Obesity and Type 2 Diabetes: What Can Be Unified and What Needs to Be Individualized?

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OBJECTIVE—This report examines what is known about the relationship between obesity and type 2 diabetes and how future research in these areas might be directed to benefit prevention, interventions, and overall patient care.

RESEARCH DESIGN AND METHODS—An international working group of 32 experts in the pathophysiology, genetics, clinical trials, and clinical care of obesity and/or type 2 diabetes participated in a conference held on 6–7 January 2011 and cosponsored by The Endocrine Society, the American Diabetes Association, and the European Association for the Study of Diabetes. A writing group comprising eight participants subsequently prepared this summary and recommendations. Participants reviewed and discussed published literature and their own unpublished data.

RESULTS—The writing group unanimously supported the summary and recommendations as representing the working group’s majority or unanimous opinions.

CONCLUSIONS—The major questions linking obesity to type 2 diabetes that need to be addressed by combined basic, clinical, and population-based scientific approaches include the following: 1) Why do not all patients with obesity develop type 2 diabetes? 2) Through what mechanisms do obesity and insulin resistance contribute to β-cell decompensation, and if/when obesity prevention ensues, how much reduction in type 2 diabetes incidence will follow? 3) How does the duration of type 2 diabetes relate to the benefits of weight reduction by lifestyle, weight-loss drugs, and/or bariatric surgery on β-cell function and glycemia? 4) What is necessary for regulatory approval of medications and possibly surgical approaches for preventing type 2 diabetes in patients with obesity? Improved understanding of how obesity relates to type 2 diabetes may help advance effective and cost-effective interventions for both conditions, including more tailored therapy. To expedite this process, we recommend further investigation into the pathogenesis of these coexistent conditions and innovative approaches to their pharmacological and surgical management.

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glycemic control simultaneously. Participants in the January 2011 conference (Supplementary Data) were tasked with examining what is known about the relationship between obesity and type 2 diabetes and the heterogeneity of these conditions, what needs to be learned, and how to direct future research in these areas to advance effective interventions and improve patient care. What follows summarizes the major issues addressed and the outcomes of the discussion.

Mechanisms of obesity-associated insulin resistance
The influence of obesity on type 2 diabetes risk is determined not only by the degree of obesity but also by where fat accumulates. Increased upper body fat including visceral adiposity, as reflected in increased abdominal girth or waist-to-hip ratio, is associated with the metabolic syndrome, type 2 diabetes, and cardiovascular disease (3), although underlying mechanisms remain uncertain. Whether subcutaneous fat lacks the pathological effects of visceral fat or is simply a more neutral storage location, for example, requires further study. Beyond differences in body fat distribution, emerging evidence suggests that different subtypes of adipose tissue may be functionally distinct and affect glucose homeostasis differentially. Adult humans have limited and variable numbers of brown fat cells (4), which play a role in thermogenesis and potentially influence energy expenditure and obesity susceptibility (5). Improved understanding of the function of different fat cell types and depots and their roles in metabolic homeostasis is a priority for investigation into the pathogenesis and complications of obesity. Likewise, adipose tissue is composed of heterogeneous cell types. Immune cells within adipose tissue also likely contribute to systemic metabolic processes. As the study of adipose biology progresses, it will be important to consider whether additional subtypes of adipocytes or other cell types can be identified to refine our understanding of obesity complications and generate novel approaches to prevention.

At least three distinct mechanisms have been proposed to link obesity to insulin resistance and predispose to type 2 diabetes: 1) increased production of adipokines/cytokines, including tumor necrosis factor-α, resistin, and retinol-binding protein 4, that contribute to insulin resistance as well as reduced levels of adiponectin (6); 2) ectopic fat deposition, particularly in the liver and perhaps also in skeletal muscle, and the dysmetabolic sequelae (7); and 3) mitochondrial dysfunction, evident by decreased mitochondrial mass and/or function (8). Mitochondrial dysfunction could be one of many important underlying defects linking obesity to diabetes, both by decreasing insulin sensitivity and by compromising β-cell function.

