suggested that, based upon morbidity and mortality trends that are occurring in our society right now, children born today may be the first in the history of the United States to have mean average life expectancy lower than that of their parents. We have never seen this happen before. This effect appears to be a consequence of the rapidly rising prevalence of obesity, not just in the older-age portion of society, but also in our youth. These are dramatic social changes that are creating pressure on the healthcare system, and a tremendous amount of human potential could be lost.

Why are we seeing this rise in obesity? Is it just because of a luxurious diet that is rich in calories? Or is it a combination of the calories, plus the way calories are constructed in processed food that is sending signals to our genes and creating a different energy economy? What about psychosocial-related issues, such as post-traumatic stress syndrome and the neuroendocrine impact of our lifestyle on our appetite and eating behaviors? Just about every field is related somehow to this problem of epidemic obesity and its subsequent health problems.

The Science of Fat

We now recognize not all conditions of overweight are a consequence of simply eating too many calories (the first law of thermodynamics: too much energy in by way of calories and not enough energy out by way of activity). There are metabolic differences in the way individuals process calories. Those differences affect the way he or she stores, loses, or maintains certain body mass sectors, particularly body fat.

We used to think of body fat as benign storage tissue. We now recognize it is tissue that is generating its own messages by upregulating gene expression within the adipocyte, the fat cell. Inflammatory mechanisms and messages are being produced that interact with dopamine, serotonin, and neuropeptide-Y. The adipocyte also produces the hormone leptin, which influences acetylcholine and melanocyte-stimulating hormone, the cytokines and nitric oxide, and insulin and insulin receptors.

Certainly, the calorie is a valuable concept. But the calorie would imply that all calories are processed in the same way, regardless of the food that they are delivered in. Whether it is a calorie coming from fat or one from protein or carbohydrate would really not matter, because they are all energy units, which is the ability to do work, or to produce heat. Now we recognize that different nutrients may have differing influences on how those calories of potential energy are actually converted into various forms of metabolic energy. That is a remarkable change in our understanding of the role that diet and nutrients play in the regulation of metabolism.

Measuring Body Fat

The type of fat of most concern is not that which accumulates in the limbs, but that which accumulates around the abdomen, the so-called visceral adipose tissue, or VAT. The VAT (inter-abdominal body fat) is that which appears to present the greatest risk to age-related, chronic illness such as heart disease, diabetes, some forms of cancer, and perhaps also to cholelithiasis (gallstones) and gall bladder disease. It is these types of regional fat depositions that seem to be strongly associated with disease related to obesity or adiposity.

One of the first things one needs to look for clinically is how much body muscle has been replaced by body fat, or the percentage of body fat, and the best way is to determine body composition. Traditionally, the simplest method is to measure height and weight and develop what is called the body mass index (BMI). Using a nomogram scale, the height can be determined in inches versus the weight in

pounds to develop a BMI number. BMI>25 is overweight; BMI>30 is obese; BMI>40 is morbidly obese. (The only exception might be for individuals with heavy musculature, such as highly-trained athletes.) For the average individual, the BMI is a pretty good approximation of body composition, or percent body fat.

BMI is often coupled together with the waist-to-hip ratio. That ratio is achieved by measuring the circumference of the hips at the widest point and the waist circumference, about an inch or two above the umbilicus. Dividing the waist number by the hip number provides the ratio. If that number is greater than 0.8 for a woman, or greater than 1.0 for a man, it suggests increased incidence of abdominal obesity associated with increased BMI. Increased BMI and increased waist-to-hip ratio represent the VAT. Only a tape measure is needed to gather some inferential information about body composition.

