Literature review

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The Therapeutic Potential Of Short Chain Fatty Acids In Elderly Type 2 Diabetes Patients With Sarcopenia

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1. Abstract

The correlation between short-chain fatty acids (SCFAs) in the intestinal flora and sarcopenia in patients with type 2 diabetes is a topic of growing interest in recent research. The role and therapeutic potential of SCFAs for sarcopenia in elderly type 2 diabetes are anticipated. In this essay, we will explore the relationship between SCFAs and sarcopenia in patients with type 2 diabetes, and discuss the potential mechanisms and treatment underlying this correlation.

2. Keywords:

Short-chain fatty acids; Type 2 diabetes; Sarcopenia; Probiotics

3. Introduction

The 2019 Asian Sarcopenia Working Group (Asian Working Group for Sarcopenia, AWGS) defined sarcopenia as a disease [1] of decreased skeletal muscle mass and strength and (or) functional decline with aging. Sarcopenia can cause adverse health outcomes such as physical function decline, fall disability, reduced quality of life, and even increased mortality in the elderly population. In recent years, several studies have found a close relationship between T2DM and sarcopenia. Mori et al [2] proposed that diabetes is an independent influencing factor of sarcopenia and also independently predicted all-cause mortality in this population. SCFAs as a group of metabolites produced by gut microflora, it is associated with various health benefits in human body. Recent studies suggest that SCFAs can exert its beneficial effects on muscle mass and function through several mechanisms of energy metabolism regulation, enhanced inflammation inhibition, increased insulin sensitivity, and regulated protein synthesis and breakdown. It suggests that SCFAs may play a role in the prevention and treatment of sarcopenia in patients with type 2 diabetes. This article will explore the relationship between short-chain fatty acids and sarcopenia in patients with type 2 diabetes, including the mechanisms of this relationship and potential therapeutic implications.

4. Materials and Methods

We conducted an extensive research using literature published over the last twenty years, up until October 2023, regarding the intricate mechanisms that connect SCFAs with the development of sarcopenia and type 2 diabetes. The US National Library of Medicine (PubMed), Web of Science and China National Knowledge Infrastructure (CNKI) were the electronic databases used as sources for relevant articles related to our subject. Studies published between the 1 January 2003 and the 1 October 2023 were selected to avoid any outdated data. We used different combinations of the following keywords: “gut microbiota”, “short-chain fatty acids”, “insulin resistance”, “type 2 diabetes”, “sarcopenia”,“immunologic pathways”, “dysbiosis”and “therapy”. Various article types such as clinical trials, randomized controlled trials, multicenter studies, reviews, guidelines and meta-analysis were included. We primarily screened the articles by title and abstract. After that,we proceeded to full-text evaluation. The focus of this narrative review is on three major key-points. All the relevant information extracted from the selected articles is summarized in text form. Firstly, we summarize the newly found connection between the gut microbiota compositional changes and the development of type 2 diabetes and sarcopenia, especially the effect of a reduction in SCFAs production on them. After that, we show how these pathological changes lead to sarcopenia in patients with type 2 diabetes. The last part of this review is focused on potential therapeutic options. The screening process is shown in Figure 1. After reviewing the type of literature and course content, 51 studies were included in this review (Figure 1).

Figure 1: The flowchart for literature screening.

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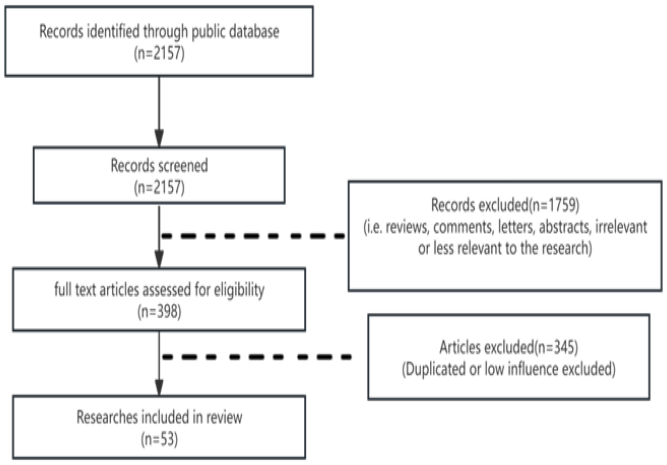

