Type 2 Diabetes And Other Metabolic Consequences Of Obesity

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INTRODUCTION

That a large number of Americans are awash in a sea of adipocytes is not a question. Nearly one third of Pennsylvania school children from K-6 are either overweight or obese. Adult obesity also has dramatically increased in the last 20 years, with the CDC reporting in July 2009 that in 32 states at least one quarter of the population is categorized as obese. The Agency for Healthcare Research and Quality (AHRQ) states that healthcare spending has increased more than 80 percent from 2001 to 2006, much of that associated with issues in the obese.

Let's look at some of the pathophysiologic bases and treatments of Type 2 Diabetes (T2DM) as well as other metabolic consequences as they relate to obesity. The issues are complex and they interrelate with many other systems and diseases. We do not have a clear or full picture of a "master initiator" or controller of the processes involved. It may be hidden in our genetic background and/or environmentally in our habits of eating and physical activity. What do we know? Man has only had a surplus of food in the last 100 years. The high caloric diet with relative physical inactivity has enabled the epidemic of overweight and obesity, affecting one of every two Americans. In fact, it's said that only 8% of the US population is "healthy" as defined by: not using tobacco, being within five pounds of ideal body weight, exercising for 30 minutes daily, and consuming five fruits/vegetables daily.

PATHOPHYSIOLOGY

The metabolic consequences of obesity are greatly dependent on central or visceral fat distribution, which is highly correlated with insulin resistance, increased cancer incidence, inflammation, high LDL, low HDL, endothelial dysfunction, procoagulation, hyperglycemia, hypertension, and hypertriglyceridemia. Many of the above consequences are included in the definitions of Metabolic Syndrome (MetS). Let's look at some of these in more detail.

Fat Distribution and Type: White fat causes abdominal obesity, especially in older adults, and when assessed by waist-to-hip ratio (WHR), the measurement predicts risks of T2DM and all-cause mortality independent of BMI or waist circumference. Even in individuals with normal weight, increased WHR is clearly associated with an increased risk of coronary heart disease (CHD). A relatively new finding is that brown fat, found in some adults, can actually be switched from a passive to a calorie-burning mode, and might be harnessed as an anti-obesity weapon, especially if we can figure out how to make more of it. The latest news about body measurement states that a thigh circumference *under* a threshold of about 60 cm increases CHD greatly.[1] More research will be needed to see if this adds anything to clinical management.

Insulin Resistance (IR): This is a condition in which normal amounts of insulin do not produce an adequate response from fat, muscle, and liver cells, and it is one of the key accepted causes for the clinical MetS. Possible mechanisms include pre-receptor, receptor, and post-receptor defects.[2] Genetic predisposition to obesity and/or T2DM can be caused by changes in the peroxisome proliferator-activated receptor (PPAR) genes which increase IR.

Overweight individuals have significant elevation of serum non-esterified fatty acids (NEFAs), cholesterol, and triacylglycerols regardless of dietary intake of fat. Adipocytes in fat overproduce several hormones like leptin, and several cytokines such as tumor necrosis factor-alpha, all of which appear to cause cellular IR. These same adipocytes can decrease production of other hormones like adiponectin, which in effect decreases insulin response. In turn, IR in fat tissue causes more production of lipase, which creates more NEFAs. Since higher NEFA concentrations produce IR in muscle and liver, the release of NEFAs may be the single most important factor in determining insulin sensitivity.

Early in the clinical course, the pancreas controls the blood sugar by overproducing insulin. As a result, at the outset many obese individuals have normal blood sugars and high insulin levels, with IR in the peripheral tissues. High insulin levels excite the

sympathetic system, and cause sodium and water retention, vasoconstriction, and hypertension. Excess NEFAs in the liver are transformed into triacylglycerol and cholesterol. These are released as very low density lipoprotein (VLDL) particles, which leads to more triacylglycerol and cholesterol. Eventually the pancreas loses its capacity to overproduce insulin, and impaired glucose tolerance with higher blood sugars ensue.