There are more accurate methods of determining body composition, such as computed tomography (CT) scanning, neutron activation (not available to most individuals unless they are in a research situation), and bioelectrical impedance analysis (BIA), which uses resistance and conductivity measurements of the body done with a specialized machine. BIA is a reasonable technology for evaluating body composition in a person who is properly hydrated and appropriately nourished relative to their normal diet. Except for those who have very ponderous physiologies, the BIA regression equations built into the machines that give rise to the percent body fat, percent body muscle, and percent intracellular water calculations, are quite accurate and correlate nicely with other more sophisticated technologies. As a person reaches a very high BMI, this equation tends to break down. In these cases, the BIA calculation from normal bioimpedance analysis tends to be less accurate. For people in the normal or overweight range of body composition (19-30), the BIA machines provide accurate regression calculations compared to those determined by other methods. The simplest in-office technology for evaluating body composition that has the most qualitative inference is height-to-weight ratio and BMI. BIA renders a quantitative calculation that gives more compartmental and regional aspects of body composition and intracellular fluid.

The Concept that Links Obesity & Inflammation

For several years, researchers have been examining the idea that obesity may be considered a low-grade systemic inflammatory disorder that interacts with a variety of neuroendocrine immune hormones ranging from neurotransmitters to immune modulators. “Meta-inflammation,” rather than just inflammation, is a relatively newly coined term. It’s a low-grade systemic form of inflammation that seems to run throughout the body, particularly through the epithelial tissue. Proinflammatory and anti-inflammatory loads that would contribute to meta-inflammation, including things like nutrition, obesity, inactivity, smoking, and exposure to oxidant stress in the atmosphere. The total load of all these environmental factors are picked up by receptor mechanisms at our cellular level and transmitted into genes and into an alarm reaction that has been given this term “meta-inflammation.”

Garry Egger, MD, PhD, an Australian physician and researcher currently investigating the relationship between obesity, climate change, environment, and economic growth, describes the concept of meta-inflammation this way:

"The theory is that the immune system is reacting to our lifestyle, not to microorganisms as it has done over the past and with which we are very familiar (we've known this for 2000 years). The response is to inflammation. Now we are saying that it is reacting—it's responding—to our lifestyle. Nobody wants to give up the modern lifestyle, of course, because this is the spectral progression and we've gotten enormous advantage out of the modern industrial way of life, but there are obviously disadvantages and the immune system just hasn't had time to adjust to these."

Systemic inflammation associated with obesity may involve more than physical disability, pain, and loss of bodily function. It may also represent an early risk factor for much more serious, life-threatening conditions. That risk was the subject of an article in the *Journal of the American Medical Association* in 2000.[3] In this article, authors Alexandros Vgontzas and Edward Bixler, from the Pennsylvania State University College of Medicine, reported that patients with elevated BMI demonstrated a positive association between obesity and plasma interleukin-6 (IL-6) levels. Levels of IL-6, which were significantly increased in middle-aged individuals, were also positively associated with sleep apnea, a common symptom in individuals with increased BMI.

This complex neuroendocrine/immune relationship gives rise to a different physiological state of the individual. It is not just that fat causes diabetes or heart disease. Fat changes the body's function by regulating genes to produce new, different messengers. Fat plays a role in modifying the orchestration of our body talk, and these different mediators are influencing function at the neuroendocrine and immune system levels.

The Metabolic Implications of Bariatric Surgery

Bariatric surgery is the most dramatically increasing surgical procedure performed in the western world, and is included in more and more training programs for surgeons, particularly the new microsurgery technologies.

Health status can create the need for a bariatric procedure, but the procedure itself can also have an impact on nutritional status and metabolism. Some publications on nutritional management of patients after bariatric surgery are based on observations of professionals who have performed this procedure and have studied the outcome in their patients. One such article is 'Nutritional Management of Patients after Bariatric Surgery,' from the *American Journal of Medical Science*.[4]

Bariatric procedures are surgical procedures that change gastric physiology and absorptive surface areas. Malabsorption syndrome associated with deficiencies of iron, folate, vitamin B12, and even the fat-soluble vitamins (particularly vitamins A, K, and E) is being seen in these patients. Essential fatty acid malabsorption is suggested as well. Wernicke-Korsakoff syndrome has also appeared in some bariatric

surgery patients; this is a thiamin deficiency associated with hepatic encephalopathy and often connected with alcoholism. Some of these consequences are the exact conditions that a practitioner may be trying to treat by doing gastric bypass surgery on a morbidly obese patient.

