REVIEW

Impacts of Selected Dietary Nutrient Intakes on Skeletal Muscle Insulin Sensitivity and Applications to Early Prevention of Type 2 Diabetes

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ABSTRACT

As the largest tissue in the body, skeletal muscle not only plays key roles in movement and glucose uptake and utilization but also mediates insulin sensitivity in the body by myokines. Insulin resistance in the skeletal muscle is a major feature of type 2 diabetes (T2D). A weakened response to insulin could lead to muscle mass loss and dysfunction. Increasing evidence in skeletal muscle cells, rodents, nonhuman primates, and humans has shown that restriction of caloric or protein intake positively mediates insulin sensitivity. Restriction of essential or nonessential amino acids was reported to facilitate glucose utilization and regulate protein turnover in skeletal muscle under certain conditions. Furthermore, some minerals, such as zinc, chromium, vitamins, and some natural phytochemicals such as curcumin, resveratrol, berberine, astragalus polysaccharide, emodin, and genistein, have been shown recently to protect skeletal muscle cells, mice, or humans with or without diabetes from insulin resistance. In this review, we discuss the roles of nutritional interventions in the regulation of skeletal muscle insulin sensitivity. A comprehensive understanding of the nutritional regulation of insulin signaling would contribute to the development of tools and treatment programs for improving skeletal muscle health and for preventing T2D. *Adv Nutr* 2021;12:1305–1316.

Keywords: nutritional intervention, skeletal muscle, insulin sensitivity, glucose utilization, protein turnover, type 2 diabetes

Introduction

Insulin controls carbohydrate, lipid, and protein metabolism through the canonical insulin signaling cascade, which comprises insulin receptors (IRs), insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K), and serine/threonine kinase 1 (AKT). Insulin resistance, defined as defective signal transduction and biological actions in response to insulin stimulation, is a fundamental mechanism resulting in type 2 diabetes (T2D), which is usually accompanied by macrovascular and microvascular complications (1). It has been estimated that 463 million adults (aged 20–79 y) experienced diabetes in 2019 globally (2) and nearly one-third of the US population will be afflicted by 2050 (3).

Major risk factors related to the epidemic of T2D (1), mechanisms of insulin resistance (4), and the future of precision medicine for T2D (5) have been well discussed in recent years. As the largest insulin-sensitive tissue in the body, skeletal muscle accounts for ∼80% of postprandial glucose disposal and its reduced response or resistance to insulin is characteristic of T2D. In fact, insulin sensitivity declines decades before the onset of T2D, which can be mostly attributed to the impaired glucose metabolism

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Address correspondence to JY (e-mail: yinjd@cau.edu.cn).
Abbreviations used: AA, amino acid; AAA, aromatic amino acid; AKT, serine/threonine kinase 1; AL, ad libitum; ALA, α-lipoic acid; AMPK, AMP-activated protein kinase; APS, astragalus polysaccharide; ASC, adipose stromal cell; BCAA, branched-chain amino acid; CR, caloric restriction; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C motif chemokine receptor 4; DAG, diacylglycerol; EAA, essential amino acid; ERK, extracellular receptor kinase; FoxO, forkhead box O; GLUT4, glucose transporter type 4; GSK3β, glycogen synthase kinase 3β; HFD, high-fat diet; HFHS, high-fat, high-sugar; IRS, insulin receptor substrate; KIC, α-ketoisocaproate; KO, knockout; L-NAME, N-ω-nitro-L-arginine methyl ester; MR, methionine restriction; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; NEAA, nonessential amino acid; PGC1α, PPAR-gamma coactivator 1α; PI3K, phosphatidylinositol 3-kinase; PR, protein restriction; S6K1, S6 kinase 1; ScAT, subcutaneous adipose tissue; SCD1, stearoyl-CoA desaturase 1; Sirt1, sirtuin 1; STAT3, signal transducer and activator of transcription 3; T2D, type 2 diabetes; TXNIP, thioredoxin-interacting protein; VDR, vitamin D receptor; 2DG, 2-deoxyglucose; 3-HIB, 3-hydroxyisobutyrate.

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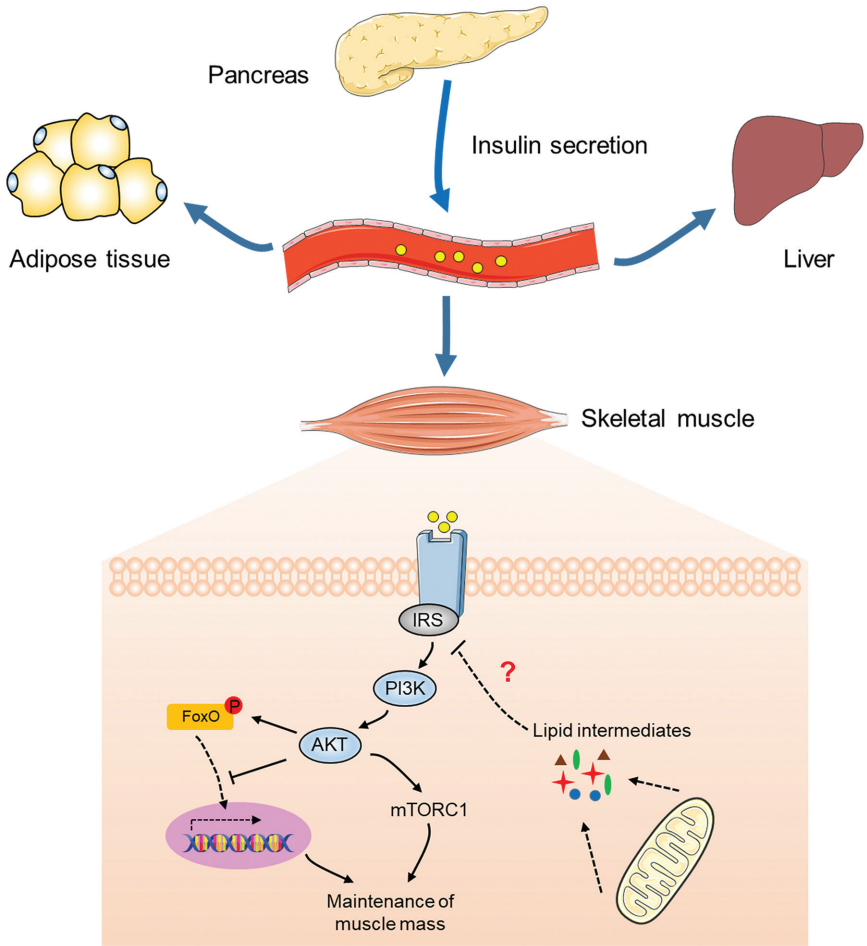

