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Essential Amino Acid Ingestion as an Efficient Nutritional Strategy for the Preservation of Muscle Mass following Gastric Bypass Surgery

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Abstract

Loss of skeletal muscle in patients that have undergone gastric bypass is a consistent observation. Skeletal muscle constitutes the largest protein/amino acid pool in the body, and loss of skeletal muscle has important implications in health and disease. Sustaining a given level of muscle protein requires a balance between the rates of muscle protein synthesis and breakdown. Current evidence suggests that reduced rate of protein synthesis is implicated in the loss of muscle after gastric bypass. This is not surprising given a less than optimal dietary protein intake following the gastric bypass and because, unlike other macronutrients, protein/amino acids are not stored in the body. Ingesting essential amino acids, which cannot be synthesized de novo and have the primary role in the regulation of muscle protein synthesis, can potentially ameliorate loss of muscle protein after gastric bypass. At the same time, ingestion of essential amino acids provides a more efficient nutritional approach (i.e., greater stimulation of protein synthesis relative to the amount of amino acids ingested) to enhance muscle protein synthesis compared to the ingestion of intact protein in the gastric bypass patient. Changing current dietary practices towards increasing ingestion of essential amino acids provides an approach that can potentially prevent loss of lean body tissue and ultimately achieve a more sustained level of health in patients that have undergone gastric bypass.

Keywords

protein; supplements; muscle; weight loss surgery

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Introduction

The greatest rate of increase in obesity in the US over the last few years is observed in individuals with severe obesity (BMI≥40; [1]). Although obesity cases over the next 20 years are expected to increase by ~30%, the cases of severe obesity are expected to grow by ~130% [2]. Individuals with either BMI ≥40 or BMI ≥35 with co-morbid conditions are candidates for bariatric surgery when less invasive approaches of weight loss fail to address the body weight/co-morbidity [3]. Bariatric surgery has become more frequent over the last ten years, with more than 340,000 procedures performed worldwide in 2011 [4]. One third of these procedures were performed in the US/Canada [4].

Bariatric surgery is expected to play an even bigger role in addressing the obesity epidemic in the near future, as benefits beyond weight loss are continuously described and bariatric procedures are recognized as effective treatments for Type 2 diabetes [5–7], hyperlipidemia [5, 6, 8, 9], hypertension [5–7], fatty liver disease [10, 11], and obstructive sleep apnea [5, 7], and ultimately linked to improved quality of life. When the effectiveness of the bariatric procedures is considered in parallel with the dramatic decrease in the mortality rates associated with these procedures [12, 13], and the fact that recent technological advances have made such procedures safer and more readily available, it is reasonable to expect that the number of obese individuals undergoing bariatric procedures will grow.

Among the bariatric procedures employed, Roux-en-Y gastric bypass (RYGB) has been the most preferred form of bariatric surgery [4, 14, 15]. Although gastric bypass effectively addresses the need for weight loss and improves health and quality of life, an interest has been built in the scientific and medical communities regarding the long-term effectiveness and risks associated with the gastric bypass [16]. RYGB results in loss of body weight associated with loss of not only fat tissue, but also fat-free tissue [17, 18]. RYGB patients lose on average 17% of limb lean tissue mass during the year following the procedure [18], a loss that is considerably greater than that of even an age-associated loss of lean tissue observed at a comparable period of time in older adults (i.e., only about 0.8%) [19]. Currently, there are no effective approaches to prevent the loss of lean body mass following gastric bypass.

Importance of lean body mass and skeletal muscle in health and disease

When protein intake is restricted or limited, skeletal muscle protein and its breakdown have the primarily role in replenishing the plasma amino acids taken up by tissues (i.e., liver, heart, skin) [20, 21], and in maintaining the protein levels in these tissues given the constant breakdown of protein. When nutrients, such as carbohydrate, are also absent, amino acids support the process of hepatic gluconeogenesis [22] to sustain plasma glucose homeostasis. Amino acids from skeletal muscle protein breakdown provide also the substrate for the synthesis of acute phase protein in the liver during stress states, such as sepsis or tissue injury [23].