Mechanisms of progressive β-cell dysfunction in obese individuals
The link between obesity and hyperinsulinemia, first identified ~50 years ago (9), reflects compensation by insulin-secreting β-cells to systemic insulin resistance. Although mechanisms underlying this coupling (e.g., mild hyperglycemia and raised levels of circulating free fatty acids) remain elusive, obese normoglycemic individuals have both increased β-cell mass and function (9–12). Obesity-induced glucose intolerance reflects failure to mount one or more of these compensatory responses (13).

Factors predisposing to β-cell decompensation could also be primarily genetic or epigenetic. A clear, mechanistic basis for this decompensation has remained elusive. Genetic studies have helped identify the role of some key molecules in β-cell biology that may be important in this regard. For example, recent rodent studies have demonstrated diabetogenic effects of reduced pancreatic β-cell biology that may be important in this regard. For example, recent rodent studies have demonstrated diabetogenic effects of reduced PDx1 gene (14,15). While these animal studies have demonstrated PDx1 deficiency relates mechanistically to diabetes through β-cell apoptosis, and PDx1 deficiency is linked to MODY4 (16), it is not clear yet that PDx1 deficiency has a role in common forms of type 2 diabetes in humans. This example illustrates how a growing understanding of genetics and cellular function of the β-cell can identify potential mediators predisposing obese individuals to type 2 diabetes and further may provide insights for the development of new therapeutic agents.

Genetic factors linking obesity and diabetes
Genome-wide association scans (GWAS) and candidate gene approaches now have identified ~40 genes associated with type 2 diabetes (17,18) and a similar number, albeit largely different, with obesity. Most type 2 diabetes genes appear to be related to β-cell dysfunction, with many fewer involved in pathways related to insulin resistance independent of obesity (19,20). Not surprisingly, many obesity gene variants appear to be involved in pathways affecting energy homeostasis. Although numerous diabetes- and obesity-associated genes have been identified, the known genes are estimated to predict only 15% of type 2 diabetes and 5% of obesity risk (21). Although additional genes with important roles will undoubtedly be discovered, this low predictive power may reflect the importance of environmental factors, less frequent genetic variants with stronger effects, or gene-environment, gene-gene, and epigenetic interactions that are not readily identified through methods based on population genetics. Methods for detecting gene-gene interactions exist, but the population size needed to detect them is substantially greater than is required for detection of single genes of relatively small effect. Alternatively, pathway analyses or a systems biology approach combining information from DNA variations with transcript, protein, and metabolite profiles may better capture the genetic influences on metabolism than studying single genes. One should also keep in mind that the missing heritability could be an illusion of inferring additive genetic effects from epidemiological data (22).

Does a shared pathogenesis underlie both obesity and type 2 diabetes?
Although the link between obesity and type 2 diabetes is widely held to involve two discrete lesions—obesity-induced insulin resistance and β-cell failure—both disorders may share an underlying defect. This “unified field theory” raises questions about whether defects favoring progressive weight gain and metabolic impairment also contribute to β-cell decompensation.

One potential link could be sustained cell exposure to nutrient concentrations exceeding energy requirements. Deleterious cellular effects of nutrient excess can include impaired inflammatory signaling, endoplasmic reticulum stress, excess production of reactive oxygen species, mitochondrial dysfunction, accumulation of triglycerides and/or fatty acyl intermediates, and activation of serine-threonine kinases (23). These responses are not mutually exclusive, and induction of one may trigger another, leading to a cascade of damage. Obesity-associated cellular injury can in turn recruit and activate...
macrophages and other immune cells that exacerbate tissue inflammation (23,24). Collectively, these responses contribute to the pathogenesis of insulin resistance in the liver, skeletal muscle, and adipose tissue, and some (e.g., acquired mitochondrial dysfunction and inflammation) may occur in β-cells as well via mechanisms discussed above. In susceptible individuals, therefore, obesity-induced metabolic impairment can favor insulin resistance on the one hand and progressive β-cell dysfunction on the other. Reduced insulin secretion can in turn worsen the nutrient excess problem by raising circulating concentrations of glucose, free fatty acids, and other nutrients. In this way, a vicious cycle arises whereby obesity-induced nutrient excess triggers inflammatory responses that cause insulin resistance, placing a greater demand on the β-cell, and as β-cell function declines the cellular toll taken by nutrient excess increases. Since not all obese individuals develop hyperglycemia, however, an underlying abnormality of the β-cell must coexist with nutrient excess to promote type 2 diabetes (13).