Metabolic Syndrome (MetS): Ibarra discussed this syndrome in the Fall 2009 issue of JLGH.[3] There are five current clinical definitions of MetS, which was once called "Syndrome X." Though the ranges vary, all of the definitions include the risk factors of blood pressure, triglycerides, HDL cholesterol, fasting blood glucose, and a definition of central obesity. The National Heart, Lung, and Blood Institute estimates that nearly one quarter of U.S. adults have the abnormalities known as Metabolic Syndrome, or Insulin Resistance Syndrome. Despite the differing names and definitions, the ultimate issue is the most appropriate treatment for those with diseases accompanying MetS.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes don't recognize MetS. Their recommendations are to screen for the disorders not already found and to treat to the individual goals for those conditions. Various definitions and treatment areas conflict and are amended often, making it difficult for the clinician to decide on the best therapy. New versions of the Adult Treatment Panel and Joint National Committee guidelines were published in January 2010. To this point in time, I believe that MetS is best summed up by Church et al,[4] who concluded that the presence of T2DM was associated with a threefold higher mortality risk from cardiovascular disease (CVD), but identifying MetS did not modify this risk. Their findings support the fact that physicians should be aggressive in using CVD risk-reducing therapies in all diabetic patients regardless of MetS status. At present, no unifying pathogenic mechanism has been identified to explain MetS and therefore there is no unique treatment for it.

Multiple "fellow travelers" of MetS, IR, and obesity are seen in our daily practice. They include, among others, polycystic ovary syndrome, infertility, chronic kidney disease, atherosclerosis, non-alcoholic fatty liver disease, hypertension, sleep apnea, kidney stones, cancer, cholelithiasis, and gout. Many of these have been addressed elsewhere in *JLGH*.

When T2DM is the concern at initial evaluation, obesity alone was the best predictor of undiagnosed diabetes among diagnostic models containing various risk factors (odds ratio = 3.2; 95% CI, 2.0 – 5.2; area under the curve = 0.63).[5] Additional limited evidence suggests that the fasting glucose alone may be as good an indicator of diabetes as MetS.[6] We also now have the hemoglobin A1c value of 6.5 and above as another accepted definition for T2DM.

PREVENTION AND MANAGEMENT OF DIABETES AND OBESITY

U.S. patients spend more than $71 billion each year just on prescriptions for metabolic and cardiovascular drugs, the number one and two types of medication prescribed in America. Yet we are losing the war against diabetes and obesity. What are some of the reasons?

The two top considerations for these problems are our high caloric intake and our low rate of expenditure of those calories. For example, there are 29 grams of fat in a typical Big Mac, and over 550 million are consumed each year in the U.S. alone. Fast-food outlets in the U.S. are expected to see $164 billion in sales this year, up from $107 billion in 2000. A stock investment in one of those companies has returned 330% since January 2003. Children and adults are bombarded with advertisements for those foods rather than for healthy eating and exercise.

New studies have shown that many people no longer eat just because they are hungry. More often today eating is for entertainment and to feel good. Decreased portion sizes (often with higher prices) help many, but I am waiting for the day restaurant menus list the calorie count beside each selection with the amount of physical activity needed to burn those calories. (For example, an extra 100 calories/day from a bagel is 9-10 lbs/year in weight gain.)

To combat obesity and diabetes we need education and willpower. We must enlist the nutritionist and psychologist with the physical trainer and the physician. Does it cost more to eat a healthful diet (such as the Mediterranean diet) full of vegetables, unground whole grains, beans, seed, nuts, fruits, fish, and wine? A recent article in *The Journal of Epidemiology and Community Health* states that those eating and scoring in the highest quintile for the "western" diet (more like the average American) spent $0.80 less per 1000 Kcal on daily food than those in the lowest quintile for the western diet.[7] Inversely, those eating and scoring in the fifth quintile for the Mediterranean diet spent $0.90 more per 1000 Kcal on daily food than those

in the first quintile. After adjusting for confounders, higher daily food costs were significantly associated with greater weight gain as individuals chose the cheaper, less nutritious foods. Especially for those in lower income groups, the extra calories (and other unhealthful ingredients) increase the incidence of obesity and diabetes. It's well known that diabetics eating the Mediterranean-style diet (<50% of daily calories from carbohydrates) lose more weight than those on a low fat diet (less than 30% of daily calories from fat) and also experience greater improvement in control of glycemia and coronary risk factors.[8]

The CDC released a set of community strategies (Morbidity and Mortality Weekly Report- July 24, 2009) to prevent obesity. They reference a study in Health Affairs showing that an obese (BMI > 30 kg/m2) person spends $4829 per year on healthcare compared with $3400 per year spent by a normal weight (BMI 18.5-25 kg/m2) person with similar characteristics. The CDC report lists 24 strategies, each with a corresponding measurement that can be used to assess a strategy's implementation. The methods are all evidenced based. Although this evidence is not perfect, it is the best available to date. The goals are to promote the choice of available and affordable healthy foods and beverages, encourage breastfeeding, push young people to exercise, and create safe environments for physical activity. One of the possible plans is for a soda tax, which I previously broached in the Fall 2009 issue of the *JLGH*.[9]

