Skeletal muscle is a dynamic system with respect to its contractile and metabolic properties. Highly trained endurance athletes are lean, and their muscle is enriched with slow oxidative fibers that comprise types I and Ila myosin heavy-chain (MHC) proteins and are abundant in oxidative enzymes and mitochondria. Slower-twitch fibers demonstrate slow cross-bridge cycling and low abundance and activity of energy-consuming calcium pumps in the sarcoplasmic reticulum. These characteristics significantly decrease the demand for ATP, contribute to their resistance to fatigue, and allow for prolonged bouts of low- to moderate-intensity activity (reviewed in Ref. 4). In contrast, strength and power athletes are hypermuscular yet lean, and their muscles are enriched with fast glycolytic fibers that express types Ila, IIX, and IIb (in rodents) MHC proteins. These fibers possess metabolic machinery to enhance glucose utilization and ATP generation that is useful for the performance of short bouts of high-intensity physical activity. The rapid cross-bridge cycling and dramatic calcium fluxes in the faster-twitch fibers result in much higher energy demands and add to their susceptibility to fatigue. These two extremes bookend the broad contractile and metabolic spectrum of skeletal muscle.

Beyond human performance, there is great interest in modulating skeletal muscle metabolism to counter the epidemics of obesity and type 2 diabetes mellitus (T2DM). Intriguingly, recent work has supported two very different approaches to address systemic metabolic dysfunction through skeletal muscle: 1) promoting the phenotype of the endurance athlete to augment fatty acid oxidation and mitochondrial biogenesis, and 2) the focus of this review, promoting the phenotype of the strength and power athlete through resistance training, genetic alterations, and/or pharmacological strategies to increase the abundance and activity of principally glycolytic fibers. In the following paragraphs, we review key molecular pathways regulating muscle growth and metabolism and highlight the recent literature in mice and humans that supports resistance training and resistance training-like strategies for metabolic dysfunction.

**Increasing Skeletal Muscle Mass pour Diabète Gras**

Muscular work as a therapy for human diabetes is not a new concept. In the mid-1800s, Apollinaire Bouchardat witnessed the ameliorative effects of hard physical labor on hyperglycemia and glycosuria (12). Bouchardat noted that these benefits were prominent in older obese persons with the more common yet less severe form of diabetes, termed diabète gras (diabetes of the fat) by his contemporary, Étienne Lancereaux (40). Shortly thereafter, Elliot Proctor Joslin emphasized the role of physical work in the prevention of diabetes, a penalty of obesity, given the striking increase in the number of persons affected in 1915 compared with 1900 (36). Despite the keen observations and influence of these pioneers, not until recently...
have the metabolic benefits of physical work in the form of resistance training been appreciated, and today T2DM affects nearly 24 million individuals in the United States.

In the past decade, a number of clinical studies have clearly demonstrated that resistance training lowers the percentage of glycosylated hemoglobin, increases glucose disposal, and even improves the lipid and cardiovascular disease risk profile of patients with T2DM (e.g., Refs. 20, 31, 33, 34, 92 and thoroughly reviewed in Ref. 94). However, there is limited insight into how these adaptations occur. By gaining a more thorough understanding of the molecular and physiological mechanism by which resistance training improves systemic metabolism, the frequency, duration, and intensity of exercise programs can be optimized, and this could also lead to the development of novel pharmacological therapies for obesity and T2DM. Fortunately, there has been significant progress in our general understanding of the molecular underpinnings of cellular growth and metabolism that are operational in skeletal muscle.

