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Commentary

Management of chronic diseases in preventive cardiology: Revisiting “the Problem of Obesity.”



In a 1997 article in the American Heart Association Journal *Arteriosclerosis, Thrombosis, and Vascular Biology* entitled “Body Weight Regulation and the Problem of Obesity,” [1] Schwartz and Brunzell had a radical but deceptively simple message for researchers and practitioners on the front lines of cardiovascular disease risk reduction. Obesity is a chronic disease, so let’s start treating it like one.

They carefully laid out the evidence that defines the key components of all chronic diseases, whether it be type 2 diabetes, hyperlipidemia, hypertension, or in this case, obesity. First, the body has a normal physiology consisting of both “sensing” and “response” systems that homeostatically maintain a vital bodily process within a narrow normal range, now commonly referred to as a “set point (range).” For blood pressure regulation, these systems include reflexive baroreceptor responses to sudden positional changes as well as the renin-angiotensin-aldosterone system and osmoreceptors that detect larger fluctuations in plasma volume and concentration, eliciting responses leading to salt and water conservation. Two important points to make about homeostatic systems are that they operate without our conscious control (we don’t tell our heart rates to speed up upon standing or our kidneys to secrete renin when renal artery pressures drop from dehydration) and they may include observable behaviors that are biologically driven. For example, activated osmoreceptors increase thirst. When a dehydrated athlete seeks liquid replenishment, we do not describe them as being “addicted to water” or “weak willed” for giving into their thirst. Nor, when they are guzzling water, do we describe them as “binge drinkers.” They will, however, continue to drink water until their hypothalamic receptors register restoration of normal osmolarity, at which point they will be satisfied and put their cup down. Schwartz and Brunzell pointed out that body weight is similarly homeostatically regulated by an interaction between three major organ systems: the brain and brainstem, which are command central for integrating peripheral hormonal “sensing” signals from the gastrointestinal tract (stomach and intestines) as well as from fat tissue. Consumed nutrients stimulate secretion of a pattern of gut hormones that signal to the brain the availability, composition, and amount of calories consumed (calories “in”) [2]. The summation of these hormones also conveys a satiety signal that at its peak determines when we are satisfied with the amount of food eaten and put our forks down. Simultaneously, secretion of ghrelin, the putative “hunger” hormone, is suppressed and reaches nadir levels after roughly 90 minutes before progressively rising again until the next meal is initiated [3]. Like thirst, these observed behaviors of satiety and hunger that govern our food seeking behaviors are driven by endogenous biological signals that might be ignored for a period of time but cannot be willed away. They will remain active until sufficient calories are again found and consumed. These same brain centers contain leptin receptors that convey alterations

in fat mass through changes in leptin levels [4]. These two sets of signals are integrated continuously by the brain and brainstem to maintain weight stability, typically to within a 5 lb. range. If the brain senses a drop in calories (reduced secretion of gut hormones), body weight (reduced leptin), or both, effector systems are activated that increase food seeking behavior, calorie intake, and reduce energy expenditure (energy “out”) to limit weight loss and ultimately re-establish equilibrium once again when weight is restored. As could be imagined for a system so vital for both survival and fertility [5], it is complex, has multiple redundancies built in, and is extremely resilient in resisting weight loss.