An example of a community activity as suggested by the CDC is "Wild and Wonderful Trails for Every Child," involving Dr. Mark Cucuzzella of West Virginia. This is a four year plan to reshape the already built environment and nutritional policies to align with principals of healthy living. More grants are needed to support after-school programs on local trails, teach nutrition through "edible" gardens, and hopefully reattach children back to nature. Safe routes to work and school for walking and biking should bring health values back to adults as well as children. Obviously if one wants to decrease diabetes in adults, we need to pay more attention to our children. In a recent article in New England Journal of Medicine,[10] obesity, glucose intolerance, and hypertension in childhood have been found to be strongly associated with increased rates of premature death from endogenous causes. However, childhood hypercholesterolemia was not found to be a major predictor of premature death from endogenous causes.

Concerning physical activity, the intensity required to prevent or reverse MetS has yet to be definitely determined.[11] A recent article in the American Journal of Medicine,[12] however, states that overweight men did not significantly reduce their risk until the frequency of vigorous activity reached five or more times weekly. But regardless of age, athletes (of any weight are more insulin sensitive than sedentary subjects of normal weight, who are more insulin sensitive than obese subjects. Multiple groups have encouraged 30-60 minutes of moderate-intensive aerobic activity such as brisk walking on most days of the week, with added daily lifestyle activities like walking breaks at work, gardening, and household work. (Level of Evidence -LOE I(B).[13] Resistance training 2 days/week is encouraged [LOE IIb(C)]. Medically supervised programs are advised for high-risk patients [LOE I (B)]. Beneficial metabolic changes associated with aerobic exercise training include improved glycemic control and clearance of postprandial lipids, as well as preferential utilization of fat during sub maximal exercise [LOE (B)]. Moderate intensity and aerobic exercise has been shown to reduce total body fat, but not fat-free mass in overweight middle-aged and older adults [LOE (A/B)].

Aids to continuing exercise long term include: doing something that you enjoy as exercise, exercising with others (walk with a friend, relative, or dog), or learning something new like taking dancing lessons. Boredom seldom allows one to persevere with exercise. Start slowly and build on it if you are starting to exercise. Even the truly old can usually do some yoga or t'ai chi or walk. (The percentage of those engaging in leisure-time strengthening activities decreases in every decade over 18 years of age.)

PHARMACOLOGIC THERAPY

The traditional pharmacologic methods as the only treatment of diabetes, obesity, and their complications have not been a resounding success. To review the research studies and the recent joint position summary of the ADA, AHA, and The American College of Cardiology, please see my *JLGH* article Summer 2009.[14] Specific therapy for many diseases associated with diabetes, for example—CVD, hypertension, and others, is found in the other articles on obesity in this series in JLGH.

In addition, I would like to comment on a recent study in *non*-diabetic, insulin-resistant patients with non-alcoholic steatohepatitis (NASH). Metformin (titrated to 1000 mg daily), compared with placebo, appears to have a very minimal effect on blood chemistry or liver histology.[15] However, weight loss utilizing the DASH diet and regular aerobic exercise significantly improved IR, serum transferases and liver histology in NASH. The

Diabetes Prevention Program showed that exercise and diet were twice as effective as metformin in reducing the risk of progressing from IR to diabetes.

Sibutramine, a centrally acting appetite suppressant, Orlistat, a locally acting inhibitor of nutrient absorption, and Rimonabant, a selective cannabinoid-1 receptor blocker, may help some patients in supporting their overall comprehensive weight loss plan, but they do not causally target the pathogenesis of metabolic syndrome. My experience with Orlistat is that if the patient can keep fat from their diet, it is somewhat effective in aiding weight loss. Most of my patients stop the drug because of diarrhea or don't take it when they know they are to eat fat.

Many medications can actually induce weight gain and subsequently cause secondary complications from it. Many of the antidepressant and schizophrenia drugs induce weight gain, as do most anti-diabetic medications except metformin. Insulin itself induces increased weight, at least in the first 18 months of treatment, after which time weight has been shown to plateau or decrease.