FIGURE 1 Insulin signaling promotes the maintenance of skeletal muscle mass and might be repressed by lipid metabolic intermediates, such as diacylglycerol, ceramides, and intermediates of incomplete fatty acid oxidation. The skeletal muscle, adipose tissue, and liver are the major insulin-sensitive tissues/organs. In the fed state and under normal conditions, insulin activates mTORC1 and suppresses the translocation of FoxO from the cytoplasm to the nucleus through the IRS-PI3K-AKT pathway in the skeletal muscle, contributing to the maintenance of skeletal muscle mass. The insulin signal may also be inhibited by lipid intermediates, although the causal relation between increased lipid content in the skeletal muscle and insulin resistance is still under debate. AKT, serine/threonine kinase 1; FoxO, Forkhead box O; IRS, insulin receptor substrate; mTORC1, mammalian target of rapamycin complex 1; p, phosphorylated; PI3K, phosphatidylinositol 3-kinase.

and glycogen storage in the skeletal muscle (6). In turn, muscle dysfunction is inevitable once insulin resistance occurs.

Currently, the application of gastric banding surgery, antidiabetic drugs, and dietary and lifestyle intervention constitute the main treatments of T2D. It is noteworthy that, although susceptibility to T2D has a strong genetic basis (7), as a metabolic disease it is nutritionally preventable. People with prediabetes or impaired glucose tolerance should undertake preventive measures, such as healthy diets. However, comprehensive discussions of dietary strategies to improve insulin sensitivity in the skeletal muscle are scarce. Herein, the aim of this review is to analyze the relation between insulin sensitivity and skeletal muscle health and provide an overview of feasible dietary strategies to improve insulin sensitivity in the skeletal muscle. It is essential to provide more targeted dietary advice, especially for the early prevention of T2D.

Insulin Sensitivity and Skeletal Muscle Mass Maintenance

While amino acids (AAs) are available, insulin increases muscle protein synthesis in healthy individuals but not in those with diabetes (8). Importantly, the coordinated changes in the mammalian target of rapamycin complex 1 (mTORC1) and Forkhead box O (FoxO) contribute to insulin-mediated protein synthesis and muscle hypertrophy (**Figure 1**). In addition, insulin exerts a definitive function in reducing muscle protein breakdown independent of AA availability, resulting in an increase in protein acquisition (8), and mechanisms underlying insulin-regulated proteostasis have been reviewed by James et al. (9). In particular,

insulin resistance has been involved in the development of sarcopenia, and in turn, muscle loss during aging might adversely affect glucose disposal and metabolism, thus setting up a vicious cycle. The bidirectional relation between T2D and sarcopenia is beyond the scope of this article, and readers can refer to Mesinovic et al. (10) for further reading.

Insulin Sensitivity and Lipid Accumulation in the Skeletal Muscle

Lipids are normally present within the skeletal muscle, and their accumulation is often linked to the destruction of muscle integrity. Insulin promotes lipid biosynthesis and inhibits lipolysis in adipose tissue (4) but does not stimulate lipid accumulation in skeletal muscle under normal and insulin-resistant conditions (11). Conversely, numerous studies have demonstrated that ectopic lipid accumulation in the skeletal muscle weakens insulin signaling, contributing to the reduced glucose uptake and insulin resistance in the skeletal muscle (12, 13). Paradoxically, increased lipid content was shown in insulin-sensitive, endurance-trained athletes, the so-called "athlete's paradox" (14). Therefore, the relation between insulin sensitivity and total lipid accumulation varies under different conditions.

Rather, in the case of cellular lipid overload, a number of lipid intermediates have been identified as drivers of insulin resistance (Figure 1), such as diacylglycerol (DAG) (15), ceramides (16), and intermediates of incomplete fatty acid oxidation (17). However, other studies showed paradoxical observations that no association existed between DAGs or ceramides and insulin resistance (18, 19). Therefore, the causal link between specific lipid species in the skeletal muscle and insulin resistance is still under debate.

Depicting molecular networks that manipulate ectopic lipid deposition and insulin action in the skeletal muscle is essential for developing new strategies to treat T2D. Herein, we summarized some novel targets controlling ectopic lipid storage and insulin action in the skeletal muscle that have been reported in recent studies. Expression levels of MondoA, serine/threonine protein kinase 25, phosphoinositide 3-kinase enhancer A, and vascular endothelial growth factor B were positively associated with ectopic lipid deposition and insulin resistance (20–23). Moreover, in contrast to the detrimental effects of the target genes described above, studies have reported that IL-18 (24) or arylamine N-acetyltransferase 1 (25) attenuated high-fat-diet (HFD)–induced ectopic lipid accumulation and enhanced insulin signaling by activating AMP-activated protein kinase (AMPK) signaling or inhibiting protein kinase C θ activation. In light of the above-mentioned findings, we propose antagonisms or analogues of newly discovered targets as promising pharmacological approaches for T2D therapy, targeting lipid deposition as a way to stimulate insulin signaling in the skeletal muscle.

