The Obesity Quagmire: a Brief Neuroendocrinological Commentary

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Attitudes of the public and the medical profession toward obesity have evolved through history.[1,2] Excessive body fat was once considered to be a sign of good health, wealth, and even beauty. However, expanding medical knowledge about the detrimental impact of obesity on health, and changing aesthetic standards have dramatically altered perceptions of obesity. Paradoxically, despite predominantly negative current opinions of obesity, its prevalence is on the rise.[3]

Scientific information about obesity apparently abounds. There are voluminous chapters in medical textbooks, and hefty monographs dedicated to the subject. The number of research papers dealing with various aspects of obesity is staggering. In fact, there are numerous journals dedicated solely to publication of basic and clinical studies of obesity. A search of the National Guideline Clearinghouse reveals more than 400 guidelines related directly or indirectly to obesity and overweight. Unfortunately, this spurious plethora of scientific knowledge does not translate into efficient and effective clinical strategies. Medical management and prevention of obesity remains extremely challenging and frustrating.

Disappointment with the scientific approach to weight control prompted a disillusioned public to search for alternative solutions. Sadly, those alternatives offer brief hope followed by no solid results. The popular press and social media are inundated with flashy commercials promoting allegedly "marvelous" anti-obesity supplements, "groundbreaking" weight control programs, and "miracle" diets, all to no avail. The prevalence rates of obesity are still rising.[3]

Is It Always Bad To Be Obese?

Surprisingly, the answer appears to be: not necessarily. The negative health consequences of obesity in the general population are well supported by a long line of evidence.[4,5] However, the health outcomes in specific subgroups appears to be improved at an increased body mass index (BMI). Those subgroups include patients affected by renal disease, cardiovascular disease, hip fractures, rheumatoid arthritis, and tuberculosis.[6-12] The terms obesity survival paradox and BMI paradox have been coined to denote this phenomenon. This puzzling anomaly was initially described in 1999 in overweight and obese hemodialysis patients.[6] Similar observations in the aforementioned pathological conditions have followed. Moreover, further research has revealed that it was not obesity per se that seemed to exert that unexpectedly positive effect on survival. The common comorbidities of obesity such as hypercholesterolemia and hypertension appeared to improve survival as well in certain subpopulations, especially in patients with end-stage renal disease (ESRD).[13,14]

These counter-intuitive findings were hard to explain and led to formulation of the "reverse epidemiology" hypothesis.[15,16] In brief, this hypothesis is an over-arching concept that purports to explain the unusual association between traditional risk factors such as obesity, hypercholesterolemia, hypertension, and improved clinical outcomes in patients with certain chronic conditions. The as-yet-untested extension of this hypothesis postulates further that "low normal" BMI, cholesterol level, and blood pressure may be medically unfavorable by inducing higher morbidity and mortality in asymptomatic people belonging to certain sub-populations, such as the elderly.

These theories have baffled the academic community. Some researchers treat the reverse-epidemiology hypothesis with skepticism, pointing out that the unusual findings can be explained by residual confounding of malnutrition and competing mortality risks in the years preceding development of chronic conditions such as ESRD.[17] Indeed, the phenomena underlying the "reverse epidemiology" do not necessarily implicate that the pathological mechanisms operate differently in selected groups of patients, as opposed to general population. The unusual effects of the traditional risk factors may be simply secondary to co-existence of certain confounders that cause reversal of typical relationships between risk factors and outcomes.

Debate continues, and the conundrum of "reverse epidemiology" remains unsolved. For now, one can conclude that the adage "take everything in moderation" as the best way to live still holds true. Morbid obesity is clearly lethal in the general population, but the aesthetically promoted lean-and-mean phenotype may be not best for certain specific sub-groups.

What Causes Obesity?

It is undisputed that the etiology of obesity is far more complex than the simplistic paradigm of imbalance between energy intake and output.[18] Unfortunately, a majority of the general public and many clinicians still base their understanding of obesity on this traditional concept. This situation is understandable. The model of obesity based on energy disequilibrium is alluring in its simplicity. However, both research and clinical practice show that this theory is highly inaccurate.