A second component of all chronic diseases is that they arise when this normal homeostatic physiology no longer operates within what is considered a healthy range. When the set point for blood pressure regulation rises, pre-hypertension and hypertension develop. For glucose regulation, patients progress from prediabetes to type 2 diabetes. And when the body weight set point rises, patients will enter into a temporary state of involuntary positive energy balance resulting in unwanted weight gain to become overweight or obese before re-establishing a new neutral energy balance, albeit at a high body weight than before. To the best of our understanding, each of these chronic diseases results from pathophysiological changes in the normal regulatory systems ultimately establishing a new, higher set point that is homeostatically defended just as it was at the lower set point. This means that in most patients, once a chronic disease is manifest, it is unlikely to be corrected exclusively by changes in lifestyle but will require medical (pharmacologic) intervention. These therapies were often developed based on our understanding of the normal physiology. For example, lifestyle management temporarily stabilizes blood glucose levels in patients with newly diagnosed type 2 diabetes, but most patients will still experience a progressive decline in islet cell secretory capacity that necessitates eventual medication initiation for glycemic control. These include drugs that stimulate insulin secretion, enhance insulin sensitivity, or directly replace the deficient insulin hormone [6]. For patients with newly identified hypertension, the average systolic blood pressure lowering response to a dietary intervention including salt restriction is roughly 7 mm Hg [7]. For a patient with a blood pressure of 150/90 mm Hg, this will help but not prevent the need for an anti-hypertensive medication such as a diuretic, beta-blocker, or ACE inhibitor. And for weight loss, the best evidence for intensive lifestyle management outcomes comes from the Diabetes Prevention Program, which resulted in an average weight loss approaching 8% after one year but backtracking to 4% after four years [8]. For a patient who weighs 200 lbs. and a body mass index of 36 kg/m², we can properly counsel them that as a result of their best efforts to eat healthy, curb their portions, and exercise regularly they can expect to lose an average of 8 lbs. long-term. The major difference in how a patient with

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obesity is managed compared to a patient with type 2 diabetes or hypertension is that most practitioners will not then take the next step to initiate a weight loss medication or counsel them on the possibility of weight-loss surgery. Telling a patient with obesity to eat less and exercise more without follow-up and initiation of a weight loss medication when indicated is akin to telling a patient with hypertension who does not respond to salt restriction to drink less fluid and sweat more. Their blood pressure will drop as their plasma volume decreases, but they will be tired, orthostatic, have limited exercise capacity, and continuously be driven by thirst to drink until their plasma volume, and hypertensive range blood pressures, are restored to previous levels.

The third component of any chronic disease is that long-term exposure to the increased set point (range) leads to impaired health. For adiposity, this can result from accumulation of excess total weight and fat mass, specific fat depots (e.g., visceral or epicardial adipose tissues), and intra-organ lipid (ectopic fat). Patients most severely affected by their adiposity have some combination of all of these. However, it is possible to be normal weight or overweight by accepted BMI criteria but still be centrally “obese,” especially for Asian populations who are experiencing explosions in type 2 diabetes [9]. Which really means we need more sophisticated clinical tools to gauge adiposity risk, since BMI alone is often inadequate. In the context of a preventive cardiology practice, overweight and obesity greatly increases the risk of, or is the direct causative factor in, the four current health care “epidemics”: type 2 diabetes [10], non-alcoholic fatty liver disease, which is replacing infectious hepatitis as the leading cause of end stage liver disease [11], heart failure with preserved ejection fraction [12], and cardiovascular disease and death [13,14]. Yet instead of recognizing and managing overweight and obesity, practitioners opt instead to manage the complications, greatly increasing the drug burden on our patients and health care costs to the individual patient, insurance companies, and the government [15,16].

What is needed is to incorporate weight management into our practices at the earliest stages and in those with the greatest risks. Weight-loss medications should not be considered “adjuncts” to lifestyle management any more than statin medications are “optional” only when dietary therapy fails to achieve target LDL levels for primary and secondary prevention of heart disease. This means instituting lifestyle recommendations that are either followed by weight loss medications in some patients (those do not have a meaningful weight loss response or achieve a BMI less than 27 kg/m²) or begun simultaneously in others. This also means that we need to identify appropriate “first line” medications for weight management—the equivalent of metformin for diabetes or a statin for heart disease risk reduction—so that general practitioners can initiate applicable therapy in their offices rather than refer every eligible patient to a specialist for weight management. Current FDA-approved weight-loss medications result in significantly greater weight loss compared to placebo plus lifestyle (3–10%), have additional benefits on cardiovascular risk factors, and have been shown to be either non-inferior or superior to placebo in major adverse cardiovascular events trials (Table 1). Specialists need to be comfortable with combination therapies for weight loss just as combination medications are now the norm for long-term management of hypertension, type 2 diabetes, and cardiovascular disease. Finally, we need to acknowledge the safety [17, 18] and benefits of metabolic-bariatric surgeries on weight loss (averages closer to 25% to 30% long-term), reduction in obesity complications, reduction in cardiovascular diseases and heart failure, and the remarkable improvements in mortality for our patients, especially those with type 2 diabetes [19–23], and refer them to the surgeons for this option when appropriate (BMI > 30-35 kg/m² with an obesity complication) [24].

