Clinical nutrition management of sarcopenia/T2DM utilizing amino acids

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Sarcopenia develops over time as a result of aging, and typically leads to muscle loss, a concurrent increase in fat mass, and a variety of health issues leading to an overall poor quality of life. There is some evidence that sarcopenia may be a contributing to the development of type 2 diabetes mellitus (T2DM) in the elderly, and therefore nutritional management is key in the prevention of both sarcopenia and T2DM. The primary focus of nutritional management lays in the amount and quality of protein intake, which has led to the development of clinical nutritional therapies involving amino acids to improve muscle protein synthesis and decrease sarcopenia symptoms. In the work herein, we present and evaluate data derived from human trials regarding the utilization of hydroxyl-methyl butyrate (HMB), L-leucine (Leu), L-glutamine (Gln) and L-arginine (Arg) supplementation for optimal management of sarcopenia in geriatric patients, a topic of significant clinical nutrition interest which may have important implications in T2DM management.

Keywords: Amino Acids ; Clinical Nutrition ; Medical Nutrition Therapy ; Sarcopenia ; Type 2 Diabetes Mellitus

1. Introduction

Aging is defined as the progression of deterioration with diminishing life functions, gradually leading to the end of life[1]. Aging is a phenomenon that has been well studied, but many factors are involved in this progression, one being the progressive loss of muscle mass over time[2]. Muscle strength is reduced by 8%–10% per decade while an average of 5% of actual mass is lost every decade after the age of 40[3][4][5]. This age-related progressive loss of muscle mass is termed sarcopenia (derived from the Greek σαρξ (sarc): “of flesh”, and πενία (penia): “poverty”, hence sarcopenia literally meaning: “poverty of the flesh/muscle”). While adults age, their risk for sarcopenia increases, as it is typically accompanied by decreased physical activity and protein-energy malnutrition[6][7].

The most common effects of sarcopenia are muscle fiber reduction, muscle atrophy, and decreased oxygen consumption as a result of decreased muscle mass, all without changes in overall body weight but significant changes in body composition[8]. In fact, sarcopenia potentially can lead to weight gain, as the fat to muscle ratio in the body increases[9]. This introduces lateral affects as well, including the increased risk of metabolic consequences, involving insulin resistance and eventual type 2 diabetes mellitus (T2DM) onset[10]. Considering that 80% of glucose clearance is achieved by muscle tissue, under euglycemic conditions[11], it is plausible that a decline in muscle mass and/or quality, may directly and dramatically interfere with glucose clearance capacity, thus leading to hyperglycemic episodes and gradually increased T2DM risk. Improving sarcopenic status may prove critical not only for the muscle functional considerations but also as a means of T2DM prevention and/or management.

Typically, with sarcopenic patients, the major goal of medical nutrition therapy is to prevent/delay further muscle decline, improve muscle mass quality, while support immunity and wound healing. Studies with such patients have evaluated the effectiveness of nutritional supplementation in the clinical setting with very limited evidence, suggesting that there may be some positive effects on muscle mass quality and function through amino acid supplementation[11]. In a 2018 study, 68 individuals aged 70 and older were evaluated for their amino acid profile. Of these participants, 38 had physical frailty and sarcopenia, and 30 non-sarcopenic, non-frail individuals served as controls. It was determined that the sarcopenic individuals had higher serum levels of asparagine, aspartic acid, citrulline, ethanolamine, glutamic acid, sarcosine, and taurine. The non-sarcopenic individuals, on the other hand, displayed elevated amounts of α-aminobutyric acid and methionine only[12]. This provides some insight as to which amino acids truly are necessary for supplementation, and which are the most beneficial for muscle synthesis and/or protection against degradation and loss. Since amino acids are sourced from protein, increased dietary intake of high-quality protein might be an effective mode for stimulating muscle protein synthesis and promoting gains in muscle mass, strength and function, while further enhancing exercise-induced physiological adaptations[13], although whether such practice would practically suffice remains unclear.

Among the four nutritional substrates that affect muscle proteolysis, hydroxyl-methyl butyrate (HMB) is an active metabolic form of leucine (Leu); Leu, along with glutamine (Gln) are essential amino acids (EAA), while arginine (Arg) is a semi-essential amino acid (SEAA). All of the aforementioned compounds extend anti-catabolic and anabolic stimuli for muscle synthesis, performance and immune system improvement[13][14]. Further, Gln is one of the most abundant amino acids that may become essential in critical conditions[15]. A mixture of HMB, Leu, Gln and Arg was recently evaluated in the context of nutritional status, quality of life, treatment side effects, serum parameters, anthropometric data, and bioavailability in elderly patients undergoing cardiac surgery[16]. HMB, Gln and Arg were shown to be effective in slowing muscle loss and reducing circulating levels of muscle protein amino acids [16].

The work presented investigates and discusses the limited available evidence regarding strategies of supplementation, including amino acids. Although not commonly used, such strategies show promise for the nutritional management of sarcopenia with potential implications for T2DM.

2. Considerations for HMB, Gln, Arg, Leu

2.1. *Supplementation with HMB*

HMB has been shown to extend a notable antica abolic effect on skeletal muscle by minimizing muscle damage and muscle proteolysis[17]. It is thought that HMB affects muscle mass in its own right, independently of Arg and Gln[17]. HMB, in conjunction with Arg and Gln, improves nitrogen metabolism in critically ill patients, increases protein synthesis over prolonged use and has been demonstrated to reduce protein degradation, thereby effectively defending lean body mass[18][19]. Several studies have linked HMB supplementation with extended anti-inflammatory effects[20], reduced muscle degradation[18], and increased lean muscle mass[21], suggesting that HMB could be a beneficial dietary supplement to reduce sarcopenia risk in elderly patients.