Low lean body mass is associated with increased rates of mortality in patients with heart disease [24], cancer [25], burn injuries [26] and peritoneal dialysis [27]. There is a direct role of skeletal muscle mass in regulating optimal bone “mass” over the course of life [28],

and skeletal muscle mass is correlated positively with bone mineral density [29]. At the same time, decreased skeletal muscle mass in older adults is associated with increased risk of falls [29]. Increased lean body mass, on the other hand, is positively associated with whole-body resting energy expenditure, and skeletal muscle is an important contributor to whole-body energy expenditure [30]. Variations in the muscle component of lean body mass are largely responsible for variations in resting energy expenditure because of the muscles' overall size and the possible variations in muscle mass that are observed within and between individuals [31].

Concerns related to loss of skeletal muscle specific to the RYGB patient

Because low lean body mass is linked to increased mortality rates under various pathophysiological circumstances (i.e., heart disease, cancer, burn injuries, etc.), decrease in lean body mass after RYGB can offset positive effects stemming from the gastric bypass itself on overall health/mortality if such pathophysiological circumstances were to arise in the RYGB patient. The loss of lean tissue in the RYGB patient is documented as a dramatic decrease in skeletal muscle [32]. Because of the direct link between skeletal muscle and resting energy expenditure [30], it is not surprising that reduction in skeletal muscle in patients that have undergone gastric bypass is manifested in parallel with a reduction in the resting energy expenditure [18, 33]. At the same time, because the processes implicated in the synthesis of proteins in skeletal muscle contribute largely to the energy expenditure of the resting muscle [31], a decrease in the rate of muscle protein synthesis after RYGB results in decreased rate of not only absolute resting energy expenditure but also resting energy expenditure for a given amount of muscle [18, 34]. This decrease in the overall rate of resting energy expenditure in RYGB patients has been linked to undesirable weight re-gain observed in such patients over time [18, 35].

The loss of lean body tissue after bariatric surgery is a clinical concern that has only recently received attention. Maintaining lean body tissue while decreasing fat tissue in the months following the RYGB procedure is particularly important for the RYGB patient in the effort to achieve successful long-term outcomes [17, 36]. It is also important to note that the majority of patients undergoing gastric bypass intervention are between 40 and 50 years old [37], a period in life coinciding with an age-associated initiation of accelerated muscle loss [38, 39]. Furthermore, given the current evidence showing that bariatric procedures are an effective clinical approach to address pathophysiological circumstances also associated with older adults (i.e., > 65 years of age) [40], rates of gastric bypass in older individuals are expected to grow. Under these circumstances, the effects of age itself on muscle loss combined with the undesirable effects of gastric bypass on muscle protein metabolism can considerably accelerate the age-associated loss of muscle mass in the older RYGB patients.

Effectiveness of current interventions to ameliorate loss of muscle after RYGB

Adequate protein intake is a common recommendation for patients that have undergone gastric bypass [36, 41]. Decrease in lean body mass in gastric bypass patients, however, is observed despite dietary counseling to consume adequate amounts of protein and in the

absence of clinical evidence for protein malnutrition [18]. Protein intake apparently becomes particularly important in patients that have undergone RYGB when considering that in these patients the concentrations of plasma amino acids decrease after the gastric bypass [42–44]. Unlike other macronutrients, protein is not stored, and accretion of protein in muscle occurs when the concentration of amino acids in plasma increases during the postprandial period [45–48]. Specifically, during the postprandial period, plasma amino acids stimulate the protein synthesis in muscle by providing substrates for synthesizing proteins as well as by activating the mammalian target of rapamycin (mTOR) signaling pathway that initiates the mRNA translation process [49, 50]. The mTOR enzyme is a key nutrient sensor that is physiologically important for cell growth and proliferation. When activated by amino acids, mTOR initiates a series of processes that enhance the rate of protein translation/synthesis in skeletal muscle. The specific mechanisms involved in the signaling process, as well as the physiological importance of mTOR signaling in stimulating muscle growth have been reviewed in more details previously [51, 52].