Besides the widely documented form of lipid droplets, ectopic lipids can also exist as adipocytes between functional cells in the skeletal muscle, although the origin of these adipocytes remains ambiguous. Of note, a recent study reported that an HFD reduced the protein concentration of C-X-C motif chemokine ligand 12 (CXCL12) in subcutaneous adipose tissue (ScAT) and decreased the binding of CXCL12 with its receptor C-X-C motif chemokine receptor 4 (CXCR4), which facilitated the mobilization of $CXCR4^+$ adipose stromal cells (ASCs) from ScAT and their relocation in the skeletal muscle (26). Therefore, disturbing the liberation of ASCs from ScAT to the skeletal muscle may be an alternative strategy to inhibit ectopic lipid deposition.

Caloric Restriction to Improve Insulin Sensitivity in the Skeletal Muscle

Obesity is associated with T2D, and an inability to safely distribute excess energy could lead to insulin resistance. Therefore, reducing the overall caloric intake is highly recommended for the prevention and treatment of insulin resistance. In **Table 1**, we summarized the evidence concerning the beneficial effects of dietary caloric restriction (CR) on insulin sensitivity in the skeletal muscle using rodents, nonhuman primates, and humans.

Compared with rats fed ad libitum (AL), rats that were ~24 mo old subjected to CR had greater insulin-stimulated glucose uptake in isolated epitrochlearis and soleus muscles incubated with insulin (27, 28), although the mechanism underlying CR-enhanced glucose uptake varied slightly among different myofiber types (29). Studies of nonhuman primates also found similarly increased glucose disposal and improved insulin sensitivity among animals on long-term CR diets (30% reduction in calorie intake for at least 4 y) (30, 31). When tested in humans, a short-term (3 wk) CR intervention (1000 kcal/d) contributed to the reduced body weight and enhanced insulin sensitivity of obese adults accompanied by repressed stearoyl-CoA desaturase 1 (SCD1) expression and altered fatty acid profiles in the skeletal muscle (32). Several other studies have also revealed the beneficial effects of CR in preventing muscle loss and insulin resistance during aging in humans (33). In light of the above studies, CR-improved insulin sensitivity is usually accompanied by a decline in fat mass and body weight (28, 29, 30, 32). Taken together, this evidence from animal and human models has shown the beneficial roles of CR in the improvement in skeletal muscle insulin sensitivity. In clinical practice, CR might be a suitable dietary strategy to improve insulin sensitivity in the skeletal muscle for people with prediabetes and early T2D but not for those with advanced T2D who have already experienced severe body-weight loss.

Insulin exerts its fundamental role in glucose homeostasis through the PI3K-AKT cascade pathway. Importantly, enhanced activation of AKT may be the core mechanism for CR-ameliorated insulin sensitivity in the skeletal muscle. Indeed, in the presence of insulin, significantly increased AKT phosphorylation on T308 and S473 was observed in

TABLE 1 Summary of the effects of CR on insulin sensitivity in the skeletal muscle[1]

Experimental model and subjects[2]	CR	Response	References
Aging rats (∼24.5 mo old)	Consumption ∼65% of AL from ∼22.5 mo old for 2 mo	Insulin-stimulated glucose uptake, phosphorylation of AKT2 on Thr^{309} and Ser^{474}, phosphorylation of AS160 on Thr^{642} and Ser^{588}, and phosphorylation of filamin C on Ser^{2213} in isolated muscles ↑	(27)
Aging rats (24 mo old)	CR was initiated at 14 wk of age with 90% of AL, increased to 75% of AL at 15 wk, and to 60% of AL at 16 wk until 23 mo old. CR then received 60–65% AL intake during the final month	Food intake, body mass, and mass of skeletal muscle ↓; insulin-stimulated glucose uptake and AKT phosphorylation on Thr308 and Ser473 in both fast-twitch and slow-twitch skeletal muscle ↑	(28)
Aging rats (23–26 mo old)	∼60–65% AL consumption for 4–7 mo	Insulin-stimulated glucose uptake in type **I**, IIA, IIB, IIBX, and IIX fibers ↑; abundance of proteins involved in mitochondrial electron transport chain and oxidative phosphorylation (NDUFB8, SDHB, UQCRC2, and ATP5A) in type **I**, IIA, and IIBX fibers ↓	(29)
Fisher 344 × Brown Norway rats (4 mo old)	60% of AL intake for 20 d	Total AKT serine and threonine phosphorylation, AKT2 serine and threonine phosphorylation of insulin-stimulated muscles ↑	(34)
Male F344B/N rats	60% of AL intake for 8 wk	3-*O*-methylglucose transport, ratio of PI3-kinase catalytic to regulatory subunits, and AKT serine phosphorylation in muscle incubated with insulin ↑; IRS1 abundance ↓	(35)
Male C57BL/6 mice (12 wk old)	60% of AL intake for 20 d	Glucose tolerance, insulin-stimulated ^{3}H-2-deoxyglucose intake, skeletal muscle Sirt1 deacetylase activity, and insulin-stimulated pAKT and pAS160 ↑; p55α and p50α abundance ↓	(36)
Male adult cynomolgus monkeys (∼16 y old)	30% CR compared with AL feeding conditions for 4 y	Whole-body insulin sensitivity, protein concentrations of IRS1, IRS2, IRβ, PI3K, and GLUT4 in skeletal muscle at basal state, insulin-stimulated skeletal muscle pIRβ, pIRS1, pAKT, and PI3K activity ↑	(30)
Adult male rhesus monkeys (14–20 y)	70% of CR intake for 6 y	Whole-body insulin sensitivity ↑	(31)
Obese nondiabetic adults	CR (1000 kcal/d) for 3 wk	Insulin sensitivity ↑; specific phosphatidylcholine and triglyceride species, and mRNA expression of SCD1 ↓	(32)
Eleven obese participants (BMI = 35 kg/m^2) and 9 matched control subjects (BMI = 34 kg/m^2) between the age of 45 and 65 y	Removing 1000 kcal from the participant's daily allowance of fat and carbohydrate for 16 wk	Insulin sensitivity, nonoxidative glucose disposal, and TNXIP concentration in skeletal muscle ↑; respiratory exchange ratio ↓	(37)