2.2. Supplementation with Leu

Leucine is an essential dietary amino acid that is responsible for signaling muscle protein synthesis[20] and is of particular interest due to its association with whey protein. In several studies, whey protein supplementation has been shown to increase muscle protein synthesis[23] and improve muscle strength[24], even in the absence of exercise. However, it has also been reported that elderly patients need more whey protein than younger adults to achieve full effect[25].

It appears that increasing Leu intake chronically via the consumption of an overall high protein diet is the most effective dietary intervention toward increasing lean mass or attenuating the loss thereof during aging. However, more research investigating the optimal dose and timing of protein ingestion is necessary. Several studies have demonstrated that decreases in postprandial muscle protein synthesis as a result of increased circulating oxidative and inflammatory markers, contribute more than muscle protein breakdown to the decreases in muscle mass during disease and healthy aging[26]. Dietary interventions reducing oxidative/inflammatory stress, combined with higher protein quality and intake amounts able to overcome anabolic resistance, may enhance muscle protein synthesis response to feeding, and either increase muscle mass or attenuate loss depending on the case. Nonetheless, it remains unclear as to why chronic Leu supplementation, despite its powerful effects on acute muscle protein synthesis, only sometimes translates into increased muscle mass when evaluated chronically.

2.3. Supplementation with Arg

Arginine is a semi-essential amino acid and a precursor to nitric oxide, a major signaling molecule and vasorelaxant [27]. Supplementation with Arg has also been investigated, but it has been demonstrated that Arg supplementation alone is not enough to prevent muscle deterioration[28][29][30]. However, when combined in an essential amino acid supplement, it does appear to be effective[28][30]. Therefore, it is likely that the addition of Arg to a dietary supplement may be beneficial due to the fact that it signals hormone secretion that may be important for muscle mass development[32][33].

2.4. Supplementation with Gln

Glutamine is one of the most abundant amino acids in the body, produced mostly in skeletal muscle and metabolized by the intestine, kidney and liver[15]. Gln is not considered essential, but it can become essential in critical conditions[15]. Like Arg, it does not appear that Gln supplementation alone is enough to prevent muscle wasting. However, it has been seen to prevent muscle atrophy when paired with branched chain amino acids (BCAAs)[34], making it of interest in terms of its potential agonistic function.

While there is no single supplement that can effectively treat sarcopenia, it appears that co-supplementation with the discussed amino acids may address the major issues associated with sarcopenia, creating a more promising course of treatment through synergistic benefits (Table 1).

Table 1. Summary of various amino acid supplementation regimes and their effects on health outcomes associated with sarcopenia.

Treatment	Inflammation Prevention	Increased Muscle Protein Synthesis	Reduced Muscle Deterioration	Increased Glucose Tolerance	Other Supplementation Required?	References
HMB	Yes	Yes	Yes	No	Yes	20, 21
Leu	No	Undetermined	No	Yes	Yes	35, 23
Gln	No	Yes	Yes	No	Yes	20, 34
Arg	No	Yes	No	No	Yes	20, 29, 31

2.5. Concurrent Therapies for Type 2 Diabetes Mellitus and Sarcopenia

Since 80% of glucose clearance occurs via the muscle[14], a decrease in muscle mass and muscle quality, as a result of sarcopenia, can lead to a series of issues leading to T2DM development. This relationship has been observed, finding that T2DM is negatively associated with relative muscle mass changes[35][36]. Metabolic syndrome has also been found to be negatively associated with all measures of muscle quality[36].

Moreover it has also been observed that antioxidant and anti-inflammatory aspects of diet, seem to enhance defense of lean body mass, while simultaneously improving metabolic function and reducing the risk of insulin resistance and subsequent T2DM[37]. Therefore, the addition of a dietary supplement that includes HMB, Arg, Gln, and Leu could potentially encompass all areas that lead to muscle deterioration and sarcopenia, effectively decreasing sarcopenia and T2DM risk.

There is an evident relationship between sarcopenia and insulin resistance, and subsequently T2DM, where muscle mass degradation leads to decreased glucose clearance, resulting in increased insulin resistance and T2DM. There is also evidence suggesting that the addition of dietary supplements enriched in certain amino acids leads to improvements in muscle strength and muscle mass gain. The connections between sarcopenia, amino acid supplementation, and T2DM prevention have been supported by the literature, and evidence pointing towards a dietary supplement composed of HMB, Leu, Gln, and Arg is present, as highlighted herein. HMB and Leu have certainly been explored as sarcopenia treatment, where they function to increase muscle protein synthesis. HMB has also been reported to have upregulated function when paired with Arg and Gln. Arg does not appear to prevent muscle deterioration alone, but when combined with HMB and Leu its effectiveness seems to be increased. Similar results have also been obtained with Gln alone and in combination with other amino acids. Therefore, no individual amino acid has been established to be adequate in preventing muscle deterioration, sarcopenia, and ultimately T2DM risk. However, in certain combinations, it does appear that a dietary supplement of the above-mentioned amino acids may stimulate an increase in muscle mass and muscle strength in sarcopenic elderly individuals, possibly decreasing T2DM risk, while mitigating sarcopenic effects. The optimal duration or dosing in an ideal mixture both remain important, as yet still unfulfilled, factors.

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