**Molecular Interplay Between Skeletal Muscle Growth and Metabolic Pathways**

There is remarkable overlap between the signal transduction networks regulating skeletal muscle growth and metabolism. The highly conserved phosphatidylinositol (PI) 3-kinase/Akt pathway is central to these physiological processes and responsive to insulin, growth factors, resistance exercise, and nutritional inputs (Fig. 1). Multiple targets downstream of PI 3-kinase/Akt impact protein synthesis and degradation, glucose transport, and glycogen synthesis. Moreover, several of its effectors exhibit functional versatility; i.e., their inactivation/activation may affect multiple physiological processes including growth and metabolism (reviewed in Ref. 48). PI 3-kinase is a heterodimer that consists of a p85 regulatory subunit and a p110 catalytic subunit. The p85 subunit plays a crucial part in activating the p110 catalytic subunit (IRS). Binding of p85 to tyrosine-phosphorylated IRS-1 interacting with the scaffolding adaptor insulin receptor substrate (IRS). In response to progrowth stimuli such as insulin and IGF-I, Akt phosphorylates and inhibits the tuberous sclerosis complex (TSC1 and -2) and the proline-rich Akt substrate of 40 kDa (PRAS40), negative regulators of mTOR (39, 69, 83) (Fig. 1B). mTOR interacts with the scaffolding protein raptor, and the mTOR-raptor complex (mTORC1) promotes the phosphorylation of the eukaryotic translation initiation factor (eIF)4E-binding protein (4E-BP1) and the p70 ribosomal S6 kinase (S6K). Phosphorylation of 4E-BP1 by mTOR suppresses its ability to bind and inhibit eIF4E. This allows eIF4E to directly bind the 5′ end of mRNA to ultimately form an active eIF4F complex, a rate-limiting step in translation initiation. Moreover, the phosphorylation of S6K leads to the phosphorylation of the 40s ribosomal protein S6 and eIF4B (32). These events collectively lead to the formation of the translation initiation complex and activate protein synthesis for cellular hypertrophy. It has recently become clear that other anabolic stimuli, such as amino acids and mechanical stress, can directly activate mTOR by a PI 3-kinase/Akt-independent mechanism to drive protein synthesis (25, 37, 68) (Fig. 1C). This mechanism may possibly be exploited for metabolic benefits, too, as a recent study reported the combination of resistance training and a hypocaloric high-protein (25% total energy) diet leads to greater improvements in glycemic control and cardiovascular risk factors than a hypocaloric diet.
standard protein (15–20% total energy) diet plus resistance training (92). Activation of mTOR and S6K also triggers a negative feedback mechanism that leads to serine/threonine phosphorylation of IRS-1 (79, 82). Of note, serine phosphorylation of IRS-1 is a hallmark of insulin resistance and T2DM but appears to be instead triggered by partially esterified lipid intermediates such as long-chain acyl-CoAs, diacylglycerol, and ceramides (Fig. 1D). These lipid intermediates, in turn, activate a serine/threonine kinase cascade (which includes PKCs, Jun kinase-1, and/or IκB kinase-β) and lead to serine phosphorylation of IRS-1 and ultimately insulin resistance (46, 75). Also in the context of metabolism and of particular interest to contracting skeletal muscle is mTOR-induced expression of the transcription factor hypoxia-inducible factor 1 (HIF1α) (Ref. 5 and reviewed in Ref. 61). In addition to its well-studied role in angiogenesis, HIF1α drives the expression of GLUT1 (a non-insulin-dependent glucose transporter) and multiple glycolytic enzymes and shuttles metabolites from the mitochondria to glycolysis during hypoxic stress (38) (Fig. 1E). The regulation of these signals in skeletal muscle and how they may mediate acute and chronic metabolic adaptations to exercise are not well understood.

One of the most important physiological functions of Akt is to stimulate glucose uptake in response to insulin. Skeletal muscle is the primary site of insulin-stimulated glucose disposal and storage, and impairments in these processes are hallmarks of insulin resistance and T2DM (11, 19). The direct targets of Akt that drive insulin-mediated glucose transport have been elusive; however, the Rab-GTPase-activating protein (Rab-GAP) TBC1 domain family member 4 [TBC1D4, also referred to as Akt substrate of 160 kDa (AS160)] has emerged as one key factor (67). Phosphorylation of AS160 by Akt inhibits its GAP activity, favors Rab family GTPase(s) [e.g., Rab8A (63)] to become GTP loaded and drive GLUT4 insertion into the plasma membrane (Fig. 1F). TBC1D1 also inhibits the trafficking of GLUT4 to the fibrous membrane under basal conditions and has Akt phosphomotifs, although recent evidence suggests that it may not be controlled by insulin (reviewed in Ref. 16). Instead, other stimuli, such as exercise-associated increases in calcium and AMP, appear to have more pronounced inhibitory effects on TBC1D1 relative to AS160 (both AS160 and TBC1D1 have calmodulin binding domains and AMPK phosphomotifs) (22). The unique roles and regulation of Rab-GAPs in skeletal muscle continue to be areas of intense investigation.