[1] AKT, serine/threonine kinase 1; AL, ad libitum; AS160, AKT substrate of 160 kDa; ATP5A, ATP synthase F1 subunit α; CR, caloric restriction; GLUT4, glucose transporter type 4; IR, insulin receptor; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; NDUFB8, NADH: ubiquinone oxidoreductase subunit B8; p, phosphorylated; PI3K, phosphatidylinositol 3-kinase; SCD1, stearoyl-CoA desaturase 1; SDHB, succinate dehydrogenase complex iron sulfur subunit B; Sirt1, sirtuin 1; TXNIP, thioredoxin-interacting protein; UQCRC2, ubiquinol-cytochrome c reductase core protein 2; ↑, significant increase; ↓, significant decrease.
[2] Age at the end of study is shown.

muscles isolated from rats subjected to CR (65% of AL intake) for 2 y (28). Specifically, enhanced AKT2 phosphorylation, but not AKT1 phosphorylation, contributed to enhanced insulin sensitivity in the skeletal muscle after CR (60% of AL intake) for 20 d (34). One study using AKT2-knockout (-KO) mice revealed that insulin-stimulated 2-deoxyglucose (2DG) uptake was significantly greater in wild-type mice than in KO mice after CR (60% of AL intake) for 20 d, and CR-induced enhancement of insulin-stimulated 2DG uptake was also compromised in KO mice compared with that in KO-AL mice (38). These results suggest that AKT is a downstream effector of CR. PI3K is an upstream mediator of AKT, and the ratio of catalytic subunits (p110α and p110β) to regulatory subunits (p85α, p85β, p50α, and p55α) of PI3K is positively correlated with insulin sensitivity. In models of Fisher 344 × Brown Norway rats undergoing CR (60% of AL intake) for 8 wk, p50α and p55α abundance was ∼40% lower ($P < 0.01$) in CR muscles relative to the control, while no alteration in catalytic subunit levels was observed, contributing to the stimulation of AKT phosphorylation and 3-*O*-methylglucose transport in muscles (35).

Sirtuin 1 (Sirt1), an NAD^+-dependent deacetylase, may be a bridge linking CR and enhanced PI3K-AKT signaling in the skeletal muscle. CR can restrain the acetylation of signal transducers and activators of transcription 3 (STAT3) through reducing Sirt1 deacetylase activity and further reducing STAT3 binding to p50α and p55α promoters, resulting in decreased p50α and p55α concentrations and improved glucose disposal (36). It should be mentioned that p85α concentration is not regulated by Sirt1 (36) and

the role of p85α in the beneficial effect of CR is still controversial.

CR may also act on thioredoxin-interacting protein (TXNIP) in the skeletal muscle (39), a new potential therapeutic target for diabetes. A study demonstrated that, upon a 16-wk intervention of CR, TXNIP expression level significantly decreased after insulin clamp in the vastus lateralis, accompanied by reduced body weight and fasting insulin concentrations as well as improved insulin sensitivity of the whole body (39). However, the mechanism underlying CR-reduced TXNIP expression remains unclear. Studies conducted in myotubes and mice showed that MondoA, a muscle-enriched transcription factor, increased expression of TXNIP through binding with the carbohydrate response element of TXNIP promoter, leading to elevated muscle lipid accumulation and insulin resistance (20). Therefore, the role of MondoA in CR-repressed TXNIP merits further investigation.

Role of Protein Intake in Insulin Sensitivity

Overall CR (including carbohydrate, fat, and protein restriction) has been recognized as one of the most effective nutritional interventions to extend health span and lifespan (37). Beneficial effects of unsaturated fatty acids, especially EPA, DHA, and oleic acid (C18:1), and the detrimental effects of SFAs on insulin sensitivity have been clearly illuminated (40). The relation between dietary carbohydrate intake and insulin resistance has also been summarized, and diets with a lower carbohydrate content, higher proportion of insoluble carbohydrate, and higher fiber content were recommended for the prevention and treatment of T2D (41). In contrast, protein restriction (PR) is more complex and still under debate. A study performed in women aged 50–65 y old with obesity, who were offered a standard diet containing 0.8 g protein/(kg body weight · d) or a high-protein diet containing 1.2 g protein/(kg body weight · d), demonstrated that high protein intake impaired insulin sensitivity and insulin-stimulated glucose uptake through suppressing the phosphorylation of AKT in the skeletal muscle (42). Accordingly, dietary PR has been applied as a feasible dietary intervention to extend lifespans and improve human health, especially in terms of insulin sensitivity (43). However, low protein intake also had a negative effect on skeletal muscle mass in aged mice (44). Based on these confounding observations, it is tempting to speculate that the application of PR in patients with diabetes needs careful evaluation and long-term follow-up. PR might not be applicable for patients with sarcopenia or for vegetarians. The effect of PR on muscle insulin sensitivity and protein turnover under different conditions should be assessed further.