Brain neurocircuits governing energy homeostasis also affect insulin sensitivity in the liver and perhaps other peripheral tissues (25), and inflammation similar to that induced by obesity in peripheral insulin-sensitive tissues also occurs in these areas of the brain (26). If obesity is associated with impairment of neurocircuits regulating both energy balance and insulin action, obesity-induced insulin resistance may arise not only as a direct consequence of excessive adipose mass but via neuronal mechanisms as well. Whether disturbed neurocircuits also contribute to deteriorating β-cell dysfunction as obesity and its sequelae progress is an active area of investigation (27).

Managing body weight by behavioral change and medications
The dramatic increase in incidence and prevalence of obesity over the past 50 years, associated in part with major worldwide changes in caloric intake and dietary composition, has focused attention on lifestyle intervention to reverse or ameliorate caloric imbalance. In general, programs including individual or group counseling to modify behavior result in 5–10% weight loss and are effective for 6–12 months, after which weight regain is the rule. Some longer-term lifestyle intervention studies with sustained interventions demonstrate more durable weight loss (28,29), with extent of weight loss in the first 3–6 months generally predicting longer-term success. Successful lifestyle intervention programs typically involve self-monitoring of weight, dietary intake, and activity; behavioral modification; frequent contact; and caloric balance through diet, with or without exercise. For example, short-term intervention studies suggest that dietary changes, which emphasize less fat and refined carbohydrates, make it easier to reduce total caloric intake in obese adults and overweight children (30,31).

Medications have been used to assist in weight loss for almost 80 years, but adverse effects frequently restrict utility. Medications have been developed based on physiological insights, more recently targeting central nervous system control of appetite and metabolism, or opportunistically when weight loss was noted as a side effect of approved medications. Table 1 lists medications that have been available and others under development. In general, weight loss achieved with these medications ranges from 2 to 8% greater than placebo, with some suggestion that combination therapy may either increase weight loss or ameliorate side effects and increase tolerability. However, most drug trials last only 6–12 months, and thus there are few long-term data that weight loss can be sustained. Moreover, high drop-out rates, which approach 50%, are characteristic of many weight-loss trials and result in survivor effects in efficacy analyses, thereby potentially amplifying drug benefits and limiting generalizability. Furthermore, concern regarding adverse effects, including cardiovascular disease risk and central effects (e.g., depression) in drugs crossing the blood-brain barrier, continue to limit approval and application.

Managing body weight by bariatric surgery
Health benefits of bariatric surgery, determined largely from nonrandomized

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<tr>
<th>Medication</th>
<th>Availability</th>
<th>Serious adverse effects</th>
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<td>Withdrawn</td>
<td></td>
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<tr>
<td>Fenfluramine</td>
<td>1973–1997</td>
<td>Cardiac valvular insufficiency and pulmonary hypertension</td>
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<tr>
<td>Dexfenfluramine</td>
<td>1996–1997</td>
<td>Cardiac valvular insufficiency and pulmonary hypertension</td>
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<tr>
<td>Phenylpropanolamine*</td>
<td>1960–2000</td>
<td>Hemorrhagic stroke</td>
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<tr>
<td>Rimonabant</td>
<td>2006–2009</td>
<td>Depression and suicidal ideation</td>
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<td>Sibutramine*</td>
<td>1997–2010</td>
<td>Nonfatal myocardial infarction and nonfatal stroke (in subjects with preexisting cardiovascular conditions)</td>
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<td>Current</td>
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<tr>
<td>Phentermine#</td>
<td>1959–present</td>
<td>Palpitations and elevated blood pressure</td>
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<td>Orlistat</td>
<td>1999–present</td>
<td>Liver injury</td>
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<td>Phase 3 trials and current applications to FDA/EMA</td>
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<tr>
<td>Lorcaserin</td>
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<td>Potential valvular heart disease and psychiatric and cognitive disorders</td>
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<tr>
<td>Bupropion/naltrexone</td>
<td></td>
<td>Seizures, palpitations, and transient blood pressure elevations</td>
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<td>Topiramate/phentermine</td>
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<td>Depression, suicidal ideation, cardiovascular events, memory loss, and birth defects</td>
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<td>GLP-1 analogs</td>
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<td>Pancreatitis</td>
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EMAC, European Medicines Agency; FDA, U.S. Food and Drug Administration; GLP-1, glucagon-like peptide 1. *Phenylpropanolamine is still available in some European countries and sibutramine in some South American countries. #Phentermine is one of a class of sympathomimetic drugs that also includes benzphetamine, diethylpropion, and fenfluramine.
studies, are being increasingly recognized. These benefits include substantial and sustained weight loss (32), resolution of comorbidities such as diabetes, hypertension, and dyslipidemia (33, 34), and reduced myocardial infarction, cancers, and associated mortality (35). For extreme obesity, surgery is now the preferred and currently only effective treatment modality. Acute morbidity and mortality of surgical approaches have been dramatically reduced, enabling widespread use of these procedures. Furthermore, over the long term, bariatric surgery might reduce aggregate healthcare expenditures (36). There is also a growing movement toward using surgery to control diabetes, independent of severe excess weight, but there are currently few scientifically valid data to support this clinical path.

