REVIEW

Potential benefits of nutritional supplementation in diabetic sarcopenia

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Abstract

Type 2 diabetes mellitus, one of the metabolic diseases, is a major risk factor for impaired muscle function leading to muscle loss, weakness, and frailty. A lot of studies have suggested that the biological mechanisms which contribute to diabetic sarcopenia, including insulin resistance, altered energy metabolism, oxidative stress, and inflammation. Although different nutritional interventions for diabetic sarcopenia have not been clearly defined, there is no doubt that nutrition plays an essential role in the prevention or delay of muscle loss and maintenance of physical function. In this review, we discuss the recent literature on biological pathways for diabetic sarcopenia and potent nutrients used for attenuating diabetic sarcopenia: dietary proteins, omega-3 fatty acids, vitamin D, vitamin E, and other anti-oxidants for future research.

Introduction

Diabetes mellitus (DM) is a chronic hyperglycemic condition which is caused by low production (type 1 diabetes) or inefficient use (type 2 diabetes) of insulin. Especially type 2 diabetes mellitus (T2DM) has been globally prevalent and has become a major health problem, with around 463 million population affected in 2019 and 700 million people in 2045 (Belma et al. 2019). Chronic hyperglycemic condition in DM often triggers various complications such as neuropathy, retinopathy, and nephropathy. Among various complications related to T2DM, sarcopenia has been recently high-lightened, accompanied by an increased aged population.

Sarcopenia in DM is associated with altered energy metabolism combined with increased proteolysis and impaired protein synthesis, followed by muscle damage under hyperglycemic conditions (Smith et al. 1989, Lecker et al. 1999). Furthermore, changes in energy metabolism are linked to impaired insulin signaling, increased oxidative stress, and inflammation in diabetic pathology.

Loss of muscle mass and strength can be controlled by various lifestyle factors, mainly exercise training and diet. The role of exercise in sarcopenia has been extensively investigated. Moreover, diverse nutritional approaches to improve muscle function and strength have been conducted in various research (Nikoletopoulou et al. 2013, Zhou et al. 2016). However, research focusing on dietary intervention to ameliorate diabetic sarcopenia has not been extensively reviewed (Velázquez-Alva et al. 2020). Particularly, protein supplementation, including branched-chain amino acids (BCCA), has been frequently used to improve muscle health mostly in athletes or healthy subjects (Campbell & Rains 2015). Anti-inflammatory nutrients such as omega-3 fatty acids, vitamin D, and vitamin E have been used to ameliorate sarcopenia and boost muscle functions in DM (M ostad et al. 2006, Amin et al. 2018, Lee & Lim 2018). In addition, some anti-oxidants, including resveratrol, have shown a beneficial effect on muscle damage in DM (Goh et al. 2014, Wang et al. 2018).
In this review, we include major pathological mechanisms associated with hyperglycemia-induced sarcopenia, such as insulin resistance, altered energy metabolism, oxidative stress, and inflammation in T2DM. Furthermore, we focus on the potential benefits of dietary intervention, including proteins, anti-inflammatory, and/or anti-oxidant food components on pathological mechanisms associated with diabetic sarcopenia.

**Key pathogenic mechanisms in diabetic sarcopenia**

We demonstrated a graphical summary of the biochemical pathways involved in diabetic sarcopenia that is highlighted in Fig. 1.

**Impaired muscle mass and function in DM (morphology)**

A major metabolic defect associated with DM is the failure of appropriate glucose utilization in peripheral tissues such as skeletal muscle (Stanford & Goodyear 2014). Hyperglycemia can act as a powerful risk factor for loss of muscle mass and function called sarcopenia (Bassil & Gougeon 2013). In particular, progressive muscle mass loss, accompanied by declined muscle strength and quality, has been suggested as a potential factor for the link between DM and disability (Bassil & Gougeon 2013).

Human skeletal muscle fibers are classified as slow-twitch oxidative (type 1) and fast-twitch (type 2) fibers (Stuart et al. 2013). Slow-twitch fibers are more sensitive to insulin and have greater glucose uptake ability than fast-twitch fibers (Stuart et al. 2013). In diabetic patients, the fraction of slow fibers was lower than that in the healthy control subjects (Gaster et al. 2000). Furthermore, the expression level of glucose transporter 4 (GLUT4), which is higher in slow-twitch fibers, was reduced in T2DM patients (Hilton et al. 2008). The changes in fiber characteristics can reduce glucose utilization in skeletal muscle of T2DM (Stuart et al. 2013).