5. Discussion

5.1. SCFAs and T2DM, Sarcopenia

There are many epidemiological survey data on sarcopenia, which can be determined that it is a high incidence of disease, and chronic diseases such as diabetes have become an important risk factor for sarcopenia. An increasing number of studies report that diabetes mellitus is closely related to the occurrence and development of sarcopenia.According to the Asian Sarcopenia Working Group, the prevalence of sarcopenia in Japanese and Chinese adults with T2DM (65 and> 60 years, respectively) was 15% [3].The study by Wang et al. [4] showed that the prevalence of sarcopenia in patients with type 2 diabetes mellitus (T2DM) was 1.56 times higher than that in healthy people. With the progression of T2DM, skeletal muscle function and muscle mass will gradually decrease, and the prevalence of sarcopenia is much higher than the normal population [5]. Thus, sarcopenia has been described as a new complication of in patients with T2DM [6]. Diabetes and sarcopenia affect each other, with the same etiology and pathophysiological changes, including insulin resistance, chronic inflammation, lipid deposition, oxidative stress, accumulation of advanced glycation end products (AGEs), diabetes-related complications, etc. Both conditions have been associated with alterations in the intestinal flora composition and SCFAs production. Carbohydrates in food residues and glycoproteins secreted by intestinal epithelial cells are fermented and decomposed by colonic bacteria to produce short-chain fatty acids (SCFAs) such as acetic acid, propionic acid and butyric acid [7], also known as volatile fatty acids, which is a general term for organic fatty acids containing 1 to 6 carbon atoms.Gram-positive Firmicutes and Gram-negative Bacteroidetes have the largest number, accounting for about 98% of the human intestinal flora, and it is the dominant microflora involved in the generation of SCFAs in the gut[8].SCFAs have been shown to have important roles in energy metabolism, immune regulation, and the maintenance of gut barrier integrity[9]. Studies [10-12] have found that alterations in the gut microbiota composition and SCFAs production are associated with both type 2 diabetes and sarcopenia. In patients with type 2 diabetes, there is evidence of dysbiosis, characterized by changes in the relative abundance of specific bacterial taxa and a decrease in SCFA production [10,11]. This dysbiosis may contribute to insulin resistance and metabolic dysfunction, promoting the development and progression of type 2 diabetes. Similarly, in sarcopenia, alterations in the gut microbiota have been observed, including a decrease in SCFAs-producing bacteria and SCFAs levels [12] (Figure 2).

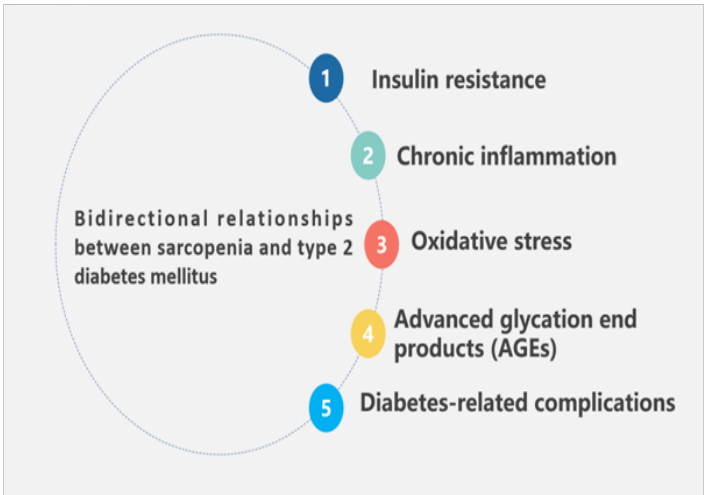

Figure 2: Bidirectional relationships between sarcopenia and type 2 diabetes mellitus.