Bariatric surgery falls into two general categories: purely restrictive procedures such as the laparoscopic adjustable gastric band devices, which appear to improve diabetes via weight loss, and procedures bypassing the proximal gut, such as the Roux-en-Y gastric bypass (RYGB) or newer gastric sleeve procedures. The latter approaches (“metabolic” surgery) appear to produce unique effects on enteroneocrino hormonaland neuronal signaling pathways and produce more weight loss and diabetes remission than banding alone (34, 37). Metabolic surgeries are associated with increases in anorexigenic and decreases in orexigenic hormones, changes largely absent in band or restrictive procedures, and may explain the differential outcomes (38). Although mechanisms leading to weight loss and diabetes remission are only beginning to be understood, the above endocrine, peptide, and neural effects may mediate these benefits because of structural changes including isolation of the gastric cardia; exclusion of the distal stomach, duodenum, and proximal jejunum; exposure of the distal intestine to undigested nutrients; and partial vagotomy. Longer duration of diabetes and insulin use, both typically associated with decreased β-cell function and possibly surrogates for reduced β-cell mass, are associated with reduced post-surgical remission rates, thus suggesting that residual β-cell function may be a critical factor for metabolic benefits (39).

Known differences in mechanism and efficacy, along with risks and patient priorities (e.g., weight loss vs. metabolic diabetes goals) already inform the choice of surgical procedure. However, many questions remain, including the following: How much weight loss is required for health benefits? What is the effect of different interventional methods on long-term outcomes? What mechanisms underlie the heterogeneous responses? Further, regarding diabetes, is the optimal timing for treatment the same or different from obesity? Are β-cells preserved or do they even grow? Why do we not see the same efficacy and durability of response for other obesity-related pathologies (e.g., hypertension) as for glycemic control? Ongoing randomized clinical trials (40) promise to answer many questions regarding patient selection, optimal procedure, when to intervene, and where initial and chronic care should be delivered.

Barriers to effective management

A vast array of barriers—ranging from deficits in basic research to socioeconomic and individual psychological factors beyond the scope of the conference—undermine current efforts to manage obesity, particularly in individuals with type 2 diabetes. Lessons learned from efforts such as those applied to tobacco cessation may be quite relevant (41).

Lifestyle programs (especially long-term) are often plagued by inadequate reimbursement. Further, there is a lack of evidence-based individualized goals and strategies combining lifestyle and medications, or appreciation of sequential (stepped) therapy. As mechanisms leading to obesity and its maintenance are not fully understood, questions remain about which interventions, be they lifestyle or pharmacological, might be most effective during various stages of weight gain, loss, and regain. In addition, medications under development may carry indeterminate risk. Likewise, surgery is an imperfect remedy due in part to perceived risks and high cost. With laparoscopic banding now approved for BMI >30 kg/m² with a comorbidity such as diabetes or hypertension, 27 million Americans would be eligible for surgery. However, the large-scale feasibility of such an approach is uncertain and compounded by issues related to reimbursement. Thus, the search must continue for how to implement optimal lifestyle interventions and to find effective drugs and/or minimally invasive devices.