Despite the emphasis on increased protein consumption, the recommended protein intake cannot be met by RYGB patients up to one year after the gastric bypass [53, 54], by which time a large amount of lean body tissue has already been lost [18]. It is not surprising, therefore, that although current clinical recommendations emphasize the need for adequate intake of protein, patients that have undergone gastric bypass still experience loss of lean body tissue.

Contributors to loss of muscle mass in the RYGB patient

Protein balance in skeletal muscle is maintained at any given time by a balance in the rates of protein synthesis and breakdown. Loss of muscle in RYGB patients, therefore, will be the direct result of decreased protein synthesis, increased protein breakdown, or both. Although direct evidence is currently lacking, decreased rate of muscle protein breakdown in the presence of decreased lean body mass following RYGB [18] suggests that the rate of synthesis of muscle proteins after RYGB also decreases. It is interesting that the decreased rate of muscle protein breakdown, which apparently provides a protective effect with respect to loss of muscle in RYGB patients, disappears after six months following the gastric bypass procedure [18]. In this case, it is possible that these patients may lose even greater amounts of muscle in the long term as a result of both an elevation in the rate of muscle protein breakdown when compared to the six-month post-RYGB period, and a continued decreased rate of protein synthesis after six months. Following RYGB, the proximal intestine where the majority of protein is absorbed is bypassed, and the protein absorptive process is relegated and limited to the distal parts of the gastrointestinal tract. Along with a decrease in the production of relevant digestive enzymes after RYGB, it has been suggested that these changes contribute to protein malabsorption in the RYGB patients [41]. Even in the absence of malabsorption, it is difficult for patients that have undergone RYGB to consume the recommended 70–100 grams of protein per day in the months immediately following the procedure [41]. When considering the reduction of the size of the stomach after RYGB, the ability to eat large volumes of food and therefore consume adequate amounts of protein is limited. Furthermore, nausea, vomiting, and food intolerance, common observations following the RYGB, result in less than optimal intake of dietary protein [36, 54].

Essential amino acids ingestion as a viable nutritional approach to prevent loss of muscle after RYGB

Although it is the increase of amino acids directly in plasma that is responsible for the stimulation of muscle proteins synthesis, oral administration of amino acids provides a practical advantage when compared to infusion of amino acids to increase the plasma amino acid concentrations. It is the stimulation of protein synthesis by the plasma amino acids over the course of the day and on a regular basis that enhances sufficiently the muscle protein synthesis, and in a way that maintains muscle mass. Currently, available evidence in older sarcopenic individuals indicates that ingested amino acids stimulate muscle protein synthesis similarly to that of intravenously infused amino acids [55]. Although theoretically the appearance of ingested amino acids into the plasma may be altered as a result of the gastric bypass, there is no evidence that RYGB affects the absorption of free amino acids. It can, however, affect the absorption of protein-associated amino acids because of decreased production of pancreatic enzymes that contribute to protein malabsorption after RYGB [41], arguing for the importance of the ingestion of free amino acids to more effectively increase the concentration of amino acids in plasma.

Because muscle protein breakdown is already decreased following RYGB [18], approaches that effectively stimulate the synthesis of protein in muscle are of primary importance in order to maintain muscle and lean body tissue in post-RYGB patients. Following RYGB, the decrease in plasma amino acid concentrations is observed specifically in the essential amino acids (EAA) pool [42, 43]. Also, absorption of branched chain amino acids (i.e., leucine, isoleucine, valine) appears reduced following intestinal bypass procedures [56]. Because the plasma EAA, when compared to the non-EAA, are primarily responsible for stimulating muscle protein synthesis [57, 58], and leucine is unique among the EAA in stimulating muscle protein synthesis [59], the specific decrease in the concentrations of plasma EAA, including leucine, is of particular concern when it comes to the role of plasma amino acids in stimulating protein anabolism in the muscle of RYGB patients. These concerns suggest the need for more targeted nutritional approaches that specifically increase the plasma concentrations of EAA to stimulate the synthesis of protein in the muscle of RYGB patients, and ultimately preserve muscle tissue during the post-RYGB period. Provision of EAA to increase plasma EAA concentration is important in any effort to maintain muscle protein synthesis because EAA cannot be synthesized de novo. In this regard, studies investigating the efficacy of intravenous versus orally-administered EAA to stimulate muscle protein synthesis after gastric bypass can effectively address the question of the dose of EAA necessary to maximize muscle protein synthesis in these patients.