Obviously, excessive energy input (caused by a high calorie diet) and/or low energy output (due to sedentary lifestyle) will

lead to accumulation of body fat. However, there are myriad confounding factors and effect modifiers that substantially influence the net effect of the processes involved in energy homeostasis. It is therefore not surprising that the simple, logical advice to "eat less, exercise more" fails miserably to deliver expected clinical outcome in the majority of patients.

Diet plays an extremely important role in obesity development. This statement is not a mere theory-driven conclusion. Numerous laboratory studies and some epidemiological data confirmed the obvious notion that consumption of high-energy-content food is related to obesity.[19] Classic medical textbooks point out that for most patients, notable weight loss is easier to achieve by simple dietary modifications than by elaborate exercise programs.[20] Consequently, dietary intervention is considered to be a mainstay of routine weight control programs. It is therefore not surprising that the consumer market is flooded with a seemingly endless stream of purportedly "effective and fail-proof" dietary programs: from Atkins to Zone. There are numerous anecdotal reports of impressive individual successes with many of those trendy diets. This optimistic picture is not confirmed, however, by the results of well-designed clinical trials.[21] It is very likely that the absolute caloric restriction rather than a relative macronutrient composition of a diet plays the key role in its effectiveness. Regrettably, as discussed below, the true voluntary compliance with calorie-restrictive diets is very hard to achieve.

Sedentary lifestyle is unquestionably an important contributor to obesity. Yet, the role of exercise in management of obesity became controversial.[22] Numerous authors recently claimed that exercise is much less effective in management of obesity than was traditionally believed.[21] To explain those findings, it was theorized that obese people who exercise vigorously have increased appetite, and that prevents them from losing weight. Other authors criticized those notions. The dispute continues, yet it appears that weight-loss strategies based on increasing physical activity alone produce very disappointing results.[22] At the same time, however, the STRRIDE Trial actually showed that just 30 minutes of exercise (in subjects on caloric restriction diet) is beneficial in terms of decreasing body weight.[23] Moreover, the positive health impact of structured exercise programs, even without substantial weight reduction, should be considered as well.

Clinicians frequently encounter patients claiming to be affected by "diet-resistant" and/or "exercise-resistant" obesity. Therefore it has been proposed that "slow metabolism" could play a role in the etiology of obesity. Surprisingly, the evidence showed a totally opposite phenomenon. Obese persons usually have greater rates of resting energy expenditure (REE) compared to height-matched lean subjects.[24] This apparent paradox actually makes perfect sense upon critical analysis. Obese persons have greater total cell mass (lean + many adipose cells) as compared to lean individuals (lean + fewer adipose cells). Since REE reflects total cell mass, subjects with larger cell mass will have larger REE.

Moreover, no abnormalities in REE or total energy expenditure (TEE) have been found in patients who claimed inability to lose weight despite self-reported strict compliance with exercise programs and low-calorie diets.[25] Research has revealed that such patients systematically underestimated their food intake and overestimated their physical activity. Studies demonstrated that they exercised much less and consumed many more calories than they self-recorded in their monitoring logs.[26] Certainly, there could be some cases of individuals with atypical metabolic rates. Those are, however, rare exceptions. Unfortunately, the myth of high prevalence of "slow metabolism" persists among the general public.

The role of physical and psychological stress in the etiology of obesity tends to be either neglected or over-emphasized. Proponents of stress-induced obesity point out that chronic stress results in mild elevation of the cortisol level. Unquestionably, chronic severe hypercortisolemia results in steady buildup of adipose tissue that is not easily amenable to reduction through diet and exercise.[20] However, does that mean that stress-related mild elevation of cortisol level is sufficient to induce severe obesity? Perhaps such mild elevation is rather a marker of the as-yet unknown process and not the main actor here. This remains to be established.

In view of all the above, the etiology of obesity is most likely multifactorial and diverse. Yet it is plausible that among the multitude of etiological factors there are some dominant integrative mechanisms that play a key role in the complex pathophysiology of obesity. Understanding those mechanisms could allow for a better management of obesity.