These barriers are further complicated in the context of type 2 diabetes. Obese patients with hyperglycemia are often poorly characterized not only in terms of their history of obesity but also in the duration of their glucose intolerance. Further, interventions are typically started late in the disease, with minimal preventive efforts. In addition, as initial weight loss is the main determinant of longer-term weight loss, the typical initial goal of ~5–10% weight loss may be inadequate to produce glycemic control (42). Furthermore, although controlling body weight (either by reduction or by prevention of further rise) improves glycemic control by ameliorating both insulin resistance and β-cell dysfunction, the impact of pharmacologically induced improved glycemic control on body weight varies by individual drug. Glucose-lowering medications can be broadly categorized into those associated with weight gain and those essentially weight neutral or promoting weight loss (Table 2). Whether weight gain offsets any benefit of reduced glycemia on cardiovascular risk needs to be determined. Further, weight changes do not necessarily predict changes in glycemcic control (43), and while specific therapies may work in certain diabetes subtypes, the response to glucose-lowering medications varies considerably. This latter topic was the focus of a similar workshop in 2009 on individualizing therapies in type 2 diabetes (44).

Equally challenging is the problem of weight regain, which usually follows any degree of weight loss, however achieved (Fig. 1). Well studied and viewed as a normal response in lean individuals, this phenomenon is equally robust among the obese. It involves complex, highly integrated physiological responses that are similar to those invoked in weight-reduced, nonobese individuals. The biologic basis appears to be the tendency to defend attained weight, whether normal or excessive, which seems to be wired in

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<th>Medication class</th>
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<td>Pramlintide</td>
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<td>Metformin</td>
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<td>α-Glucosidase inhibitors</td>
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<td>DPP-4 inhibitors</td>
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<td>Thiazolidinediones</td>
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multiple central nervous system defenses against weight loss. Current models of energy homeostasis predict genetic or acquired defects in key neurocircuits that undermine the normal response to adiposity-related humoral signals. Much of the basic science in this area has been performed in animal models of obesity (genetic or overfeeding); extrapolation to the pathophysiology of human obesity remains uncertain.

The panoply of potential mechanisms defending body weight helps explain why the field is moving toward targeting multiple pathways by harnessing additive effects of current drugs, which individually produce ~5% weight loss (45). A number of compounds, old and new, alone or in combination, are being developed. It is hoped that they may safely achieve the magnitude of change in body weight, as well as other beneficial effects such as glucose control, that has been obtained with some of the surgical approaches.

**Recommendations**

*Elucidate the pathogenesis linking obesity and type 2 diabetes.* A better understanding of mechanisms linking obesity, insulin resistance, and type 2 diabetes may ultimately facilitate more individualized treatment. One future research priority is to clarify how identified gene variants affect glucose, fatty acid, and energy metabolism at both cellular and whole-body levels. Rather than searching for a single factor or theory explaining the predisposition to β-cell decompensation in obese individuals, a multifactorial, synergistic explanation seems more compatible with current knowledge. Multiple mechanisms may link β-cell dysfunction to systemic insulin resistance, including differing cellular responses to nutrient excess and impaired brain neurocircuits governing energy homeostasis. One way to approach this complex pathophysiology is to examine glucose-tolerant obese patients and study the association with and progression to β-cell decompensation.

*Expand research on heterogeneity.* So far, genetic studies have been limited by a lack of accurate assessments of phenotype. Additional large-scale population-based analyses addressing more complex disease determinants of obesity and diabetes (beyond single genetic polymorphisms) might improve understanding of the relative impact of genetic and environmental factors linking them. Other priorities include clarifying the genetic basis for differences in fat distribution across ethnic groups (46); identifying factors that control homing of adipose tissue to the different—visceral versus subcutaneous—fat depots (47) and adipose tissue angiogenesis (48); and understanding the time course and extent of transdifferentiation of brown and white adipocytes in humans (5).

*Human β-cells*, including those from patients with type 2 diabetes, need to be made more widely available for investigational use. An additional approach would be the creation of patient-specific stem cell–derived β-cells. Moreover, longitudinal studies of β-cell dysfunction in humans should address differences in the amount of weight loss required to durably improve β-cell function. Finally, research to elucidate the intrauterine environment’s impact on β-cell development and function may provide further strategic approaches to protecting progressive β-cell dysfunction.