**Figure 1**

The plausible mechanisms of potential nutrients in skeletal muscle protein synthesis and degradation. Arrows represent activation and capped lines represent inhibition. Published effects of dietary proteins, omega-3, vitamin D, vitamin E, and other anti-oxidants on signaling pathways associated with diabetic sarcopenia. The binding of insulin to insulin receptor subunit-1 (IRS-1) can activate phosphoinositide 3-kinases (PI3K)/Akt signaling which stimulates mechanistic target of rapamycin (mTOR) pathway. mTOR stimulates protein synthesis by phosphorylation of p70 ribosomal S6 protein kinase (p70S6K). Akt also blocks proteolysis by phosphorylating and inhibiting forkhead transcription factors (FoxOs). The activation of FoxOs and induction of their target atrophic genes activate caspase-dependent proteolysis. S'adenosine monophosphate-activated protein kinase (AMPK) activation following by energy deficit in skeletal muscle inhibits mTOR activation, thereby reducing protein synthesis. In addition, reactive oxygen species (ROS) and inflammatory cytokines can lead to nuclear factor-kappa B (NF-κB)-dependent upregulation of atrophic genes including Atrogin-1 and MuRF1.
Furthermore, overweight and obesity, common characteristics in T2DM, are associated with fat infiltration into the muscle (myosteatosis) (Bianchi & Volpato 2016, Hamrick et al. 2016). Fat infiltration in the skeletal muscle can lead to abnormal muscle fiber organization and thus, affects muscle cells proliferation and differentiation (Hamrick et al. 2016). Recent data suggested that skeletal muscles of T2DM patients exhibited an increase in glycolytic fiber and a decrease in capillary density capacity (Hamrick et al. 2016). The increased production of lipid metabolites in skeletal muscle impairs the capacity for normal protein synthesis in T2DM (Bianchi & Volpato 2016). These morphological changes in muscle fiber are also associated with functional impairments in skeletal muscle, as demonstrated by muscle weakness and motor dysfunction (Punkt et al. 1999, Bianchi & Volpato 2016). Thus, the decrease in insulin sensitivity with lipid infiltration is one pathway which can directly affect skeletal muscle health in T2DM.

As a consequence, changes in muscle architecture and fiber type, with gradual loss of muscle strength, have been hypothesized as the primary biological mechanisms responsible for muscle damage in diabetic patients. The pathogenesis of diabetic sarcopenia is multifactorial and attributes to many of these causal pathways that intersect or overlap in relation to hyperglycemia in T2DM.

**Altered muscle energy metabolism in DM**

There are malfunctions in glucose influx into the skeletal muscle and its utilization of synthesizing ATP in insulin-resistant and diabetic conditions (Boersma et al. 2018, Chadt & Al-Hasani 2020). Subsequent energy deficit due to impaired glucose uptake probably contributes to the increased apoptosis rate in skeletal muscle (Wang et al. 2006). To compensate the energy deficit in muscle cells, protein degradation in skeletal muscle is stimulated (Park et al. 2009), subsequently accelerating the loss of muscle mass in DM (Park et al. 2009). Despite the increased protein catabolism, amino acids are not effectively utilized for ATP synthesis in DM. In normal conditions, BCCAs are catabolized by two main enzymes: BCAA transaminase (BCAT) and branched-chain α-keto acid dehydrogenase (BCKD) (Neinast et al. 2019). However, a diabetic condition often causes BCAA catabolic defects due to limited glucose availability and reduced BCKD activity (Holeček et al. 2018). The diabetes-mediated BCAA catabolic defects aggravate skeletal muscle energy deficit, contributing to muscle loss and dysfunction.

In addition, increased lipid mediates caused by impaired fat utilization in DM lead to activate skeletal muscle proteolysis (Kelley & Simoneau 1994, Pan et al. 1997, Sergi et al. 2019). Reduced β-oxidation triggers diacylglycerol and free fatty acids, which can inhibit insulin receptor subunit-1 (IRS-1) activation in DM (Pan et al. 1997). IRS can activate phosphoinositide 3-kinases (PI3Ks)/Akt signaling, which stimulates myogenesis by mammalian target of rapamycin (mTOR) activation and inhibition of FoxOs activation. Reduced activation of Akt decreases phosphorylation of FoxO, which induces the translocation of target genes and subsequently increases the transcription of muscle RING-finger1 (MuRF1) and atrophy-related ubiquitin ligases Atrogin-1/MAFbx (Meex et al. 2019).

All of the above-mentioned metabolic abnormalities with insulin resistance in skeletal muscle are responsible for the energy deficit related to muscle loss and its dysfunction in DM.