In the 20th century, genetics became queen of medical sciences, and the obesity answer was sought there. Initial hopes were high. Unfortunately, it soon became apparent that the genetics of obesity poses more questions than answers.

Genetic etiologies of obesity were divided into monogenetic (rare) and polygenetic (much more common). Yet, the genetic background explains only an estimated 40 percent of variance in body mass. Environmental and cultural factors play big roles, as evidenced by the different prevalence of obesity in various regions of the world in correlation with economy, sedentary lifestyles, and dietary habits. The urbanization phenomenon is being used to explain the explosion of obesity in populations that were previously lean because of doing vigorous daily physical labor. Yet, no one can explain why some members of those tribes continue to be lean, others are moderately obese, and yet others morbidly obese. Genetics does not fully account for it.

The field of neuroendocrinology appears to hold many promises of better understanding of obesity. During the last century, neuroendocrinology's scope broadened from the narrow aspect of hypothalamic control of the pituitary to studies of reciprocal relationships between the central nervous system (CNS) and all hormones. In addition to examining the intricate interplay between CNS and humoral factors in response to external and internal stimuli, neuroendocrinology focuses on various homeostatic mechanisms. Traditionally, energy and weight homeostasis were the subject of intensive neuroendocrine research. For instance, a groundbreaking research by Hetherington and Ranson demonstrated that stereotaxic destruction of the medial basal hypothalamus

resulted in morbid obesity—similar to that observed in patients with Fröhlich Syndrome (adiposogenital dystrophy).[27] From numerous neuroendocrine theories related to etiology obesity, two are worth mentioning here.

The set-point theory is an attractive explanation of many failures of classic weight management programs. This theory, propounded by G. Kennedy, posits that body weight is predetermined. Therefore, weight loss (or gain) promotes a decrease (or an increase) in metabolic rate that acts to restore body weight to a pre-set level.[28] This is an analogy to the thermostat—hence the name of "adipostat" was given to that hypothetical homeostatic mechanism. The validity of the main notions of the set-point theory has been recently questioned.[29] However, even if this theory were to be proven to be correct, the practical and safe way to change the setting of the "adipostat" for individual patients remains a mystery.

The potential role of the endocannabinoid system in the etiology and treatment of obesity is a quite novel concept that generated clear enthusiasm.[30] The endocannabinoid system (ES) is a group of neuromodulatory lipids, enzymes that synthesize and degrade those lipids, and the receptors for those lipids. ES is involved in a variety of physiological processes including appetite, pain sensation, mood, and memory. This system mediates the psychoactive effects of cannabis. The main components of ES include:

- Endocannabinoids—the endogenous arachidonate-based lipids, which serve as physiological endogeneous ligands for the cannabinoid receptors: All endocannabinoids are eicosanoids. The best known endocannabinoids include anandamide (N-arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG).
- Enzymes that synthesize and degrade the endocannabinoids: These include fatty acid amide hydrolase or monoacylglycerol lipase.
- Cannabinoid receptors: CB1 and CB2 are two G-protein-coupled receptors that are located in the central and peripheral nervous systems.

The dysfunction of the endocannabinod system is proposed to explain the behavioral changes related to abnormal appetite and compulsory food-seeking or avoidance. Changes in the endocannabinoid system may potentially explain both the anomalous increase of appetite in obese individuals and decrease in the food-seeking behavior after bariatric surgery. The initial enthusiasm related to the potential clinical utility of manipulation of ES has decreased after a major debacle of the designer drug rimonabant (Accomplia). Rimonabant is an antagonist of the endocannabinoid receptor CB1. Randomized controlled trials in obese patients have shown that treatment with this compound decreases body weight.[31] Unfortunately, the clinical development program of rimonabant was discontinued in 2008 in view of the emergence of serious side effects in form of severe psychiatric disorders.