Amino Acids Regulate Insulin Sensitivity in the Skeletal Muscle

The association between elevated AA concentrations in the skeletal muscle and diet-induced obesity has been established. Importantly, AAs not only serve as metabolic substrates but also are involved in the signaling pathways by which dietary proteins/AAs affect insulin action at the cellular and molecular levels. Long-term studies have demonstrated multiple types of AAs with the potential to regulate protein turnover and insulin sensitivity in the skeletal muscle, including branched-chain AAs (BCAAs), methionine, aromatic AAs (AAAs), arginine, and nonessential AAs (NEAAs) (**Figure 2**).

Essential Amino Acids

Leucine

BCAAs, especially leucine, account for up to 20% of dietary protein and enhance protein synthesis in the skeletal muscle. However, elevated circulating concentrations of BCAAs have also been observed in the progression of insulin resistance and T2D (45). Leucine enhanced protein synthesis in the skeletal muscle in an mTORC1-dependent mechanism in both animals and humans (46). The effect of increased leucine intake on insulin sensitivity in the skeletal muscle is controversial. Studies demonstrated that elevated dietary leucine consumption contributed to a delay in postprandial stimulation of the early steps in insulin signaling, and to overall glucose intolerance (47). Moreover, the leucine metabolite α-keto-isocaproate (KIC) suppressed insulin-stimulated glucose transport by 34% in L6 myotubes, in parallel with the increased phosphorylation of S6 kinase 1 (S6K1) and IRS1. The deleterious effect of KIC was further blocked by rapamycin treatment, implying that KIC suppressed glucose disposal in an mTORC1-dependent manner (48). Consistently, leucine deprivation improved hepatic insulin sensitivity by activating AMPK and decreasing mammalian target of rapamycin (mTOR)/S6K1 signaling (49). Considering the direct or indirect inhibitory effects of AMPK on the mTOR pathway, leucine deprivation may decrease mTOR/S6K1 signaling, in part, through the activation of AMPK. An in-depth understanding of the cross-talk between AMPK and mTOR has been reviewed previously (50).

In contrast to the deleterious effect of leucine, several studies reported that leucine facilitated insulin-stimulated glucose uptake and glycogen synthesis accompanied by the increased phosphorylation of AKT and glycogen synthase kinase 3β (GSK3β) in primary human and murine skeletal muscle cells (51, 52). This beneficial effect of leucine may be due to the strengthened mTORC1 and mTORC2 in skeletal muscle cells. The facilitating effects of leucine were eliminated after rapamycin treatment, suggesting that a certain level of mTORC1 activity was required for insulin signaling. In light of these findings, the effect of leucine supplementation on insulin sensitivity in the skeletal muscle is still controversial. The effectiveness and the possible adverse effects of leucine supplementation on skeletal muscle health need to be examined.

Isoleucine and valine

It has been observed that isoleucine supplementation improved glucose uptake in skeletal muscle cells. In the absence of insulin, 1 mM isoleucine elevated glucose consumption