Other issues confound the weight gain picture. The Pittsburgh Health Women's Study found that an increase in BMI during the menopausal transition and beyond was "uniquely associated with reduced cerebral gray matter, apart from current BMI and other potential confounders." White matter hyperintensities were increasingly found in the brains of these women with increased BMI. It remains to be confirmed that weight gain causes alteration in brain function or vice versa.

Research in pediatric obesity also has discovered white matter lesions[16] in the brains of many of patients with Prader-Willi and early-onset morbid obesity (EMO) which are typically found in the brains of adults with Alzheimer's or children with untreated phenylketonuria. These lesions could be affecting food-seeking centers of the brain, causing those afflicted to feel hungrier. They are most likely a result of metabolic changes from low grade inflammation. These findings should lead us to look beyond just "eating too much and moving too little."

BARIATRIC SURGERY

Although this subject was addressed in detail by Dr. Alan Brader,[17] I would particularly note that the metabolic syndrome was prevalent in 52% of morbidly obese patients having surgery for obesity. Significant weight loss one year after surgery markedly improved all aspects of MetS and resulted in a cure rate of 95.6%. Note that this is the only mention I have made of "cure." The most effective treatment for morbid obesity and diabetes is bariatric surgery. Patients frequently become euglycemic, with sleep apnea no longer an issue, lipids dropping significantly, and other metabolic issues normalizing. These outcomes reduce medication use, outpatient visits, and hospitalizations over a lifetime with an ensuing long-term decrease in cost of healthcare.

OTHER MISCELLANEOUS MATTERS

1. *Cinnamon:* Some have commented that therapeutic cinnamon helps decrease blood sugar. This, however, sets up a risk for increased bleeding as most commercial cinnamon preparations are from Cassia (Cinnamomum aromaticum) which also has included anticoagulants. True cinnamon (Cinnamomum zeylanicum or sp. verum) does not. Allergic reactions can occur. Those with liver damage should use cinnamon with caution.
2. *Omega 3's:* Can increase insulin sensitivity. Some monounsaturated fatty acids and saturated fat increase insulin resistance. Trans fats are even worse.
3. *Micronutrients:* Magnesium intracellularly increases glucose uptake. Daily added Mg decreases IR and decreases incidence of diabetes. Calcium and potassium also decreased MetS. Chromium and vanadium are controversial in diabetes because of potential side effects and drug interactions. Vitamins and nutrients from foods are generally better than added vitamins in tablet form.
4. *Glycemic Index (GI) and Glycemic Load (GL):* These terms should be used primarily by researchers. GI is a ratio of how high an individual food raises blood sugar compared to how table sugar raises it. To calculate GL the grams of carbohydrate in a serving of food are multiplied by that food's GI. Carrots and potatoes, for example, both have a high GI; but using the GL, carrots go from a GI of 131 to a GL of 10 and potatoes from a GI of 121 to a GL of 45. That's why Glycemic Load is a more useful number. Carrots are an obvious better choice for diabetics and those overweight. A recent study[18] proved that a low-carbohydrate ketogenic diet led to greater improvements in glycemic control and more medication reduction than a low Glycemic Index diet.
5. *Worst Foods, Best Foods:* Flour products of bread, spaghetti, macaroni, bagels, rolls, pretzels, cookies, crackers, refined corn products, and white rice, along with all sugar-added products, generally cause blood sugar to rise quickly. Instead, reach for the vegetables, un-ground whole grains, beans,

seeds, nuts and fruit. Concerning nuts, a Harvard studyfound that those eating nuts 5 times per week were far less likely to develop diabetes.[19] Nuts are loaded with polyunsaturated and monounsaturated fats and preclude a high rise in sugar. However, a pound of peanuts contains over 200 grams of fat and 2800 calories so one should substitute these for refined grain products, meat, or processed foods. Don't just add nuts.