Bariatric Surgery

There is no question that results of bariatric surgery are very impressive, as compared with any other available method of weight control. It has been demonstrated that observed weight reduction and metabolic changes that follow bariatric surgery cannot be explained simply by decreasing the absorptive surface of the gut, or speeding up transit. However, the question remains, what mechanisms play a role in this phenomenon? Various hypotheses have been proposed. The following theories have gained popularity recently:

Role of the Gut Hormones

An excellent review by Troke et al. succinctly summarizes the purported role of the gut-brain neuroendocrine axis in the effectiveness of bariatric surgery.[32] The authors make a compelling case about the positive impact of bariatric surgery-induced changes in the gut hormones on the weight loss. They discuss the hormonal manipulation involving gut hormones as a promising treatment of obesity without surgery. They also review the known physiology of the gut hormones. They argue that the favorable effects of bariatric surgery are at least partially related to changes of gut hormones such as GLP-1, PYY, PP and oxyntomodulin, as well as changes in the ghrelin system.

Yet, a skeptical reader may notice many problems with some of those neat theories. Most of the proposed notions are theory-driven conclusions, based on studies showing correlation between bariatric surgery and changes in the gut hormones. Correlation does not imply causation. The full effect of bariatric surgery (minus mechanical effect) could not be duplicated with selected gut hormones manipulation. The explanation given is that to achieve a full effect, multiple hormonal changes have to be induced rather than using one or two of the hormones. That is quite possible; however, given the enormous complexity of the gut hormonal system, one can worry that side effects of such massive hormonal manipulation may outweigh the benefits. We really know much less about the gut hormones than we are willing to admit. Moreover, we are lacking the tools to study the very convoluted and complex system of gut hormones. This may change in the near future. For now, gut-hormone therapy for obesity remains an attractive hypothesis worthy of vigorous pursuit. Realistically speaking, the way to replicate the effects of bariatric surgery by medical means using hormonal manipulation appears to be long and treacherous.

Role of Gut Bacteria

This was a shocker for proponents of the major role of gut hormones in effects of bariatric surgery. In their elegant study, Liou and Kaplan showed that the transfer of the gut bacteria (a.k.a "gut microbiota") from bariatric surgery-operated mice to non-operated, germ-free mice resulted in weight loss and decreased fat mass in the recipient animals.[33] No hormonal manipulation was necessary. The change in the gut microbiota following bariatric surgery in humans is well established. It is a fascinating concept, but like the gut hormones theory, translation of those results to clinical practice will be very difficult.

Endocannabinoids

As discussed above, the endocannabinoid theory can

provide some additional clarifications of the effectiveness of bariatric surgery in areas that cannot be fully explained either by gut hormones or gut microbiota changes.

Conclusions

The homeostatic system related to the weight control is very complex. The simplistic model of energy balance directed by a relatively simple control mechanism appears to be invalid. Clearly, there are multiple yet unknown mechanisms involved in the pathogenesis of obesity. This explains the enormous difficulties in achieving meaningful and safe weight loss in overweight and obese patients. Despite the availability of many non-surgical options, bariatric surgery appears to be the best method available that can induce and maintain major weight loss in severely obese patients.[34-37]

Intensive translational obesity research continues. Numerous integrative approaches, including neuroendocrinology and gastrointestinal microbiology concepts, are being applied to develop a comprehensive theory of weight homeostasis. The day may come when we will fully understand the intricate pathophysiology of obesity. Based on this knowledge, safe, effective, and cost-effective methods of weight control will be developed. Until that time, clinicians and their patients are in the obesity quagmire.