*Develop innovative approaches to pharmacological and surgical management.* Innovative approaches to managing obesity may lower certain barriers under-mining treatment of both obesity and type 2 diabetes. For example, modulating the incretin axis may benefit both energy balance and glycemia. Novel pharmacological development may depend on information gained from more efficient use of genomic, proteomic, and metabolomic approaches and from information learned from studying weight-loss mechanisms in bariatric surgery. In addition, co-opting less traditional organs such as the brain and gut into the core pathophysiology of type 2 diabetes may reveal new biomarkers and/or targets for therapeutic intervention. Finally, safe and effective centrally acting drugs that decrease appetite or increase satiety are urgently needed. However, as regulatory agencies increase the need for safety testing, fewer new and innovative approaches for weight loss are being developed because of the prolonged time and immense expense involved.

*Emphasize primary prevention of obesity and type 2 diabetes.* Current clinical approaches to obesity continue to focus on secondary and tertiary intervention. Physicians often introduce secondary interventions when patients surpass some dichotomous BMI threshold or when patients self-identify, for cosmetic or health reasons. They introduce tertiary intervention when obesity-related complications responsive to weight loss, such as diabetes, hypertension, or sleep apnea, develop. Because weight problems develop over the entire life span, however, emphasizing obesity prevention is urgent and must include cooperation of public health institutions, the school systems, and the private (e.g., food industry) sector. The likelihood of sustained benefits of weight reduction on β-cell function and glycemia in patients with early-onset versus more prolonged durations of type 2 diabetes needs to be determined.

Although intensive lifestyle modifications and medications have been
conclusively demonstrated to slow the development of type 2 diabetes in those with impaired glucose metabolism (28,49), regulatory authorities have still not approved medications for preventing type 2 diabetes, nor have they provided a regulatory framework to do so. Guidance on what would be required to approve medications for treating high-risk individuals would foster more scientific investment in this area and subsequent availability of additional preventive options.

Adopt a chronic disease model linking obesity to diabetes care. Current understanding of both pathophysiology and management suggests the need to adopt a chronic disease model of care linking obesity and diabetes care management systems. Besides including stepped-care approaches similar to those used for other chronic diseases, this model involves basing interventional (pharmacological and surgical) approaches on severity, duration, and individual risk/benefit. The common perception that the obesity problem is insurmountable leads to some degree of clinical inertia. What is needed is similar to what occurred with tobacco—a comprehensive social, economic, and workplace approach to prevention and intervention. In addition, community-setting approaches supplemented by physician involvement can work when combining treatment modalities (50). Furthermore, multidisciplinary teams including nutritionists, exercise physiologists, and behavioral/mental health professionals can achieve both initial and sustained weight management and glucose control (28,29). This approach to attaining and maintaining weight reduction is critically important both in alleviating the intensive defense of body weight by multiple biological systems and in reducing risk of β-cell decompensation and, over the long term, diabetes complications.

Summary and conclusions
Improved understanding of obesity’s heterogeneity, including interindividual differences in pathogenesis, propensity to regain lost weight, development of obesity-related complications including diabetes, and response to therapy, is critical to advance the development of effective and cost-effective interventions. The insights that improve obesity prevention and treatment will almost certainly benefit the incidence and care of type 2 diabetes. The converse may not be true since current treatments of diabetes can have differential effects on weight. Even so, we have reached a point when we can begin to consider innovative and potentially more effective approaches to managing both obesity and type 2 diabetes. Increased understanding of the pathogenesis of obesity and type 2 diabetes, for example, should not only help differentiate responders from nonresponders but also make tailored therapy a reality. Equally beneficial will be incorporating these ideas into a chronic disease model of care linking obesity management to diabetes care systems, including multidisciplinary approaches to patient care designed to prevent weight regain that is almost universal when therapy is stopped.

Presently, some of the major questions linking obesity to type 2 diabetes that need to be urgently addressed include the following:

1. Why do not all patients with obesity develop type 2 diabetes?
2. Through what mechanisms do obesity and insulin resistance contribute to β-cell decompensation, and if/when obesity prevention ensues, how much reduction in type 2 diabetes incidence will follow?
3. How does the duration of type 2 diabetes relate to the benefits of weight reduction by lifestyle, weight-loss drugs, and/or bariatric surgery on β-cell function and glycemia?
4. What is necessary for regulatory approval of medications and possibly surgical approaches for preventing type 2 diabetes in patients with obesity?

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