Skeletal muscle is the largest reservoir of glycogen in the human body. Glucose storage in the form of glycogen is regulated by the protein kinase glycogen synthase kinase-3β (GSK-3β), another direct target of PI 3-kinase/Akt. Increased expression and activity of skeletal muscle GSK-3β have been implicated in the pathogenesis of insulin resistance (57). In the absence of insulin resistance, insulin-stimulated serine phosphorylation and inactivation of GSK-3β lead to the dephosphorylation of glycogen synthase and activation of glycogen synthesis (Fig. 1G). Inhibition of GSK-3β also appears to repress TSC2 and subsequently activate mTOR and drive GLUT1 expression (14). Akin to other downstream targets of PI 3-kinase/Akt, GSK-3β is a multifunctional kinase that also represses fiber growth as a constitutive inhibitor of eIF2B. Phosphorylation of GSK-3β by Akt relieves the inhibition of eIF2B, triggers formation of the translation initiation complex, and activates protein synthesis (64). Thus, GSK-3β is another direct target of PI 3-kinase/Akt signaling that is fundamental to metabolic homeostasis as well as anabolic processes.

It is important to note that in humans with T2DM the anabolic and metabolic adaptations to resistance training include increased expression and/or responsivity of several insulin-signaling intermediates (e.g., insulin receptor, Akt, GLUT4, and glycogen synthase) in skeletal muscle (Fig. 1H). However, distinct from endurance training, the activity of key oxidative enzymes and aerobic capacity are not enhanced (31, 34).

Molecular Aspects of Skeletal Muscle Atrophy and Metabolism

In addition to stimulating protein synthesis, glucose transport and glycogen synthesis, the PI 3-kinase/Akt pathway negatively regulates myofibrillar protein degradation. The massive contractile apparatus of muscle is the largest reservoir of proteins in the body, and it can provide a vital source of calories by degrading protein and supplying amino acids to the liver to serve as substrates for gluconeogenesis. This beneficial program is often pathologically activated in chronic diseases, including cancer, sepsis, and renal and heart failure, independently of caloric intake. The ATP-dependent ubiquitin-proteasome system predominates under conditions of muscle wasting (55). Two muscle-specific ubiquitin ligase genes, muscle atrophy F-box (MAFbx, aka atrogin-1) and muscle ring finger 1 (MuRF1), regulate this proteasome system and are markedly induced in diverse models of muscle atrophy (10). MAFbx and MuRF1 are regulated by the PI 3-kinase/Akt pathway. Akt phosphorylates the forhead box class O (FOXO) transcription factors 1, 3, and 4 and inhibits their nuclear transport (71, 76) (Fig. 1J). Under condition of muscle atrophy, including insulin resistance (84), the deactivation of Akt results in the nuclear accumulation of FOXO factors, which in turn induce the transcription of MAFbx and MuRF1 leading to an increase in protein degradation. In addition, FOXO proteins activate the autophagocytic program, thereby coordinating organelle removal with the breakdown of macromolecules (47, 95).