One of the key signaling molecules regulating energy metabolism is 5′ adenosine monophosphate-activated protein kinase (AMPK). AMPK, a well-known energy sensor, is activated when ATP is rapidly consumed, generating high amounts of AMP. Phosphorylated AMPK increases sirtuin 1 activity which would result in the deacetylation of peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) (Cork et al. 2018). PGC1α, as a master regulator of mitochondrial biogenesis, is associated with metabolic regulation such as anti-oxidant defense system and inflammation in skeletal muscle. PGC1α induces glucose uptake in the skeletal muscle by increasing the GLUT 4 translocation (Cork et al. 2018, Kou et al. 2018). In the case of T2DM, the decreased level of PGC1α causes the production of lipid metabolites which can lead to insulin resistance and aberrant energy metabolism (Waldman et al. 2018, Zhou et al. 2019, Lantier et al. 2020, Coppi et al. 2021). Therefore, the regulation of insulin signaling along with AMPK/SIRT1/PGC1α pathway is important for energy homeostasis in various tissues, including skeletal muscle.

**Hyperglycemia-induced oxidative stress in skeletal muscle**

Hyperglycemia is a major problem in diabetic conditions, working through several mechanisms such as increased production of reactive oxygen species (ROS) and advanced glycation end products (AGEs) (Giacco & Brownlee 2010). AGEs interact with a receptor of AGE (RAGE) present in the cell surface, thus, altering the cell signaling and gene expression. Recent studies showed that an increased level of AGEs in skeletal muscle could cause impaired muscle strength in the elderly (Giacco & Brownlee 2010, ...
Momma et al. 2011). Furthermore, glucose auto-oxidation and protein glycosylation produce ROS, leading to oxidative stress in various tissues, followed by inflammation in DM (Giacco & Brownlee 2010, Luc et al. 2019). In particular, oxidative stress impairs insulin signaling through IRS serine/threonine phosphorylation and decreases GLUT4 translocation and then disturbs glucose uptake in skeletal muscle (Giacco & Brownlee 2010). Patients with T2DM showed excessive oxidative stress in skeletal muscle (Luc et al. 2019). Individuals with poor glycemic control causing oxidative stress also exhibited decreased muscle strength and mass (Sugimoto et al. 2019).

Furthermore, excessive ROS production is indicated as a major factor in muscle protein hyper-catabolism through the activation of the ubiquitin–proteasome pathway (Korovila et al. 2017). Oxidative stress increases the expression of FoxO3a, which activates ubiquitin–proteasome systems such as atrogin-1/MAFbx and MuRF1 in DM (Korovila et al. 2017).

Another T2DM-related factor in the progression of sarcopenia through oxidative stress is impaired mitochondrial dysfunction (Wiegman et al. 2015). As mentioned before, mitochondrial dysfunction due to the accumulation of oxidative damage may trigger apoptosis-induced muscle dysfunction (Korovila et al. 2017). It also has the capacity to dysregulate satellite cell activity that accompanies muscle damage (Xu et al. 2019). Therefore, oxidative stress interfering with muscle growth and development may cause ubiquitin and apoptosis, resulting in diabetic sarcopenia.

**Hyperglycemia-induced inflammation in skeletal muscle**

Chronic hyperglycemia in T2DM leads to localized inflammation, which can arise through increased immune cell infiltration in inter-myocellular and adipose tissue (AT) around the muscles (Lontchi-Yimagou et al. 2013, Wu & Ballantyne 2017). In addition, increased immune cells in visceral AT can accelerate the release of free fatty acid and migrate to myocytes, causing myocyte inflammation (Hilton et al. 2008). Increased infiltration of immune cells in skeletal muscle activates pro-inflammatory cytokines, which negatively regulate myocyte metabolic functions (Lontchi-Yimagou et al. 2013, Wu & Ballantyne 2017). Skeletal muscle secretes a variety of cytokines such as interleukin (IL)-6, IL-8, and IL-15 and other molecules such as fibroblast growth factor 21 (FGF21), irisin, myonectin, and myostatin (Bonaldo & Sandri 2013). Differentiated cultured myocytes isolated from subjects with T2DM secreted more cytokines such as tumor necrosis factor-alpha (TNF-α) and chemokines such as monocyte chemoattractant protein 1 (MCP-1) compared to those of lean controls (Pedersen et al. 2003, Abbatecola et al. 2004, Muñoz-Cánoves et al. 2013). In T2DM patients, muscle mass and strength were decreased compared to those in non-diabetic controls, and it was in accordance with the increased levels of plasma pro-inflammatory cytokines, including IL-6 and TNF-α (Tsuchiya et al. 2010, Sugimoto et al. 2019, Xu et al. 2019). These inflammatory mediators impair the insulin signaling pathway by inhibiting tyrosine phosphorylation of IRS with modifications of GLUT4 translocation in myocytes (Abbatecola et al. 2004, Tsuchiya et al. 2010, Muñoz-Cánoves et al. 2013, Sugimoto et al. 2019).