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REFERENCES

1. Brown PJ, Konner M. An anthropological perspective on obesity. *Ann NY Acad Sci* 1987;499(1):29-46.
2. Sikorski C, Luppa M, Kaiser M, Glaesmer H, Schomerus G. The stigma of obesity in the general public and its implications for public health—a systematic review. *BMC Public Health* 2011;11:661.
3. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014;311:806-814.
4. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res* 1998;6(Suppl 2):51S-209S.
5. Wellman, NS, Friedberg B. Causes and consequences of adult obesity: health, social and economic impacts in the United States. *Asia Pac J Clin Nutr* 2002;11(Suppl 8):S705-S709.
6. Kopple JD, Zhu X, Lew NL, Lowrie EG. Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 1999;56:1136-1148.
7. Kragelund C, Hassager C, Hildebrandt P, Torp-Pedersen C, Køber L. Impact of obesity on long-term prognosis following acute myocardial infarction. *Int J Cardiol* 2005;98:123-131.
8. McAuley P, Myers J, Abella J, Froelicher V. Body mass, fitness and survival in veteran patients: another obesity paradox? *Am J Med* 2007;120:518-524.
9. Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007;120:863-870.
10. Lea JP, Crenshaw DO, Onufrak SJ, Newsome BB, McClellan WM. Obesity, end-stage renal disease, and survival in an elderly cohort with cardiovascular disease. *Obesity* (Silver Spring) 2009;17:2216-2222.
11. Van der Helm-van Mil AH, van der Kooij SM, Allaart CF, Toes RE, Huizinga TW. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. *Ann Rheum Dis* 2008.67:769-774.
12. Leung CC, Lam TH, Chan WM, et al. Lower risk of tuberculosis in obesity. *Arch Intern Med* 2007;167:1297-1304.
13. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int* 2002;61:1887-1893.
14. Klassen PS, Lowrie EG, Reddan DN, et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 2002;287:1548-1555.
15. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003;63:793-808.
16. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004;43:1439-1444.
17. Chertow, GM, Hsu CY, Johansen KL. The enlarging body of evidence: obesity and chronic kidney disease. *J Am Soc Nephrol* 2006;17:1501-1502.
18. Hamdy O. Obesity, *Medscape*, Apr 7, 2014. Available at: http://emedicine.medscape.com/article/123702-overview. Accessed May 21, 2014.
19. Drewnowski A, Almiron-Roig E, Marmonier C, Lluch A. Dietary energy density and body weight: is there a relationship? *Nutr Rev* 2004;62:403-413.
20. Kronenberg H, Williams HR. *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: Saunders/Elsevier; 2008:xix, 1911.
21. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2014;99:14-23.
22. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS. The role of exercise and physical activity in weight loss and maintenance. *Prog Cardiovasc Dis* 2014;56:441-447.
23. Slentz CA, Duscha BD, Johnson JL, et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE—a randomized controlled study. *Arch Intern Med* 2004;164:31-39.
24. Ravussin E, Burnand B, Schutz Y, Jéquier E. Twenty-four-hour energy expenditure and resting metabolic rate in obese, moderately obese, and control subjects. *Am J Clin Nutr* 1982;35:566-573.
25. Skov AR, Toubro S, Buemann B, Astrup A. Normal levels of energy expenditure in patients with reported "low metabolism." *Clin Physiol* 1997;17:279-285.
26. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med* 1992;327:1893-1898.
27. Hetherington AW, Ranson SW. Hypothalamic lesions and adiposity in the rat. *Anatomical Record* 1940;78:149-172.
28. Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. *Proc R Soc Lond B Biol Sci* 1953;140:578-596.
29. Weinsier RL, Nagy TR, Hunter GR, et al. Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. *Am J Clin Nutr* 2000;72:1088-1094.
30. Vickers SP, Kennett GA. Cannabinoids and the regulation of ingestive behaviour. *Curr Drug Targets* 2005;6:215-223.
31. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006;295:761-775.
32. Troke RC, Tan TM, Bloom SR. The future role of gut hormones in the treatment of obesity. *Ther Adv Chronic Dis* 2014;5(1):4-14.
33. Liou AP, Paziuk M, Luevano JM Jr, et al. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Sci Transl Med* 2013;5(178):178ra41.
34. O'Brien PE, Dixon JB, Laurie C, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med* 2006;144:625-633.
35. August GP, Caprio S, Fennoy I, et al. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab* 2008;93:4576-4599.
36. Aills L, Blankenship J, Buffington C, et al. ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient. *Surg Obes Relat Dis* 2008;4(5 Suppl):S73-S108.
37. Klein S. Obesity. In: *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: Saunders/Elsevier; 2008:1623.