6. *Stevia:* It appears to be healthier (no calories) compared with other sweeteners, but costs more.[20] At the 2009 Annual Meeting of the Endocrine Society, data were presented to show that—compared to nonusers—those using earlier artificial sweeteners were heavier and more likely to have diabetes and be insulin-resistant. At least previous artificial sweeteners activate sweet taste receptors in enteroendocrine cells, leading to release of incretin, which is known to contribute to glucose absorption. We will have to see what future studies show with Stevia and other sweeteners yet to be released.
7. *Alpha Lipoic Acid (ALA):* The Mayo Clinic discovered that this OTC drug helps decrease symptoms of nerve damage such as burning pain and paresthesias.[21] It is an antioxidant and protects nerves from sorbitol which can permanently damage the cells. Further studies are to be done but at 600 mg a day it seems to be well tolerated with rare side effects of hypoglycemia, rash, possible interaction with treatment of hyper or hypothyroidism, and thiamine deficiency in those at risk.
8. *Thiamine:* A small study[22] has found this B vitamin at 300 mg daily decreases microalbuminuria in early-stage diabetics by up to 41% at 3 months. Again there seems to be no adverse reactions or interactions. Larger studies are needed.
9. *Sleep*: Findings in the *Journal of Clinical Endocrinol Metabolism*[23] show that recurrent sleep restriction (5.5 hours) led to reduced glucose tolerance, reduced insulin sensitivity, decreased glucose effectiveness, and increases in 24-hour epinephrine and nighttime norepinephrine levels. (See *JLGH* Summer 2008.[24])
10. *Fiber:* This is associated with reduced diabetes risk secondary to decreased inflammatory markers (CRP, IL-6), increased insulin sensitivity and decreased hepatic fat deposition. The theory is that fiber helps keep food in the stomach longer and sugar is absorbed more slowly, preventing free fatty acids from rising too high.
11. *Smoking:* No one should smoke for any reason.
12. *Vitamin D:* This hormone, in addition to helping our bones, increasing lower extremity strength, improving balance, significantly aiding immunity, and a myriad of other healthful benefits, aids insulin sensitivity and improves blood sugars. There is a strong correlation between serum vitamin D and insulin sensitivity, plasma adiponectin, and HDL cholesterol. Higher doses of vitamin D show more positive responses. (See *JLGH* Winter 2006 on Vitamin D and Top Tips in that issue.)
13. *Flossing:* Dental flossing decreases periodontal disease. By doing so it decreases bacterial invasion as well as their inflammatory byproducts. Studies have shown decreased risk of diabetes, CVD, and stroke in those who floss regularly.
14. *Coffee:* Caffeinated as well as decaffeinated coffee decreases the risk of developing diabetes. (See *JLGH* Winter 2007-2008.[25]) Once one becomes a diabetic, however, studies show reduced insulin sensitivity from drinking caffeinated coffee. Decaffeinated coffee seems best for known diabetics.
15. *Fructose and Other Sugars:* All sugared drinks contribute to obesity and therefore diabetes. The theory is that when you eat sugar in solid food, your brain recognizes the calories and you eat fewer calories from other sources. When you drink the same amount of sugar, your brain fails to recognize those calories and you are likely to eat more. Pure crystalline fructose raises uric acid and triglycerides more than glucose.[26] It also increases insulin resistance, LDL, triglycerides, and MetS. Fruit sugar contains 50% fructose and 50% glucose. High fructose corn syrup contains 55% fructose and 45% glucose. (See also *JLGH* Winter 2008[19] and also Dr. Bonchek's editorial in *JLGH* Summer 2009.[27])
16. *Fat-Free Foods:* There are over 1000 so-called fat-free foods. When sugar replaces fat in these foods, however, there is often little difference in calorie content as compared with full-fat versions. Consumption of fat-free foods does not necessarily reduce calorie intake. Read the caloric value on the labels.
17. *Niacin:* This is another B vitamin that decreases the amount of small dense LDL, triglycerides and Lp (a) and raises levels of HDL2. Issues include a large number of patients that can't tolerate therapeutic doses and the dose must be increased slowly over time. Niacin can also have effects that increase uric acid and increase levels of abnormal function tests.

SUMMARY

Currently no unifying pathogenetic mechanism has been found to be the endocrine "master switch" that explains the metabolic syndrome and obesity, so there is no unique treatment for it. It seems that studies of policy and socioeconomic factors are disconnected from research in obesity and metabolism. For example, 94% of primary care providers recently surveyed believe nutrition plays a major role in prevention and treatment of obesity, yet costs for referrals to nutritionists are frequently not reimbursed. Another study in *The Journal of Applied Research in Clinical and Experimental Therapeutics*,[27] states that patient non-adherence results in $8.5 billion in hospital costs yearly. The same study shows 125,000 patients with treatable ailments die in the US yearly because they don't take or even get their medication.

I believe that if we truly want to decrease the obesity and diabetes epidemics, we need to create a unique "Marshall Plan" involving children and adults, including education, advertising, and counseling for prevention and treatment. We need to utilize community, academic, professional, and governmental agencies, working together toward the same goal—that of a truly healthy America.

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