5.2. Mechanisms behind the correlation between SCFAs, T2DM and Sarcopenia

SCFAs play a critical role in muscle physiology and metabolism. They can act as an energy source for muscle cells, stimulate muscle protein synthesis, and regulate muscle fiber composition. Decreased SCFAs production may disrupt these processes, leading to muscle wasting and the development of sarcopenia.In addition to their direct effects on muscle metabolism, SCFAs can also influence systemic inflammation and immune responses, which are implicated in both type 2 diabetes and sarcopenia. Dysbiosis-induced changes in SCFA production can modulate the release of pro-inflammatory cytokines and affect immune cell function, contributing to chronic inflammation and muscle dysfunction. Several mechanisms have been proposed to explain the correlation between SCFAs, type 2 diabetes, and sarcopenia (Figure 3).

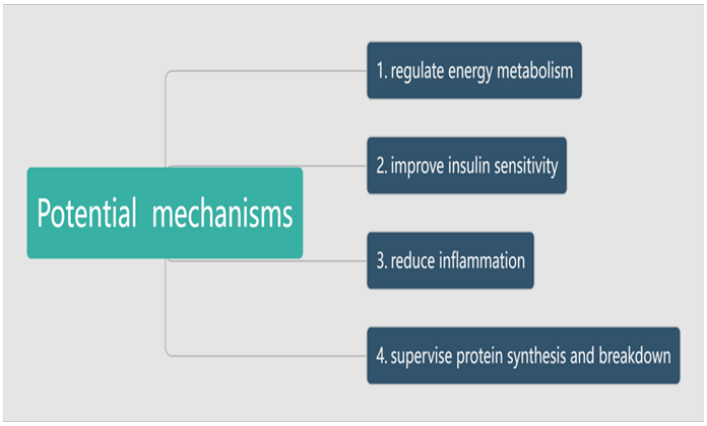

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Figure 3: Patients with type 2 diabetes can exert their beneficial effects on muscle mass and function through SCFA by the following mechanisms regulate energy metabolism,improve insulin sensitivity,reduce inflammation and supervise protein synthesis and breakdown.

5.3. Regulate Energy Metabolism

SCFAs regulates energy metabolism by promoting the oxidation of fat and glucose in skeletal muscle, which leads to increased energy and improved muscle function. Studies have shown that SCFAs plays an important role in maintaining the balance of energy metabolism (mainly glucose metabolism) and increasing the body's insulin tolerance[13,14]. It is estimated that about 80% of all patients with T2DM are overweight or obese, and excessive energy intake leads to ectopic accumulation of adipose tissue in the liver, skeletal muscle and other [15]. SCFAs has also been shown to increase fat oxidation in skeletal muscle, thereby improving muscle function and preventing muscle atrophy. Lin et al [16] found that butyrate, propiate, and acetate prevented high-fat-induced obesity and insulin resistance in mice. Furthermore, SCFAs was able to increase AMP expression and AMP / ATP ratio in skeletal muscle tissue, thereby inducing the activation of AMPK in myotubes and skeletal muscle, and subsequently promoting fatty acid uptake and oxidation, glucose uptake and gluconeogenesis, and inhibiting lipogenesis and glycolytic[17,18].

5.4. Improve Insulin Sensitivity

Insulin resistance is a major risk factor for sarcopenia in T2DM patients. Type 2 diabetes has reduced amino acid metabolism, and insulin resistance increases the activation of the ubiquitin proteasome pathway, causing decreased protein synthesis and increased degradation, leading to degradation of muscle proteins [19].SCFA has been shown to improve insulin sensitivity, which may contribute to reduce muscle loss and improve muscle function. Kimura et al [20] found that the binding of SCFA and GPR-43 inhibited insulin signaling and inhibited adipogenesis in vivo, while the activation of GPR-43 pathway also enhanced insulin sensitivity by promoting the release of GLP-1 in the intestine. CANFORA et al [21] believe that adequate dietary supplementation of some short-chain fatty acids (SCFA) can improve blood glucose levels and enhance insulin sensitivity.