On the other hand, increased circulating pro-inflammatory cytokines directly upregulate several protein hydrolysis pathways, resulting in skeletal muscle degradation (Bonaldo & Sandri 2013, Zhou et al. 2016). Increased IL-6 activates Janus kinase/signal transducers and activators of transcription (JAK/STAT) catabolic pathway. TNF-α is also the major factor that induces cellular apoptosis in muscle mainly by activating NF-κB and MyoD to cause muscle loss (Mourkioti & Rosenthal 2008, Zhou et al. 2016). NF-κB leads to activate E3 ubiquitin ligase, lysosomal-proteasome, and apoptosis which promote protein degradation in the skeletal muscle. NF-κB also regulates the expression of various pro-inflammatory mediators, which act as positive feedback to activate NF-κB itself, causing continuous muscle damage (Mourkioti & Rosenthal 2008).

These characteristics can interfere with muscle homeostasis and cell death mechanisms promoting losses in skeletal muscle mass, strength, and function, which are considered as the principal components of sarcopenia.

**Potential nutritional intervention for diabetic sarcopenia**

Previous research has suggested that nutrition plays a major role in diabetic sarcopenia, and nutritional interventions may prevent or reduce muscle loss and maintain physical function. Different nutritional approaches have been studied, focusing on regulating glucose homeostasis through reduced intakes of energy and saturated fat and increased intake of dietary fiber in DM (Nikoletopoulou et al. 2013, Zhou et al. 2016).

Other major pathogenic mechanisms that can be used for the prevention of diabetic sarcopenia.
are hyperglycemia-induced oxidative stress and inflammation. Sarcopenia is a state of increased oxidative stress and inflammation, causing apoptosis and ubiquitin-proteasome pathway in DM. Hence, we have introduced not only protein sources that help in muscle protein synthesis (MPS) but also dietary anti-inflammatory (vitamin D, omega (w)-3 fatty acids) and anti-oxidant compounds (vitamin E, ultra-trace minerals, and natural compounds) as potential nutritional interventions for diabetic sarcopenia, as summarized in Table 1.

**Dietary proteins**

The beneficial effects of dietary proteins have been investigated, but there is insufficient research focusing on the effects of protein supplementation on diabetic sarcopenia (Campbell & Rains 2015, Velázquez-Alva et al. 2020). As protein stimulates MPS by the availability of BCAAs, it can play a central role in skeletal muscle growth. Recent studies have found that protein supplementation attenuated the decline in muscle mass and insulin resistance that potentially prevented the development of T2DM and sarcopenia (Campbell & Rains 2015, Velázquez-Alva et al. 2020). Especially, amino acids are known to induce mTOR pathway. mTOR is conserved serine/threonine kinase and regulates anabolic and catabolic signaling of skeletal muscle. mTOR pathway is activated by its upstream signaling P13K (Ferretti et al. 2018) and then leads to an increase in S6K1 which stimulates protein synthesis (Bodine et al. 2001).

Researchers have demonstrated that various sources of dietary protein have different effects on muscle health. In a recent study, nil whey protein supplementation improved repetition maximum, peak oxygen consumption, and vastus lateralis muscle thickness in T2DM patients (Gaffney et al. 2018). Furthermore, it ameliorated glucose disposal rate, fasting blood glucose level, and homeostatic model assessment of insulin resistance (Gaffney et al. 2018).

Some previous studies showed that intake of high-quality amino acids effectively reduced muscle mass loss (Campbell & Rains 2015, Pai et al. 2020, Dollet et al. 2022). Among various amino acids, glutamine, the most abundant free amino acid in the body, is known to stimulate protein synthesis and inhibits protein degradation, thereby protecting muscle function in diabetic rats (Dollet et al. 2022, Lambertucci et al. 2022). A recent study demonstrated that glutamine supplementation attenuated insulin resistance in obesity by reducing inflammatory markers and promoting skeletal muscle insulin sensitivity (Dollet et al. 2022). Glutamine also has regulatory roles in enhancing plasma anti-inflammatory monocyte and regulatory T cells in diabetic mice (Pai et al. 2020).