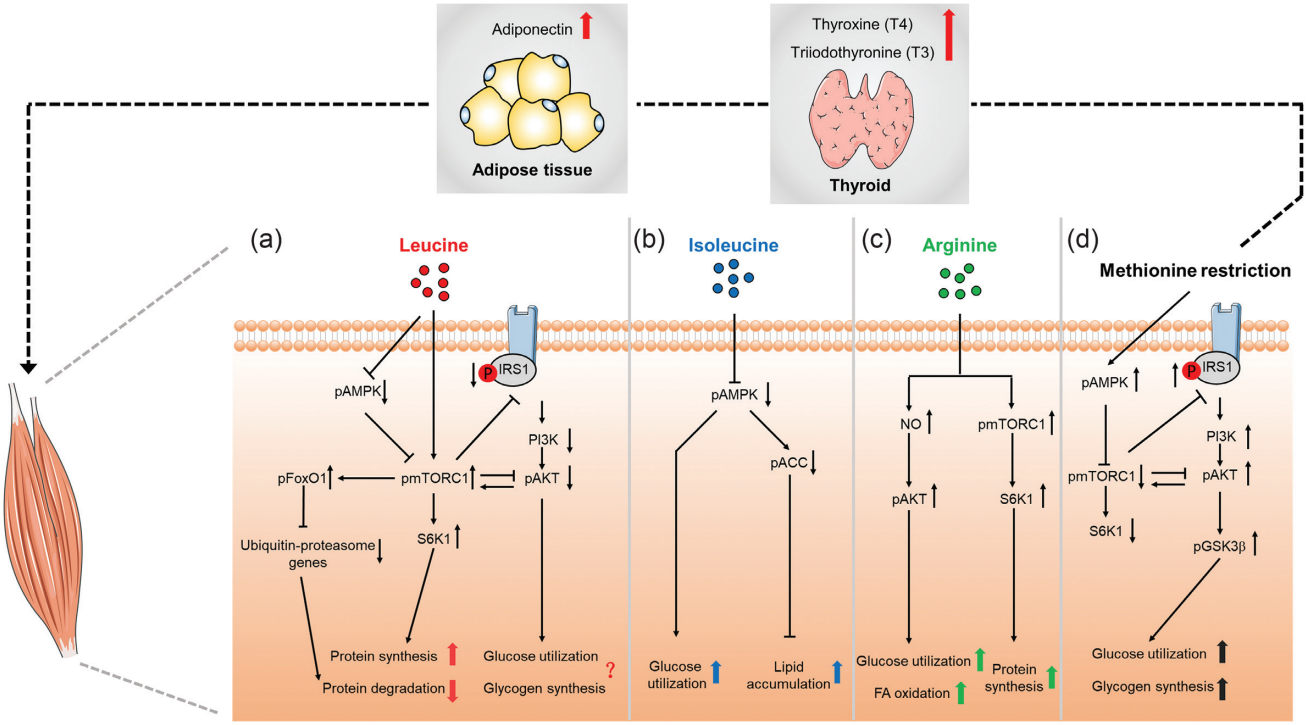

FIGURE 2 Multiple amino acids regulate insulin sensitivity in the skeletal muscle. (A) Leucine promotes protein synthesis and inhibits protein degradation through the activation of mTORC1, which, in turn, negatively regulates insulin sensitivity. However, a beneficial effect of leucine on insulin sensitivity is also observed. (B) Isoleucine enhances glucose utilization and lipid accumulation in the skeletal muscle through the inhibition of AMPK. (C) Arginine could stimulate glucose disposal and fatty acid oxidation in an NO-dependent manner and promote protein synthesis through the mTORC1-S6K1 pathway. (D) Methionine restriction is a feasible approach for improving insulin sensitivity in skeletal muscle through regulation of the AMPK-mTORC1-S6K1-IRS1 pathway and the coordinated increase in circulating concentrations of adiponectin, thyroxine (T4), and triiodothyronine (T3). ACC, acetyl-CoA carboxylase; AKT, serine/threonine kinase 1; AMPK, AMP-activated protein kinase; FA, fatty acid; FoxO1, Forkhead box O1; GSK3β, glycogen synthase kinase 3β; IRS1, insulin receptor substrate 1; mTORC1, mammalian target of rapamycin complex 1; p, phosphorylated; PI3K, phosphatidylinositol 3-kinase; S6K1, S6 kinase 1.

in C2C12 myotubes by 16.8% but did not affect glycogen synthesis (53). Consistently, isoleucine administration in rats decreased AMPKα2 activity and potentiated glucose uptake in the skeletal muscle by >70% (54). In addition, dietary isoleucine supplementation for 30 d depressed AMPKα–acetyl CoA carboxylase (ACC) activity, stimulated expression of SCD1, and increased lipid accumulation in the skeletal muscle of pigs (55). In short, isoleucine intake improved glucose uptake in the skeletal muscle; further studies are required to determine the mechanism by which isoleucine intake enhances glucose uptake.

Unlike leucine and isoleucine, the influence of valine supplementation on muscle glucose uptake is limited (53). However, some valine metabolites secreted by muscle cells are implicated in insulin resistance. For example, serum 3-hydroxyisobutyrate (3-HIB) promoted fatty acid uptake and lipid accumulation in muscle by activating endothelial fatty acid transport in a PPAR-γ coactivator-1α (PGC1α)–dependent manner (56). What was found were elevated concentrations of 3-HIB in mice and humans with diabetes, meaning that 3-HIB was a potential biomarker of diabetes (56). Another valine metabolite, β-aminoisobutyric acid, improved glucose homeostasis in mice (57). In the future, a metabolic profiling approach should be further used to discover functional BCAA metabolites secreted by myocytes and, in turn, to develop metabolite-based dietary strategies or pharmacotherapies to improve skeletal muscle insulin sensitivity, especially in early prevention of T2D.

Methionine

Dietary methionine restriction (MR) has been shown to exert beneficial effects on metabolic health, such as causing weight loss, decreasing inflammation and oxidative stress, and improving insulin sensitivity in humans and animals (58, 59). In obese mice, dietary MR by ~80% for 24 wk ameliorated obesity-induced hyperglycemia and hyperinsulinemia (60). In particular, MR increased glycogen concentrations and stimulated glycolysis in the gastrocnemius muscle through the AMPK-mTORC1-S6K1-IRS1 pathway, which may be regulated by the increased circulating concentrations of adiponectin (60). Furthermore, MR by ~80% also prevented thyroid dysfunction, increased circulating concentrations of thyroxine and triiodothyronine, and upregulated protein concentrations of thyroid hormone receptor α1 in the skeletal

muscle of obese mice (61). In short, it is reasonable to speculate that MR-improved insulin sensitivity in the skeletal muscle is mechanistically correlated with the repair of hormone secretion from adipose tissue and the thyroid gland that are impaired by obesity and, therefore, involves cross-talk between skeletal muscle and other tissues. Furthermore, despite the beneficial effects of MR on insulin sensitivity under some circumstances, delicate manipulation of dietary methionine is also needed in practice given its unique role in translation initiation and DNA methylation.

AAAs and other essential amino acids

As shown in metabolomics studies, the concentrations of plasma AAAs, including phenylalanine and tryptophan, were elevated in young adults with obesity and insulin resistance (62). However, knowledge about the specific role of AAAs as well as other essential AAs (EAAs) in the development of T2D for humans, including lysine and threonine, is yet scarce.