Currently, there are nutritional guidelines for the management of bariatric surgical patients after surgery, but in most surgical centers these guidelines are not rigorously adhered to. Nutritional intervention is simplistic at best. A number of patients develop problems with hair loss, muscle wasting, skin problems, digestive difficulties (nausea and vomiting), and generally altered immunological status as a consequence of nutrient insufficiencies. These insufficiencies may be related to protein/calorie malnutrition (particularly protein), but also the micronutrient problems that I have been describing. It is really necessary to look at the results of bariatric surgery and learn from them.

Postoperative nutritional status is a very big area of concern; we know there is an impact of varying levels of protein intake on muscle mass accrual after bariatric surgery. In an article that appeared in *Obesity and Surgery,* the authors discuss how protein has a very important role to play in modulating body composition after surgery.[5] With bariatric surgery patients, it is not adequate to measure just the weight loss; you must also measure where that weight is being lost from. If weight loss is from the muscle mass compartment via the loss of body protein, this may result in the patient being in a less helpful situation postoperatively. We know from other studies that both the quality and quantity of protein in the diet can greatly influence the type of tissue that is maintained during weight loss; that is, whether or not lean mass is conserved compared to fat mass.

Are there recommendations regarding obesity surgery in terms of nutritional follow-up? These guidelines are still in a state of evolution. There are some enlightened surgeons who seem to have a better understanding of these nutritional variables, and then there are others who are fairly naïve about how to evaluate nutritional status properly and understand the trajectory that a patient has after surgery relative to his or her health.

In a 2005 article in *Current Gastroenterological Reports*, the authors state that 16 million Americans are currently candidates for weight loss surgery.[6] This could be more people than all of the surgical centers, surgeons, and surgical teams in the United States could handle. What are we going to do? We are going to have to utilize lifestyle, diet, and other technologies (maybe even pharmacology) to try to gain control over this epidemic. The problem may start early in life, as alterations in our lifestyle and eating habits. This includes the types of foods we eat, the information that food provides as signals to our genes (that create differences in insulin signaling), and this complex network of neuroendocrine hormones that regulate things like appetite, thermogenesis, metabolic function, and adipogenesis.

Many of the problems that patients have as a consequence of morbid obesity may dramatically and rapidly improve after gastric bypass surgery. Ironically, those improvements often occur much more quickly than you would expect based upon the amount of weight that is lost. Why would that be? Bypass surgeries, such as the Roux-en-Y procedure, change the absorptive surface area and the size of the stomach. After surgery, the flux of information molecules from the diet is greatly reduced. This cools off (or calms down or quiets) the neuroendocrine arousal that has come from the loud voice--maybe even chaotic voice--that has come from excessive calories that contain the wrong information. By cooling that voice down--quieting it--the effect on gene expression that results in the stress responses that we see as insulin resistance and hyperlipidemia and inflammatory markers seem to all be remarkably improved. This implies that these metabolic consequences of obesity are not solely a consequence of the fat itself, but a consequence of what occurs metabolically from signaling that is

associated with fat accumulation.

How much weight does a patient have to lose to get a dramatic and favorable impact on his or her metabolism? Could it be that just small amounts of weight loss (but improvements in physiological function), could then dramatically reduce some of the metabolic disturbances that associate themselves with diabetes and heart disease and cancer and so forth? It is an interesting question because for years it was felt that this was all a problem of excessive calories and extra body fat; there was a presumed direct relationship between incremental increase in body fat and decrease in metabolic performance. What we are talking about now is another variable beyond that of just fat itself. It has to do with the impact of diet and lifestyle on our gene expression patterns, which ultimately can regulate the metabolic outcomes that are associated with disease.