Ingestion of amino acids in their free form allows manipulation of the amino acid content of the ingested amino acids by incorporating twice as much EAA for a given amount of energy or weight of amino acids found in intact protein, given that intact protein inevitably contains as much as 50% non-EAA. It is noted that, unlike the EAA that need to be provided through the diet, non-EAA can be synthesized in the body and therefore, directly participate as substrates for protein synthesis without the need to be obtained through diet. At the same time, ingestion of free amino acids allows enriching the EAA mixture with leucine. EAA,

and particularly leucine, are powerful stimuli of molecular mechanisms implicated in muscle protein synthesis by activating the mTOR and its downstream targets involved in mRNA translation initiation, such as ribosomal S6 kinase 1 and eukaryotic initiation factor 4E-bindings protein 1 [49, 50]. Previous evidence has shown that the RYGB does not affect either the basal mTOR phosphosphorylation or the insulin-stimulated increase in mTOR phosphorylation [43], suggesting that mTOR signaling remains responsive to physiological stimuli, including amino acids, following gastric bypass.

Based on the above discussion, a nutritional approach that emphasizes EAA can maximize the acute anabolic response within muscle for any given amino acid load ingested in the form of dietary protein or protein supplement by the RYGB patient. Further support for this argument comes from findings showing that ingestion of EAA results in greater stimulation of muscle protein synthesis compared to intact protein in older individuals [60]. In this regard, EAA can be consumed in the form of supplements between meals or replace protein supplements, commonly used by these patients. There is clear need for studies that will determine the composition and smallest amount of EAA that optimize the acute stimulation of muscle protein synthesis in gastric bypass patients and demonstrate the efficacy of EAA ingestion in preventing loss of muscle in the RYGB patient. Such an efficient stimulation of muscle protein synthesis is particularly important during the early period after the RYGB when the amount of food that can be reasonably consumed is very small.

From a practical perspective, EAA in their free/powder form can be incorporated in the form of liquid supplements (i.e., dissolved), and as part of the overall patient's diet in the months following the RYGB, and similar to current approaches related to protein supplementation. We have shown that as little as 7 grams of a leucine-enriched EAA supplement is sufficient to acutely stimulate muscle protein synthesis in older sarcopenic adults. Approximately 7 [61] or 11 [62] grams of EAA consumed twice daily improve lean body mass at 3–4 months after the initiation of the supplementation in the latter population, and in association with improvements in muscle protein synthesis [61]. Additionally, 20 grams of EAA consumed twice daily for 3 weeks attenuated the loss of muscle resulting from total knee arthroplasty [63]. Although research is needed to test the efficacy of such intervention specifically in the RYGB patient, these lines of evidence provide strong support for ingestion of small amounts (i.e., 7–20 grams) of EAA in a similar fashion (i.e., daily supplements) as a potential nutritional strategy to improve muscle protein synthesis and ameliorate loss of lean body mass in gastric bypass patients.

Conclusions

Patients undergoing gastric bypass lose substantial amounts of muscle following the procedure. Currently, there are no dietary approaches that have been demonstrated to preserve muscle mass following gastric bypass. Changing current dietary practices towards increasing ingestion of essential amino acids provides an approach that can potentially prevent loss of lean body tissue and ultimately achieve more sustained level of health in patients that have undergone gastric bypass.

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Highlights

- Loss of skeletal muscle is common observation following gastric bypass.
- Preventing loss of muscle is key to achieve long-term success after gastric bypass.
- EAA ingestion improves muscle mass under various pathophysiological conditions.
- EAA can be a nutritional strategy to prevent loss of muscle after gastric bypass.