Conditional EAAs

For humans, conditional EAAs consist of arginine and histidine. In terms of insulin sensitivity in the skeletal muscle, a randomized, double-blind, crossover study showed that arginine intake (9 g/d) for 6 wk improved glucose tolerance in Euripides prediabetic men but did not affect muscle glucose uptake (63). In addition, as the main biological precursor of NO, arginine was shown to increase glucose uptake and glycogen synthesis, upregulate the expression of phosphorylated AKT (p-AKT) and glucose transporter type 4 (GLUT4), and improve fatty acid oxidation in rat L6 myotubes via an NO-dependent mechanism (64). Conversely, arginine-induced protein synthesis in C2C12 myotubes was not influenced by treatment with the NO synthase inhibitor N-ω-nitro-L-arginine methyl ester (L-NAME) but was inhibited by rapamycin treatment (65), implying distinct mechanisms underlying improved glucose disposal and protein synthesis by arginine treatment in myotubes. Overall, arginine intake may be one feasible dietary strategy to improve muscle insulin sensitivity, even though human studies on the relation between arginine intake and metabolic syndrome are still limited.

NEAAs

Restriction of protein and specific EAAs, including BCAAs and methionine, contributes to the enhanced insulin sensitivity in the skeletal muscle. However, the ingestion of protein or EAAs was typically restricted by ≥50% in previous studies, which will lead to malnutrition if applied over a long-term period. Therefore, it would be worthwhile to investigate whether NEAA restriction can be an alternative to EAA restriction in improving insulin sensitivity. In pig models, the ingestion of diets with NEAAs restricted by 15–25%, in which EAA supply was guaranteed by the supplementation of crystal EAAs, decreased circulating insulin concentration and HOMA-IR, and stimulated the IRS1-AKT signaling pathway in the skeletal muscle (66), suggesting that dietary NEAA restriction improved insulin sensitivity as well. These results demonstrate that NEAA restriction can be a substitute for protein/special EAA restriction in improving insulin sensitivity, and in which the integrated remodeling of gut and liver metabolism exerts a vital role. However, studies concerning the utilization of NEAA restriction in preventing metabolic disorders are still limited. Further studies should be conducted to compare NEAA concentrations between those with and without diabetes to detect whether there is a correlation between NEAA intake and T2D.

Micronutrients Abate Insulin Resistance in the Skeletal Muscle

Given the unavailability of CR and PR in some conditions, multiple dietary strategies, such as the intake of trace mineral elements and vitamins, should also be considered to provide a more comprehensive and balanced regime for the prevention and treatment of T2D. Trace mineral elements like zinc and chromium, and vitamins such as vitamin D, α-lipoic acid (6,8-dithio-octanoic acid, ALA), tocopherol, vitamin C, and biotin, are recognized as mediators of insulin responses in the skeletal muscle, modulating muscle glucose uptake capacity.

Zinc and chromium

Concentrations of micronutrients, such as zinc and chromium, are significantly reduced in the blood and scalp-hair samples of T2D patients compared with those of nondiabetic control subjects (67). The deficiency of zinc and chromium often present in Western diets, and an inverse association between the dietary intake of zinc or chromium and the risk of T2D, has been identified in previous studies (68, 69). In human and mouse skeletal muscle cells, the physiological level of plasma zinc (20 μmol/L) exerted an insulin-mimetic effect on glucose consumption accompanied by the activation of extracellular receptor kinase (ERK) 1/2 and GSK3β (70). Enhanced glucose consumption was also observed in insulin-resistant L6 myotubes treated with zinc supplementation through the activation of insulin-signaling cascade (AKT, GLUT4, and GSK3β) and downregulation of the mTOR-S6K1 pathway (71). Similarly, dietary supplementation of 80 μg/(kg body weight · d) chromium in obese KK/HIJ diabetic mice or 40 μg/(kg body weight · d) chromium in Holstein calves enhanced skeletal muscle glucose utilization through activating the IRS1-PI3K-AKT pathway and downregulating c-Jun N-terminal kinase activity (72, 73). However, chromium supplementation had no effect on glucose metabolism in healthy subjects (74).

Vitamin D

Vitamin D deficiency is a key factor that may accelerate the formation of insulin resistance, and mechanisms related to vitamin deficiency and insulin resistance have been well discussed previously (75). Vitamin D intake is thus inversely associated with the risk of diabetes and insulin resistance. In C57BL/6L mice subjected to a high-fat, high-sugar (HFHS) diet for 8 wk, vitamin D supplementation

along with HFHS intake for the next 8 wk abated HFHS-induced insulin resistance and lipid accumulation in the skeletal muscle, accompanied by the decreased Ser307 phosphorylation of IRS1 and increased phosphorylation of AKT and GSK3β in the muscle (76). Additionally, vitamin D combined with whey protein/EAAs or metformin improved muscle mass and strength in elderly people with sarcopenia (77), or reduced insulin resistance in rats with T2D (78). These results suggest that vitamin D supplementation alone or synergistically with other nutrients is a promising strategy to treat insulin resistance and age-related sarcopenia, especially for those who are vitamin D deficient.

Skeletal muscle–specific deletion of vitamin D receptor (VDR) led to insulin resistance and glucose intolerance and increased the expression and activity of FoxO1 (79). Furthermore, vitamin D inhibited FoxO1 activation in a VDR-dependent manner (79). Given the versatile role of vitamin D in regulating the insulin sensitivity of skeletal muscle and whole-body immune response, its role in vivo in different populations merits further investigations.

ALA, tocopherol, and ascorbic acid

It has been shown that ALA promotes glucose uptake in L6 muscle cells, diabetic rodents, and all types of myofibers in normal mice (80). ALA also increased fatty acid oxidation through enhancing AMPK-PGC1α–mediated mitochondrial biogenesis, and attenuated protein synthesis by downregulating the mTOR signaling pathway (81). In addition, ALA, with its antioxidant properties, can prevent H_2O_2-induced deterioration in insulin signaling by increasing the concentration of glutathione and decreasing the activation of p38 mitogen–activated protein kinase in L6 muscle cells (82).