5.5. Reduce Inflammation

Diabetic patients are in a long state of low-grade inflammation, and these inflammatory markers in the body are closely related with insulin resistance [22]. Chronic low-grade inflammation is also an important cause for the development of sarcopenia. Studies have shown that inflammatory markers are negatively associated with muscle mass and muscle strength, and are currently considered the main component of sarcopenia [23]. Long-term chronic inflammatory response and immune disorders make the damaged islet cells and the occurrence of insulin resistance, if no intervention, will eventually lead to the occurrence of T2DM [24]. SCFA is thought to have immunomodulatory effects and can reduce intestinal permeability and reduce inflammatory[25].In the immune system, FFAR2, the receptor of SCFA, expresses[26,27] on eosinophils, basophils, neutrophils, monocytes, dendritic cells and mucosal mast cells. They can modulate the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and promote the release of anti-inflammatory cytokines.Dysregulation of SCFA production may contribute to chronic low-grade inflammation, which is associated with both type 2 diabetes and sarcopenia.

5.6. Supervise Protein Synthesis and Breakdown

SCFAs can supervise the synthesis and breakdown of proteins in skeletal muscle, which leads to an increase in muscle mass and an improvement in muscle function. Administration of short-chain fatty acids, especially butyrate, in aging mouse models may prevent age-related loss of muscle mass and even promotes muscle synthesis [28, 29]. It was shown that after a protein-restricted diet, microbial-derived amino acids, such as threonine and lysine, are incorporated into the free plasma amino acid repertoire [30].This suggests that disruption of the gut microbiota environment may inhibit the production ofby microbial-induced amino acids and may contribute to muscle anabolic resistance [30].Walsh et al [28] found that compared with controls without butyrate, a butyrate-rich 10-week diet improved mitochondrial biogenesis, insulin sensitivity, and muscle (quadriceps and gastrocnemius) quality in older mice, while no significant differences were observed between the younger groups.These data suggest that SCFAs administration may contribute to attenuate muscle anabolic resistance in mice.There is evidence that L. plantarum may exert muscle anabolic effects by enhancing protein assimilation and upregulation of mTOR activation as a molecular driver of muscle protein synthesis [31,32].Altered SCFAs levels may disrupt the balance between protein synthesis and degradation, leading to muscle wasting and sarcopenia.

6. SCFA-Based Microbial Therapy

As mentioned above, short-chain fatty acids have a strong relationship with intestinal microbial metabolites in the treatment of sarcopenia, type 2 diabetes, and the repair of intestinal function. Certain drugs and microbe-directed therapies can be used to help elderly diabetics reduce the incidence of sarcopenia, triggering the gut microbial metabolism in the body. In particular, some bacteria can increase the production of SCFA, which could be one of the treatments for sarcopenia and related diseases.

6.1 Diet Therapy

The production substrates of SCFAs are mainly dietary fiber, resistant starch, and oligosaccharides. Diet structure can directly affect the abundance of SCFAs, and then affect the incidence and therapeutic effect of sarcopenia. Insufficient dietary fiber intake may increase the susceptibility to inflammatory diseases [33], and higher intake of dietary fiber-rich vegetables, fruits and whole grains can slow the progression of sarcopenia. Some studies show that tea leaves can increase the abundance of SCFAs in the intestine. Gao et al [34] found that black tea could increase the α-diversity of the intestinal microflora of Sprague-Dawley rats, regulate the β-diversity, increase the abundance of SCFAs, and enhance the intestinal barrier function. However, due to the variability of

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intestinal bacterial activity, increasing SCFAs generation by dietary fiber supplementation is not predictable and not necessarily stable to reach the desired concentration.