As illustrated in Fig. 1, myostatin is also of interest in the context of skeletal muscle atrophy. It is a highly conserved member of the extracellular transforming growth factor-β (TGF-β) superfamily and a powerful negative regulator of muscle mass. The mature form of myostatin binds the activin type IIB receptor (ActRIIB) and the ALK4 and/or ALK5 coreceptor and stimulates the phosphorylation of Smad2 and Smad3 proteins (Fig. 1J). In developing or regenerating skeletal muscle, this inhibits muscle-regulatory factors and the differentiation of myoblasts to mature myotubes. Recent work has demonstrated that myostatin also inhibits the Akt pathway and directly affects protein synthesis and protein degradation in adult muscle (49, 74, 80, 93). The subsequent repression of mTORC1 formation contributes to a feed-forward mechanism that potentiates the activation of Smad2 by myostatin and impairs activation of Akt in response to growth factors. Given the molecular interplay between insulin and atrophy pathways, it is not surprising that factors such as myostatin have been implicated in the pathogenesis of obesity and T2DM. In fact, increased myostatin expression and, more impressively, secre-
tion have been observed in skeletal muscle and adipose tissue samples derived from obese and extremely obese women, and increased circulating levels of myostatin in this cohort were found to be correlated with insulin resistance (30). Moreover, myostatin expression in skeletal muscle was significantly decreased in response to weight loss in obese patients undergoing gastric bypass surgery and was associated with increased insulin action (53, 59). Increased expression of myostatin was also recently detected in skeletal muscle biopsies of healthy but at-risk first-degree relatives of patients with T2DM in concert with induction of genes of the insulin-signaling pathway (i.e., PI 3-kinase, TBC1D4, FOXO3A, S6K) (58). Thus, myostatin may contribute to alterations in skeletal muscle quantity, quality, and metabolism in conditions of obesity and T2DM and a pharmacological strategy to disrupt myostatin signaling (e.g., myostatin peptides, propeptides, neutralizing antibodies, or soluble decoy receptors) may potentially prevent, attenuate, or reverse their progression (Fig. 1K).

It should be noted that other factors exhibit dual functionality with respect to myofiber atrophy and metabolism. One of these involves the PGC-1 coactivators, master regulators of mitochondrial biogenesis and ancillary programs in skeletal muscle (reviewed in Refs. 7 and 29). Transgenic expression of PGC-1α or -β in skeletal muscle uniformly converts fibers to an oxidative type (8, 44) and increases maximal running capacity on treadmills (8, 15). Catabolic states like cancer, sepsis, denervation, and renal failure strongly suppress PGC-1α and -β expression in most skeletal muscles (66, 70). Overexpression of PGC-1α in skeletal muscle blocks the atrophy induced by denervation of the hindlimb by constitutively active FOXO3 (70), by statin-induced muscle damage (28), and by advanced age (87), although the mechanism remains unclear. PGC-1α is more highly expressed in oxidative fibers than in glycolytic fibers and is preferentially expressed in types I- and IIa-rich muscle beds like the soleus or deep gastrocnemius (44). The lower abundance of PGC-1 coactivators in glycolytic fibers (8, 44) may therefore partly explain why glycolytic fibers atrophy faster than do oxidative fibers during food deprivation (42, 78) and cachexia induced by sepsis (54), uremia, cancer (1), heart failure (43), and various forms of muscular dystrophy. With respect to glucose metabolism, PGC-1α promotes glucose transport by coactivating MEF-2c and increasing GLUT4 expression (52), and represses glucose oxidation (and thus enhances glycogen synthesis) by coactivating ERRα and increasing PDK-4 expression (86). The regulation of PGC-1α and -β expression in glycolytic fibers by resistance training or other anabolic therapies is not well understood. The reader is referred to the excellent recent review on the regulation of PGC-1 in skeletal muscle and its complex role in modulating insulin sensitivity (45).

Overall, it is impressive to note the diverse roles many of the discussed molecular targets play in protein synthesis, protein degradation, glucose transport, and/or glycogen synthesis. Our understanding of the dual impact of some of these targets on physiological processes of growth and metabolism has been further validated and advanced by studies in mice in which they have been genetically or pharmacologically modified.