Another study showed that leucine treatment induced protein synthesis by the activation of mTOR signaling (Velázquez-Alva et al. 2020). l-Leucine enhanced muscle glucose uptake with concomitant suppressed proteolytic, glycogenolytic, and gluconeogenetic activities while modulating glucose homeostasis in isolated rat psoas muscle ex vivo (Erkainure et al. 2021). However, leucine treatment did not affect muscle strength and muscle fiber type characteristics in T2DM patients (Leenders et al. 2011).

In summary, supplementation with dietary proteins and amino acids is a promising strategy to increase MPS and attenuates diabetic sarcopenia, although positive evidence was limited. Therefore, further studies are needed to establish the appropriate dosage and timing of supplementation of dietary proteins and amino acids for the management of diabetic sarcopenia.

**Omega-3 fatty acids**

As an anti-inflammatory agent, omega-3 fatty acids have a beneficial role in skeletal muscle metabolism and function. Omega-3 fatty acids are known to affect muscle health by regulation of the ratio between muscle protein synthesis and breakdown through decreasing inflammation (Huang et al. 2020, Okamura et al. 2020). As natural ligands for PPARy, omega-3 fatty acids increase the activation of PPARy, which suppresses NF-xB activation. Omega-3 fatty acids can prevent NF-xB activation and transcription of inflammatory mediators such as COX-2 and TNFα (Vanden Berghe et al. 2003, Liu et al. 2013, Calder et al. 2015). This action prevents the expression of muscle-specific E3 ligase, including MuRF1 and MAFbx/Atrogin-1 causing protein degradation in skeletal muscle (Huang et al. 2011, Ikeno et al. 2022).

In particular, eicosapentaenoic acid (EPA) treatment also enhanced mitochondrial fusion and insulin signaling by the inhibition of inflammation in human primary myotubes (Sergi et al. 2021). Treatment with EPA attenuated muscle loss by the suppression of the ubiquitin–proteasome pathway in rodent models following resistance exercise (Whitehouse & Tisdale 2001, Siriguleng et al. 2021). Another in vivo evidence shown in normal mice demonstrated that docosahexaenoic acid (DHA)-enriched diet supplementation increased skeletal muscle glucose uptake and reduced inflammation (Lam et al. 2011).

Another beneficial effect of omega-3 fatty acids on muscle health is associated with the regulation of lipid metabolism. Abnormal energy metabolism in DM leads to...
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<th>Nutrient</th>
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| Protein          | Nil whey protein             | Adults with T2DM performed high-intensity mixed-mode interval training    | † Fasting blood glucose and homeostatic model assessment of insulin resistance  
† Repetition maximum, peak oxygen consumption, and vastus lateralis muscle thickness.                                                                                                                | Gaffney et al. 2018             |
| Leucine          | Adults with T2DM             | 2.5 g/day for 6 months                                                    | No changes in lean tissue mass, fat percentage, muscle strength, and muscle fiber type characteristics                                                                                                   | Velázquez-Alva et al. 2020      |
| Glutamine        | Diabetic mice with limb ischemia | AIN-93 diet in which a part of the casein was replaced with glutamine     | ↑ Anti-inflammatory monocytes and regulatory T cells in the blood  
↓ The percentage of M1 macrophages in muscle tissues  
↓ The muscle M1/M2 ratio  
↓ Gene expression of IL-6  
↑ The levels of PPARγ and myogenic differentiation 1 genes                                                                 | Pai et al. 2020                 |
| Glutamine        | Diabetic rats                | 1 g/kg BW for 15 days                                                    | ↑ Protein synthetic pathway (mTOR/Akt pathway) in skeletal muscle  
↓ Protein-degradative signaling pathways (Murf1/Astrogin-1) in Skeletal Muscle                                                                                                                 | Dollet et al. 2022              |
| Omega-3 fatty acids | Fish oil (1.8 g 20:5omega-3, 3.0 g 22:6 omega-3, and 5.9 g total omega-3 fatty acids) | Adults with T2DM 17.6 mL/day fish oil for 9 weeks                      | ↓ Insulin sensitivity  
Alters carbohydrate and fat utilization                                                                                                           | Mostad et al. 2006              |
| EPA              | C2C12 myotubes exposed to palmitate (500 μM) | 30 μM                                                              | ↓ Protein kinase C-8 activation  
↑ Cellular acylcarnitine profile, insulin-dependent Akt phosphorylation and glucose uptake.                                                                                          | Whitehouse and Tisdale 2001     |
| DHA              | L6 myotubes In vitro         | 0.4 mmol/L                                                               | ↑ Fat oxidation                                                                                                                                        | Aas et al. 2006                 |
| Vitamin D (1,25(OH)₂D₃) | Diabetic rats               | 0.5 μg/kg BW three times weekly for 8 weeks                              | ↑ Insulin sensitivity in skeletal muscles  
Sustained muscle atrophy and inflammation                                                                                                                 | Amin et al. 2018                |
| Vitamin D (1,25(OH)₂D₃) | Obese mice                  | 7 μg/kg, three times/week for 2 months                                   | ↑ Muscle insulin signaling  
Reverted myosteatosis  
↓ NF-κB and tumor necrosis factor (TNF-α) activation  
↓ Lipogenic pathway  
↓ RAGE expression in skeletal muscle.                                                                                                      | Benetti et al. 2018             |
| Vitamin D (1,25(OH)₂D₃) | Obese mice                  | 1 μg/kg/day, every day for 6 weeks                                       | ↓ Skeletal muscle loss and insulin resistance in mice.  
Regulated glucose homeostasis                                                                                                                      | Li et al. 2021                  |