Our best response to the obesity is to prevent it from happening, either helping patients maintain their healthy weight or prevent those who are overweight from experiencing further weight gain. As with any chronic disease, healthy lifestyle practices are still the initial therapy of choice and should be continued lifelong. Since the peak age for obesity in

Table 1

Long-term weight loss and cardiovascular outcomes of currently approved FDA weight-loss medications in the United States.

Weight Loss Medications	Weight Loss	MACE Outcome	Notes
Phentermine-topiramate (Qsymia)	10.5% [30]	Relative risk: 0.24 (95% CI 0.03 to 1.70)[31]	No true RCT has been completed for the fixed combination of phentermine and topiramate. The largest MACE study to date comes from a retrospective cohort analysis using a large insurer database.
Bupropion-naltrexone (Contrave)	3.6% [32]	Hazard ratio: 0.88 (99.7% CI, 0.57 to 1.34)[32]	Analysis only includes data generated up to the 50% event rate. Study stopped prematurely by FDA due to reporting violation by the sponsoring company.
Liraglutide 3.0 (Saxenda)	6.1% [33]	Hazard ratio: 0.87 (95% CI, 0.78 to 0.97)[34]	MACE outcomes trial was conducted on the 1.8 mg dose (Victoza), which was accepted by the FDA for labeling purposes for the 3.0 mg dose (Saxenda). A MACE outcome study has not been separately conducted for the 3.0 mg dose. Progression from pre-diabetes to diabetes was also reduced by a hazard ratio of 0.21 (95% CI 0.13–0.34) compared to placebo during three years of follow-up [33].

MACE: major adverse cardiovascular events.

the US population is in the fourth and fifth decades [25], even those with a healthy weight in young adulthood should adhere to best lifestyle practices to prevent future unwanted weight gain. But once overweight and obesity become manifest, healthy lifestyle practices should be continued and patients offered medical and surgical weight loss options shown to reduce disease burden and save lives. If effective, patients will need to continue these therapies life long, in the same way that we would not start a hypertension medication and then stop it after three months, informing the patient it is now their responsibility to keep their blood pressure under control on their own.

Barriers to use of medications and referrals to bariatric-metabolic surgery are legion. These include implicit cultural bias against patients with obesity and medical bias against acceptance of obesity as a disease, failure of practitioners to keep up with the latest medical education on the science of weight regulation, lack of insurance coverage for obesity management, unrealistic expectations of lifestyle changes alone on weight loss, unfounded fears that current FDA-approved weight loss medications are “dangerous,” insecurity by practitioners and patients alike to raise the topic of obesity management during the appointment, and siloing of therapeutics so that only a specialist can manage obesity. Like any emerging or new areas of medicine, practitioners need to have a firm understating of the pathophysiological underpinnings of obesity as a chronic disease, the mechanisms of available therapeutics (in this case both medications and weight-loss surgeries), and their side effects. Then they need to begin to incorporate these new therapies into their practices. Fast-forward 25 years from Schwartz and Brunzell’s commentary and much progress has been made into the science of weight regulation and expression of obesity [26] and its management [27] but little has changed regarding cultural and clinical attitudes towards patients with obesity and how they should be treated. If we are true practitioners of preventive cardiology, then, in addition to working within a multidisciplinary healthcare team that provides nutritional counselling and skills training in physical activity, we need to expand our therapeutic toolbox to include weight management strategies such as weight-loss

medications [28,29] and, in partnership with bariatric surgeons, referral to metabolic-bariatric surgeries. Let's not let another quarter century pass before we act on Schwartz and Brunzell's message. Obesity is a disease, so let's (finally) start treating it like one.

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