The Metabolic Might of Building Muscle in Mice

Data from several mouse studies have advanced the notion that promoting muscle mass and even glycolytic capacity can bestow metabolic benefits (Table 1). A prime example is the hypermuscular and lean myostatin-null mouse (50). These mice have higher rates of carbohydrate use under fed conditions, and their skeletal muscle is composed of faster MHC isoforms and has less oxidative machinery than that of wild-type mice (24, 26). Evidence that this more glycolytic phenotype may counter obesity and insulin resistance was first conveyed in agouti lethal yellow and obese hyperinsulinemic ob/ob mice. Generation of mice harboring these mutations in the absence of myostatin revealed markedly increased muscle mass that was associated with decreased fat mass accumulation, and improved glycemic control compared with myostatin replete littermates (51). Additional work has demonstrated that muscle-specific, but not adipose-specific, deletion of the myostatin receptor prevents deleterious changes in body composition and glucose homeostasis in response to high-fat feeding (26). The therapeutic potential of myostatin inhibition for T2DM was recently highlighted in obese insulin-resistant ob/ob mice by using a neutralizing antibody for myostatin (9). Treatment of mice for 6 wk led to modest hypertrophy of skeletal muscle in a manner similar to than in resistance training and dramatically improved fasting and fed glucose concentrations and glucose tolerance. The benefits of skeletal muscle accretion were further evident in increased metabolic rate and exercise capacity. These improvements occurred in the absence of appreciable changes in body weight, fat mass, or liver triglycerides. Modest alterations were observed in the expression of genes of insulin signaling and glucose transport in the skeletal muscle of treated mice; however, improvements in metabolism appeared to be predominantly mediated by an increase in skeletal muscle mass. Myostatin neutralization was also associated with increased circulating levels of adiponectin, an anti-inflammatory adipose-derived cytokine. Similarly, administration of a soluble ActRIIB decoy receptor for 4 wk to high-fat-fed mice significantly increased muscle mass and improved hepatic insulin sensitivity (2). After 10 wk, this intervention also decreased fat mass, lowered glucose concentrations, and increased serum adiponectin concentrations. Collectively, these data suggest that myostatin is not only a fundamental regulator of growth but corroborates data discussed previously from humans that it and possibly other ActRIIB ligands significantly impact skeletal muscle and whole body metabolism.

Insights into metabolic control by glycolytic fibers were also recently obtained through the analysis of an inducible, skeletal muscle-specific transgenic mouse expressing a constitutively active Akt1 (35). Transgene induction in this model led to the selective growth of type IIB fibers with an accompanying increase in strength but a decrease in endurance in a treadmill test. Accordingly, transgene-expressing muscle exhibited modest increases in the expression of glycolytic enzymes but a marked decline in the expression of factors involved in mitochondrial biogenesis and oxidative metabolism. When the Akt1 transgene was induced in the muscle of diet-induced obese mice, there was a marked improvement in multiple metabolic parameters, including reductions in leptin, insulin, and glucose levels and im-
Table 1. Summary of mouse models in which genetic alterations or pharmacological interventions targeting skeletal muscle have been applied to understand how its modulation impacts metabolic dysfunction

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<tr>
<th>Phenotype1</th>
<th>Genetic alterations promoting a resistance-trained phenotype</th>
<th>Genetic alterations promoting an endurance-trained phenotype</th>
<th>Pharmacological interventions promoting a resistance-trained phenotype</th>
<th>Pharmacological intervention promoting an endurance-trained phenotype</th>
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<td>Act1 Tg</td>
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<td>type I fibers = glucose production = FA/TG = Chol</td>
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<tr>
<td>Myostatin KO</td>
<td>body weight muscle mass = fat mass glucose = insulin GT IS</td>
<td>type I fibers = lipids inguinal perigonadal depot weights resistin TNF-α TGF</td>
<td>HO/HSD 26, 27, 51</td>
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<td>ActRIIB DN</td>
<td>body weight muscle mass = fat mass glucose = insulin GT IS</td>
<td>fibers = lipids CSA adipocytides leptin TG 26, 41, 51</td>
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<th>Diabetes Model</th>
<th>Phenotype1</th>
<th>Global</th>
<th>Metabolic</th>
<th>Skeletal Muscle</th>
<th>Tissue and Serum Parameters1</th>
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<td>body weight muscle mass = fat mass glucose = insulin GT IS</td>
<td>Iib fiber CSA = lipids CSA adipocytides</td>
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1Compared with noninduced, wild-type or vehicle-treated control mice. 2Both studies were conducted in transgenic mice expressing PGC-1α under control of the muscle creatine kinase promoter/enhancer as originally detailed in Ref. 44. Tg, transgenic; ActRIIB, activin type IIB receptor; HF/HSD, high-fat high-sucrose diet; GT, glucose tolerance; IS, insulin sensitivity; CSA, cross-sectional area; FAO, fatty acid oxidation; G, genes; P, proteins; G, glucose transport and utilization; TG, triglycerides; FA, fatty acids; KO, knockout; HFD, high-fat diet; Ay, agouti lethal yellow mice; ob/ob, obese leptin-deficient mice; Chol, cholesterol; DN, dominant negative; DAG, diacylglycerol; dens., capillary density capillary; Adipoq, adiponectin; HDL, high-density lipoproteins.