In addition to vitamin D and ALA, tocopherol and ascorbic acid are also implicated in regulating insulin sensitivity. In studies conducted in diabetic mice and L6 cells, tocopherol supplementation resulted in ameliorated muscle atrophy, upregulated glucose intake, and increased energy expenditure through the combination of reduced oxidative stress, inflammation, and apoptosis (83). In a randomized crossover study, oxidative stress markers were also reduced following a 4-mo ascorbic acid supplementation regime in T2D patients (84).

Potentials of Natural Phytochemicals in Muscle Insulin Resistance Therapy

Many natural phytochemicals, including phenols, terpenoids, nitrogen-containing alkaloids, and sulfur-containing compounds, have been applied to prevent and treat T2D. Some natural phytochemicals, such as curcumin, resveratrol, berberine, astragalus polysaccharide (APS), emodin, and genistein, play positive roles in improving insulin signaling and glucose metabolism, particularly the activated AMPK signaling involved (85–90). It was also shown that resveratrol (86), berberine (91), or genistein (90) treatment suppressed lipid accumulation and stimulated fatty acid oxidation in the skeletal muscle or L6 myotubes. In addition, APS was reported to ameliorate insulin resistance and decrease myostatin expression in the skeletal muscle of 13-wk-old diabetic mice and in C2C12 cells exposed to palmitate by downregulating the reactive oxygen species–ERK–NFκB pathway (92). It is worth noting that curcumin treatment for 9 mo in the prediabetic population delayed the development of T2D (93), but information on the efficacy of most phytochemicals in humans is still scant. Furthermore, the effect of resveratrol on insulin sensitivity in the skeletal muscle of humans is controversial. It has been demonstrated that resveratrol intake even aggravated palmitate-induced insulin resistance in human skeletal muscle cells by inhibiting AMPK activity and stimulating endoplasmic reticulum stress (94). Therefore, substantial data from both in vitro and in vivo studies are urgently needed to evaluate the application of resveratrol in preventing and treating T2D.

Involvement of the Gut Microbiota in the Regulation of Insulin Sensitivity in the Skeletal Muscle

The effect of nutritional interference on insulin sensitivity in the skeletal muscle in vivo involves the gut microbiota, which is associated with the development of many metabolic diseases, including T2D (95). One study conducted in humans demonstrated that fecal microbiota transplantation from healthy lean donors could improve insulin sensitivity and alter the microbiota composition of recipients with metabolic syndrome (96). With regard to the association between specific taxa and T2D, it has been shown that the genera of *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, *Roseburia*, and *Akkermansia* were negatively correlated with T2D development, while the genera of *Fusobacterium*, *Ruminococcus*, and *Blautia* were positively correlated with T2D development (97). The gut microbiota affects the pathogenesis of T2D mainly through modulating inflammation, changing gut permeability, and influencing glucose and lipid metabolism in insulin-sensitive organs (96, 98). In particular, butyrate, a fermentation product in the large intestine, has been shown to protect against HFD-induced insulin resistance and enhance insulin signaling and fatty acid oxidation in the gastrocnemius muscle of mice (99).

The gut microbiota is highly adaptive to dietary intake. Dietary supplementation of leucine or isoleucine for 10 wk was found to alleviate HFD-induced insulin resistance and to decrease the ratio of *Firmicutes* spp. to *Bacteroidetes* spp. in C57BL/6J mice (100). Similarly, the abundance of *Actinobacteria* spp. and the concentrations of propionate and butyrate also increased in the colonic content of adult pigs fed a diet with an additional 1% leucine supplementation for 60 d (101). Furthermore, lower gut microbiota remodeling was observed in mice after short-term CR, and decreased weight gain as well as improved insulin sensitivity were shown in CR-microbiota–transplanted mice compared with the outcomes observed in AL-transplanted controls (102).

Although some studies demonstrated the correlation between altered microbiota composition and improved insulin sensitivity after dietary interventions, such as CR (102), BCAA restriction (103), and resveratrol (104) or berberine (105) administration in mice or humans, it is still challenging to identify the microbiota associated with the incidence of T2D in humans due to the complex background of patients, such as geographic location, health status, and drugs used. Furthermore, the exact impact of the gut microbiota and its metabolites on the pathogenesis of T2D remains to be elucidated.

Conclusions

Insulin resistance in the skeletal muscle is not only a major characteristic of but also a premonition of T2D. Reduced response to insulin leads to unbalanced protein turnover in the skeletal muscle, and in turn, skeletal muscle dysfunction can worsen insulin signals. CR/PR or supplementary intakes of specific kinds of AAs, trace elements, vitamins, and natural phytochemicals show excellent potential for improving insulin sensitivity in the skeletal muscle and may have crucial clinical application value. The intake of protein and specific AAs, especially leucine, has opposite effects on muscle glucose disposal and protein synthesis, and may act as a double-edged sword for health in some conditions, such as sarcopenia. Similarly, ambiguous effects of phytochemicals on muscle insulin signals may also exist, especially with resveratrol. Therefore, the synergy of multiple dietary strategies may be leveraged, and more attention should be paid to the regulatory mechanism of core signaling pathways, particularly the PI3K/AKT, mTOR, and AMPK pathways. Nutritional regulation of the gut microbiota in vivo and the cross-talk between skeletal muscle and other tissue/organs, such as adipose tissue, liver, and brain, also deserve further clarification. In summary, a better application of dietary strategies will improve insulin sensitivity and facilitate skeletal muscle health.

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