(Continued)
fat accumulation and produces lipotoxic compounds such as ceramide and palmitate, promoting insulin resistance. Recent in vitro studies reported that EPA and DHA improved fatty acid metabolism and then reduced insulin resistance in human skeletal muscle cells, C2C12, and L6 myotubes, notably via their abilities to increase mitochondrial β-oxidation (Aas et al. 2006, Capel et al. 2015, Katsnelson & Ceddia 2020) and Akt phosphorylation (Kim et al. 2016). In T2DM patients, fish oil supplementation increased fat oxidation and glucose utilization which can improve insulin sensitivity (Mostad et al. 2006). Taken together, the results suggest that omega-3 fatty acids may have protective effects against inflammation and abnormal lipid metabolism in skeletal muscle. Although a more detailed mechanism is required to clarify the effects of omega-3 fatty acids on diabetic patients with sarcopenia, omega-3 fatty acids at physiological doses could participate in the regulation of skeletal muscle metabolism by preventing lipotoxicity and inflammation.
**Vitamin D**

Recently, the association between vitamin D and skeletal muscle metabolism has been highlighted. Vitamin D may affect the conservation of muscle mass and strength, preventing sarcopenia and frailty (Arik & Ulger 2016).

Administration of vitamin D accelerated the functional restoration of the damaged muscle, improved cell proliferation, and reduced cell death after muscle injury (Stratos et al. 2013). In vitamin D-deficient mice, the levels of atrogin-1 and MuRF1 in skeletal muscle were increased by two-fold compared to those of the controls (Tamura et al. 2017, Dzik & Kaczor 2019). These data demonstrate that vitamin D insufficiency/deficiency is associated with the development of muscle atrophy, but more clear mechanism is needed to be explained.

Vitamin D also regulates the insulin signaling pathway in skeletal muscle (Benetti et al. 2018). Low vitamin D level has been associated with poor glycemic control and physical function (Mirtosseini et al. 2018, Dang et al. 2019). The patients with T2DM were also associated with low level of 25(OH)D (Mendoza-Garcés et al. 2021, Takahashi et al. 2021). In a recent meta-analysis, vitamin D supplementation significantly decreased fasting plasma glucose and HbA1c levels in prediabetic individuals (Poolsup et al. 2016, Pittas et al. 2019). In T2DM rats, oral administration of vitamin D improved insulin sensitivity in skeletal muscle (Amin et al. 2018, Li et al. 2021). In another study, vitamin D restored the impaired muscle insulin signaling and reverted myosteatosis by decreasing the levels of NF-κB and TNF-α (Benetti et al. 2018). However, there are conflicting findings on vitamin D supplementation influencing glucose regulation in DM (Gulseth et al. 2017, Mousa et al. 2017).

On the other hand, vitamin D deficiency in mitochondrial dysfunction can affect the progression of sarcopenia. Mitochondria play a vital role in cellular energy metabolism, but they are also major intracellular sources of ROS (Ott et al. 2007). Ryan et al. demonstrated that 1α,25-dihydroxy vitamin D3 regulated mitochondrial oxygen consumption and dynamics in muscle cells (Ryan et al. 2016). In a recent study, vitamin D supplementation in deficient rodent models improved mitochondria’s density and function and protein metabolism (Gogulothu et al. 2020). In another study, vitamin D deficiency increased oxidative stress demonstrated by increasing the expression of SOD1 in skeletal muscle mitochondria and led to lipid and protein peroxidation in patients with chronic low back pain (Dzik et al. 2018). Furthermore, vitamin D treatment protected against skeletal muscle oxidative stress by regulation of SOD and catalase in vitamin D deficiency rats (Bhat & Ismail 2015). These results support that vitamin D can attenuate oxidative stress by regulating mitochondrial ROS generation.