provements in insulin sensitivity. In this model, Akt1 transgene induction led to a 5% increase in lean mass, yet there was a 45% reduction in fat mass. These metabolic improvements did not appear to result from a reduction in fat mass per se, because transgenic mice displayed reduced hepatic steatosis, lower levels of circulating leptin, and improved glucose clearance compared with nontransgenic mice that were matched for fat mass and overall body mass. Thus, it appears that a modest increase in glycolytic muscle increases the organism’s tolerance to excess adipose tissue such that it is able to maintain metabolic parameters with a normal range. Nonetheless, the reductions in fat mass and/or improvements in adipose tissue function commonly observed in response to muscle-based interventions are of great clinical and scientific interest (Table 1). The cause and timing of these events in adipose tissue relative to the adaptations in skeletal muscle, and their relative contribution to the improvements in whole body metabolism, deserve additional study.

Collectively, these data suggest that even modest increases in skeletal muscle mass, the growth of type II/glycolytic fibers, and modest changes in glycolytic capacity can have remarkable effects on metabolic homeostasis. They also suggest that in-
interventions targeting skeletal muscle may directly or indirectly alter the metabolic profile of other organs affected by insulin resistance and T2DM.

Cross-talk Between Skeletal Muscle and Other Metabolic Tissues

It is now evident that skeletal muscle is a key node in the powerful and complex cross-talk between metabolically active tissues. In the muscle-specific Akt1 transgenic model, a decrease in the respiratory exchange ratio, which indicates an increase in fatty acid consumption, was observed (35). Whereas no evidence of elevated fatty acid β-oxidation could be detected in muscle, increased fatty acid oxidation was observed in the livers of these mice. This phenotypic shift was associated with widespread changes in the hepatic transcript expression pattern favoring the induction of lipid oxidation genes. Another example is high-fat-fed yet lean, muscular, and insulin-sensitive mice homozygous for a mutation in the myostatin gene. These mice demonstrate reduced hepatic steatosis, decreased inflammatory cytokines (i.e., 30–50% decrease in circulating TNFα), and lower macrophage infiltration and activation in skeletal muscle and adipose tissue compared with wild-type and heterozygous mice (88). As mentioned previously, postnatal blockade of myostatin has a positive effect on the adipose tissue-derived cytokine adiponectin (2, 9). The absence of myostatin also appears to exert a protective effect on dyslipidemia and atherogenesis. High-fat-fed LDL receptor-null mice normally exhibit markedly elevated levels of serum cholesterol and a propensity for atherosclerotic lesions. When cross-bred with myostatin-null mice, the LDL receptor/myostatin double-knockout mice had decreased VLDL generation, improved lipid profiles, and reduced atherogenesis progression (81). In view of the coordinated responses of muscle, liver, adipose tissue, and the vasculature highlighted in these models, it is likely that 1) increasing skeletal muscle mass will have favorable effects on affected tissues of T2DM and cardiovascular disease; and 2) a network of hormonal communication (e.g., myokines) exists between muscle and other metabolically important organs (60).

Concluding Remarks

There has been a longstanding interest in the therapeutic effects of exercise for T2DM. From a metabolic point of view, however, it remains surprisingly unclear what aspects of exercise should be mimicked and what type of muscle fiber is best targeted to improve metabolic dysfunction. It is now recommended that resistance training be incorporated into the exercise regimen of patients with T2DM (3, 6). Similarly, complementary resistance training is also recommended for patients with cardiovascular disease (62, 89). Although a growing body of experimental evidence suggests that resistance training improves metabolic homeostasis in a manner distinct from endurance training, our understanding of how this precisely occurs is rudimentary. Additional research is clearly needed to better understand how different modes of physical training (i.e., resistance, endurance, or interval exercise) change the metabolic characteristics of skeletal muscle and improve whole body metabolism. Ultimately, these studies will help identify therapeutic targets and develop pharmacological strategies to safely alleviate or reverse the manifestations of T2DM and its comorbidities.

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DISCLOSURES

No conflicts of interest are reported by the authors.

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