6.2 Probiotics

Probiotics have positive effects in regulating intestinal microecology, enhancing intestinal barrier, and reducing inflammation in the body [35,36].Inulin rich in oligofructose reduces that found in patients with T2DM inflammation, fasting blood glucose, and body mass levels were noted at [37].A murine model of leukemia found that supplementation with specific lactic acid bacteria could selectively target muscle tissue by reducing the expression of inflammation and muscle atrophy markers, thus reducing muscle atrophy [38]. Lactobacillus reuteri and Lactobacillus galneri increased the tibialis muscle weight by 8% (P=0.05) [38]. In a randomized controlled study [39], 52 patients with colorectal cancer were randomized to receive placebo or probiotics containing 30×1010 colony-forming unit (cfu) strains for 6 months after probiotic treatment. This result [39] suggests that probiotics can reduce inflammatory responses by altering the intestinal microenvironment, thereby inhibiting proteolysis of skeletal muscle associated with inflammation. Although probiotics are usually considered safe, lactic acid bacteria, bifidobacteria, white on white, and enterococcus are also found in the infection site, suggesting that probiotics may also have some infectious [40]. Prebiotics refer to certain food residues that are not digested or difficult to digest, which can be directed to stimulate the production of certain probiotics. Synthetic element refers to the composition of prebiotics and probiotics, which can act together on the body [41]. Studies have shown that synthetic elements have a better effect in regulating the intestinal flora than in using probiotics or prebiotics alone [42]. However, it needs to be further explored whether the mechanism of action of probiotics, prebiotic / synthetic probiotics and whether the therapeutic effect are related to the dose used, the proportion of bacteria, and the proportion of probiotics and prebiotics.

6.3 Fecal Bacterial Transplant Therapy

In recent years, studies have shown that the application of fecal microbiota transplantation (FMT) can regulate the composition of intestinal flora, rebuild intestinal microecology, and help reduce the adverse reactions such as malnutrition and muscle loss [35]. Haitao C et al [43] found that FMT in healthy rats was able to inhibit muscle inflammatory response by reducing the expression level of IL-6, and reversed the changes in muscle metabolites and energy metabolism in 5-fluorouracil-treated rats, such as upregulation of pyruvate and lactate, and increased ATP levels in muscle. However, the bacterial maintenance time of the recipient after a single fecal transplantation is generally 3 to 6 months, so the fecal transplantation is required for the recipient after the disappearance of some bacteria[44,45] (Figure 4).

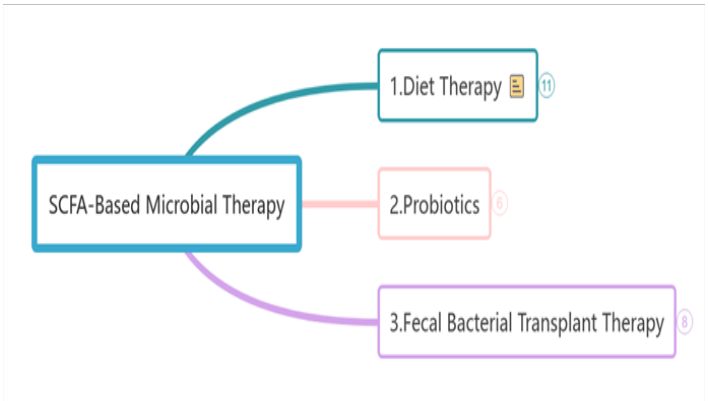

Figure 4: Certain drugs and microbe-directed therapies including diet therapy, probiotics and fecal bacterial transplant therapy can be used to help elderly diabetics reduce the incidence of sarcopenia.These could be one of the treatments for sarcopenia and related diseases.

7. Conclusions

In conclusion, there is a correlation between SCFAs in the intestinal flora and sarcopenia in patients with type 2 diabetes. Dysbiosis-induced alterations in SCFAs production may contribute to insulin resistance, metabolic dysfunction, and muscle wasting, promoting the development and progression of type 2 diabetes and sarcopenia. Consumption of dietary fiber, probiotics or fecal bacteria transplantation is a common strategy to correct the disorder of intestinal flora and increase the intestinal flora metabolite SCFAs. Further research is needed to elucidate the underlying mechanisms and explore potential therapeutic strategies targeting the gut microbiota and SCFAs production for the prevention and treatment of these conditions. It is important to note that the gut microbiota is a complex system influenced by various factors, including diet, lifestyle, and genetic factors. Future research should also investigate the interplay between these factors, SCFAs, and the development of sarcopenia in patients with type 2 diabetes, to better understand and apply this knowledge.

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