Recently published data indicated that the direct effects of circulating levels of vitamin D on skeletal muscle have to be connected with vitamin D receptor (VDR). VDR located in skeletal muscle plays pivotal roles in both glucose and muscle homeostasis linked to muscle health. Mice with myocyte deletion of VDR have sarcopenia and impaired muscle function (Girgis et al. 2019). Vitamin D treatment activated VDR signaling, thereby inhibiting FoxO1 expression in C2C12 muscle cells. In the previous study, the overexpression of VDR results in skeletal muscle hypertrophy by increasing anabolic signaling, ribosomal biogenesis, and protein synthesis (Bass et al. 2020).

Collectively, the beneficial effects of vitamin D on diabetic sarcopenia can be explained by several mechanisms, including improvement of anabolic/catabolic metabolism and amelioration of mitochondrial dysfunction with reduced oxidative stress as well as increased VDR signaling. Although sarcopenia might be attenuated by vitamin D treatment, a better understanding of the mechanisms is required.

**Vitamin E**

Vitamin E, with its anti-oxidant and anti-inflammatory properties, has known to have an important role for attenuating the progression of metabolic diseases (Momma et al. 2011, Gonzalez-Calvo et al. 2015). In particular, the potential benefits of vitamin E on muscle damage have been demonstrated in a large number of studies.

Alpha (α)-tocopherol, a predominant vitamin E in the human body, is known to improve protein synthesis and muscle repair by downregulation of oxidative stress in diabetic rats (Servais et al. 2007). Tocopherol supplementation reduced glucocorticoid-induced oxidative stress in rat skeletal muscle (Ohitsuka et al. 1998). Furthermore, α-tocopherol reduced muscle proteolysis by increasing the expression of calpains, caspases-3, -9, and -12, E3 ubiquitin ligases (MAFbx and MuRF1) with the regulation of anti-oxidant enzyme activities (SOD, CAT, GPX) in hindlimb unloading-induced muscle atrophy rodent model (Servais et al. 2007).

In addition, a number of biological properties of tocotrienol rich fraction (TRF) have been identified, such as anti-cancer, anti-diabetes, anti-oxidant, immunomodulatory, and cardio-protective properties (Aragno et al. 2004, Fang et al. 2010, Mahalingam et al.)
Some studies demonstrated that TRF ameliorated oxidative stress in myoblasts (Vasanthi et al. 2012, Lim et al. 2019). In our previous study, TRF attenuated hyperglycemia-induced skeletal muscle oxidative stress demonstrated by reduced Nrf2 related pathway in diabetic mice (Lee & Lim 2018).

On the other hand, previous research has shown that vitamin E dose not only acts as an anti-oxidant but also acts as an anti-inflammatory nutrient (Huey et al. 2008, Fang et al. 2010, Chung et al. 2018). Vitamin E attenuated lipopolysaccharide-induced skeletal muscle damage by regulation of NFκB related inflammation in mice (Servais et al. 2007). TRF also inhibited inflammation by decreasing 20S proteasome activity in myoblast (Huey et al. 2008). Moreover, our group reported that TRF ameliorated NFκB and its associated inflammatory mediators in diabetic mice (Lee & Lim 2018), which attenuates the ubiquitin–proteasome system causing protein degradation (Russell et al. 2007, Qureshi et al. 2010). As inflammation can lead to loss of muscle mass and strength, these findings suggest that muscle dysfunction in diabetic patients can be attenuated by vitamin E supplementation through suppression of NF-κB associated inflammation.

Vitamin E can also ameliorate insulin resistance causing skeletal muscle damage by regulating oxidative stress and inflammation in DM. In a previous study, gamma (γ)-tocopherols ameliorated oxidative stress-induced insulin resistance in L6 myotubes (Cai et al. 2004). Furthermore, TRF improved glucose homeostasis and insulin signaling by regulation of PPAR-related pathways in the skeletal muscle of diabetic mice (Khor et al. 2017). Our group also reported that TRF normalized the insulin signaling pathway by downregulation of hyperglycemia-induced oxidative stress and inflammation in diabetic skeletal muscle (Lee & Lim 2018).

Furthermore, vitamin E supplementation can protect against mitochondrial dysfunction causing muscle proteolysis. Especially, TRF activates PPAR α, γ, and (delta) δ, which regulate mitochondrial biogenesis and energy metabolism (Singh et al. 2008, Fang et al. 2010). Previous studies have reported the ameliorative effects of vitamin E in mitochondria-mediated cell death via the release of apoptotic proteins, causing muscle wasting (Magalhães et al. 2005, 2007, Dillon et al. 2012).