There was an article in *The New England Journal of Medicine*that focused on lifestyle, diabetes, and cardiovascular risk factors ten years after bariatric surgery.[7] This was a multi-center review, and the news was quite encouraging. After two years, weight had increased by 0.1 percent in the control group and had decreased 23.4 percent in the surgery group. There were also significant improvements in insulin sensitivity, serum lipids, and uric acid levels in the group that underwent bariatric surgery. In this particular study, the authors concluded that, compared with conventional therapy, bariatric surgery appeared to be a viable option for the treatment of severe morbid obesity, resulting in long-term weight-loss, improved lifestyle, and amelioration of the risk factors that were elevated at baseline. The one thing bariatric surgery does not appear to significantly improve over standard approaches is elevated serum cholesterol, which suggests that there are other factors associated with triggering the cholesterologenic process (seen as elevated LDL cholesterol).

After gastric bypass surgery, even before a significant amount of weight is lost, there has been demonstrated a dramatic improvement in metabolic function with reduction of risk to diabetes and heart disease and stroke. This implies that metabolism can be changed by reducing the stress on the body from extra calories containing the wrong information. A number of publications have included articles on this subject, including a very interesting article that appeared in *Current Opinions in Clinical Nutrition and Metabolic Care* in 2004.[8]

By having surgery, weight loss will improve some metabolic functions, but patients may then have new problems that are associated with macronutrient and micronutrient deficiencies. A consequence of malabsorption syndrome relates to the fat-soluble vitamins, specifically vitamin D, which is necessary for bone health. We often see patients who, after bariatric surgery, end up with bone loss and increased parathyroid hormone levels--a nutritionally-induced secondary hyperparathyroidism--resulting in increased risk to osteoporosis. For virtually all nutrients that are malabsorbed, appropriate supplementation in a form that does not produce hyperosmolarity is a very desirable feature of postoperative nutrition care.

Therapeutic Approaches

To decrease systemic inflammation that may be associated with obesity, one of the first things that might be done is to put a person on a diet as neutral and low-allergy as possible, without making sweeping changes in calorie intake. Some people call this an oligoantigenic diet; other people might

refer to it as a detoxification program. Others might call it just a good, simple, clean way of eating. Whatever term might be used, the recommended diet is one that would employ foods grown in the ground with lots of color (fresh fruits and vegetables). It would avoid the color white in the diet—white sugar, white fat, white flour, and white alcohol—and include things as organic as possible, staying away from dairy and wheat products, or glutenous grains. We cannot be certain who might have some kind of sensitivity to the food families containing proteins to which many people are sensitive, but the most common allergenic proteins are found in dairy, soy, and wheat.

When putting a person on a fairly low-allergy diet, rice protein-based approaches are often used, because rice is well tolerated in western societies and has good-quality protein. Fiber would be increased, and vegetables and fruits would be increased. There are diet plans based on the Mediterranean Diet that avoid gluten grains. When an individual has been on this program for two to three weeks, immune system responses change. A lot of water weight that might have been retained as a consequence of immune system response to a purported offending agent, i.e., an inflammatory-promoting agent, may be lost. The person is now at a baseline physiology and it is easier to examine body composition.

In terms of dietary approaches, there are many different opinions on the ratio of protein, carbohydrate, and fat amount in the diet, as well as type and percentage. What is the best *kind* of protein, *kind* of fat, and *kind* of carbohydrate? That may be more important than the relative ratio. Is it complex? Is it whole-grain? Is it unrefined? Is it white starch? Is it sugar? What *type* of fat? Is it partially hydrogenated? Is it polyunsaturated? Is it monounsaturated? Is it saturated? Is it oxidized? What *type* of protein? Is it animal or vegetable protein?

These questions are exceedingly important in determining the outcome of the body's hormonal postprandial messaging response to the diet. It is the postprandial period during which the orchestration of all sorts of hormones that sweep into the blood creates different tunes of genes downstream that ultimately regulates things like body composition. It is not as simple as just thinking about calories in and of themselves. It is the *type* of calories and *type* of nutrients that influence the messaging system of the body: the sex steroid hormones, glucoregulatory hormones, neurotransmitters, and the appetite-control hormones, including what are called adipocytokines, the fat-related neurotransmitters, neuroregulators, and immune-regulating substances.

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