Taken together, the evidence suggests that vitamin E may prevent or/and attenuate diabetic sarcopenia through amelioration of oxidative stress and inflammation accompanied by improving energy metabolism and insulin signaling pathway in skeletal muscle. However, additional investigations are required to confirm the molecular mechanism of vitamin E in protecting diabetic sarcopenia.

Others

Research continues to investigate various natural compounds and ultra-trace minerals targeting skeletal muscle to ameliorate diabetic complications. Some research in the field of diabetic sarcopenia has focused on reducing oxidative stress by anti-oxidant nutrients. In addition to vitamin E, naturally derived compounds such as polyphenols have been reported for their therapeutic potential to alleviate insulin resistance and reduce the risk of metabolic diseases. Among the prominent natural compounds, resveratrol (RSV) is one of the polyphenolic compounds known for its anti-oxidant and anti-inflammatory properties. RSV has shown preventive and therapeutic effects on metabolic diseases, including DM, obesity, and aging-associated disorders. In previous studies, RSV supplementation attenuated sarcopenia by reducing the ubiquitin–proteasome system and the mitochondrial autophagy in diabetic mice (Goh et al. 2014, Wang et al. 2018). In patients with T2DM, RSV supplementation improved energy expenditure by modulating SIRT1 expression and pAMPK/AMPK ratio in skeletal muscle (Wang et al. 2018). These observational studies suggest that RSV may have an attenuative effect on diabetic sarcopenia.

Furthermore, oligonol, mainly found in lychee fruit, consisted of catechins, procyanidins, and other phenolic compounds and is known to have an anti-oxidant effect. Oligonol treatment has been shown to attenuate ROS-related inflammation and prevent oxidative damage in in vitro model of hyperglycemia (Servais et al. 2007). In the T2DM mice model, oligonol supplementation alleviated muscle loss by suppressing atrogin-1 and MuRF1 as well as NFκB-related inflammation (Bhakta et al. 2017).

In addition to RSV and oligonol, licorice flavonoid oil (LFO) has been used for sarcopenia in diabetic mice (Yoshioka et al. 2018). Licorice, a traditional medicine, contains glabridin, which has anti-oxidant and anti-fatigue properties (Liu et al. 2017). In a recent study, LFO supplementation increased skeletal muscle mass by decreasing the expression of MuRF1 and atrogin-1 in the insulin resistance mice model (Yoshioka et al. 2018).

On the other hand, anti-oxidant effects of other ultra-trace minerals such as vanadium have been investigated. Vanadium and vanadium compounds are known to have a modulatory effect on glucose homeostasis by enhancing glucose transport, as well as IR tyrosine kinase activity (Jiang et al. 2016). In a previous study, vanadium...
administration decreased anti-oxidant enzyme levels, including catalase and SOD, in the skeletal muscle of diabetic mice (Kurt et al. 2011).

Overall, anti-oxidant products provide a promising benefit for inhibiting muscle mass loss since oxidative stress is one of the major risk factors. However, further clinical studies need to be conducted to clarify the beneficial effects of natural anti-oxidant compounds on diabetic sarcopenia.

Conclusions

Recently, numerous epidemiological and clinical research suggested that muscle dysfunction is more common in diabetic patients. Pathological mechanisms such as insulin resistance, abnormal energy metabolism, oxidative stress, and inflammation can all affect various components of muscle dysfunction. Figure 1 illustrates the plausible mechanisms of diabetic sarcopenia and how nutrients mitigate skeletal muscle dysfunction. Evidence suggests that different nutrients treatment can improve and maintain muscle mass and function in diabetic patients. However, more research with extensive investigations is required to establish the effective strategies of nutritional intervention on sarcopenia in DM, which can improve the quality of life of these individuals.

Summary

The prevalence of metabolic and musculoskeletal diseases, which affect individuals to mortality and morbidity, is increasing worldwide. Especially, T2DM characterized by insulin resistance negatively affects muscle health through impairments in protein metabolism, mitochondrial dysfunction, oxidative stress, and inflammation. However, evidence for the effective nutritional intervention for diabetic sarcopenia is lacking. In this review, we demonstrate the impact of various nutrients on attenuating sarcopenia in DM.

Declaration of interest

Yunsook Lim is an Editor of Redox Experimental Medicine. Yunsook Lim was not involved in the review or editorial process for this paper, on which she is listed as an author. The other authors have nothing to disclose.

Author contribution statement

Y L participated in the conception and design of the work. H L, S J Y, and Y L wrote the manuscript. All authors approved the final manuscript.

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