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SARCOPENIA UPDATE: ANABOLIC RESISTANCE PART III: IDEAS ON CLINICAL MANAGEMENT

INTRODUCTION

In part III of this series I would like to continue my discussion on supplemental leucine by reviewing still more research that demonstrates its positive impact on muscle protein synthesis. Then I will discuss some fascinating research on how supplemental leucine can assist in maintaining an optimal balance between anabolic hormones such as insulin and catabolic hormones such as cortisol and glucagon.

STILL MORE RESEARCH ON THE ABILITY OF LEUCINE SUPPLEMENTATION TO ENHANCE MUSCLE PROTEIN SYNTHESIS

A study published just this month adds even more weight to the suggestion that supplemental leucine can play an invaluable role in a comprehensive dietary and exercise program that is designed to optimize muscle protein synthesis. In "Leucine supplementation of a low-protein mixed macronutrient beverage enhances myofibrillar protein synthesis in young men: a double-blind, randomized trial" by Churchward-Venne et al (1) the authors evaluated 40 men between 18 and 35 years of age. All were students at McMaster University in Canada. In the quote below the overriding goal of the study is highlighted:

> **"The aim of the current study was to assess the potential to enhance the effect of a dose of protein that contained quantities of essential amino acids (EAA) previously shown to be suboptimal in maximally stimulating muscle protein synthesis (MPS) rates with feeding and after exercise on MPS rates when ingested as part of a macronutrient beverage."**

Before continuing, please note the clinical relevance of the approach taken by the authors. Instead of examining the impact of ingested nutrients in isolation, as is so often done in studies such as this, Churchward-Venne et al (1) are creating a more "real life" study design where different amounts of protein, leucine, and other branched chain amino acids are ingested as part of a mixed macronutrient meal. The authors continue with the specific study parameters:

> **"Subjects were randomly assigned to a positive control [25 g of whey protein (W25); 3.0 g leucine], a negative control [6.25 g whey protein (W6); 0.75 g leucine], or treatments that consisted of 6.525 g whey supplemented with a lower dose of leucine [6.25 g whey supplemented with leucine to 3.0 g total leucine(W6+Low-leu), a higher dose of leucine [6.25 g whey protein supplemented with leucine to 5.0 g total leucine (W6+High-Leu), or a higher dose of leucine plus isoleucine and valine [6.25 whey protein supplemented with leucine, isoleucine, and valine to 5.0 g total leucine (W6+BCAAs)."**

What were the results of the study? As you will see, the amount of leucine was the overriding factor. In fact, the amount of leucine was so important that those who ingested only 6.25 g of whey protein plus leucine demonstrated the same impact on MPS as those who ingested 25 g of whey protein:

> **"Our results showed that the addition of a higher dose of leucine to a smaller amount of protein (6.25 g) within a mixed macronutrient beverage enhanced MPS to the same level as that seen with 4 times as much whey protein."**

As I hope you realize, in today's very cost-conscious world, this finding carries tremendous importance. Per unit volume, a quality whey protein is much more expensive than leucine. Therefore, by adding supplemental leucine to a whey protein-based beverage, it may be possible to reduce the amount of whey protein ingested by your patients without sacrificing clinical efficacy, leading to substantial cost savings for your patients.

In the following quote, the authors elaborate on this important finding:

> **"Consistent with our previous results when we used protein feeding alone, we showed that a low dose of protein (W6) was suboptimal for the stimulation of maximal MPS rates compared with 4 times as much whey protein (W25) even within a mixed macronutrient beverage over the aggregate 0-4.5h postprandial period. The supplementation of this low-protein dose with a high proportion of leucine (W6+High-Leu) stimulated MPS to an equivalent magnitude and duration as that stimulated after ingestion of an energy-matched mixed macronutrient beverage that contained W25."**

Did the addition of other branched chain amino acids (Isoleucine and valine) have a positive impact?

You may have intuitively thought that the answer to this question would be yes. Surprisingly, the opposite occurred:

> **"Contrary to our hypothesis, the W6+BCAAs treatment resulted in MPS rates that were less robust than with W6+High-Leu and W25 treatments. These differences occurred despite the fact that supplemental isoleucine and valine attenuated the decline in concentrations of these amino acids in the blood compared with that observed after the high W6+High-Leu treatment; however, intracellular concentrations of isoleucine and valine were not different between these treatments."**

In contrast, protein plus BCAAs did lead to lower levels of intracellular leucine and other measurements of leucine status compared to what was seen with the W6+High-Leu treatment. Why were these findings observed? The authors hypothesize:

> **"Because BCAAs share a common intestinal transporter, differences in amino acid appearance profiles between W6+BCAAs and W6+High-Leu treatments likely represents antagonism between BCAAs for uptake from the gut, which is congruent with data showing that isoleucine and valine compete with and can impede leucine absorption. The same effect could be true for the transsarcolemmal BCAA transport because BCAAs share the same transporter at that site."**

Before continuing, I would like to comment on these findings because they address a longstanding controversy in clinical nutrition about the possible adverse effects of ingesting single amino acids on the metabolism of other amino acids. First, the quotes above affirm the need for concern about the impact of single amino acid supplementation on the absorption and metabolism of other amino acids. However, when considering BCAAs we need to decide how specifically to direct this concern. For, it appears that administration of a BCAA blend will yield lower absorption levels of each BCAA compared to administration of the BCAAs separately. In addition, it appears that administration of all the BCAAs will adversely impact intracellular uptake of leucine, which in terms of a BCAA hierarchy, is the most important when MPS is considered. Because of this hierarchy in relation to MPS, I therefore feel that we need to reconsider the long standing practice of administering all BCAAs together when attempting to stimulate MPS. Given the results of the Churchward-Venne et al study (1), it may be wise to administer only leucine when trying increase MPS. However, could long-term leucine administration have a detrimental impact on isoleucine and valine metabolism? This question will be answered at the end of this newsletter when I discuss the paper by Leenders and van Loon (2).

The impact of the carbohydrate and fat portion of a mixed meal on the ability of protein and leucine to stimulate MPS

As I have stated previously in other newsletters, some published literature has suggested that ingesting the carbohydrate maltodextrin in conjunction with a protein-based supplement would yield an additive effect due to its ability to optimize insulin metabolism. Can the same be said for all carbohydrates? In addition, can the same be said for fat? As noted in the following quote from the Churchward-Venne et al (1) study, the answer is no. The carbohydrate source in the beverage used by the authors was sucrose. In addition, the fat source was hydrogenated coconut oil:

> **"A novel aspect of our current study was that protein and amino acids were co-ingested with carbohydrate and fat. In our previous work, in which protein and free amino acids were ingested in isolation, the supplementation of 6.25 g whey to contain 3.0 g leucine induced peak blood amino acid concentrations ~550.0 μM, whereas in the**

current study, the same protein dose supplemented up to 5.0 g leucine was necessary to achieve similar peak blood leucine concentrations when co-ingested with carbohydrate and fat as part of a mixed micronutrient beverage. Thus, as has been reported previously, the co-ingestion of protein with additional macronutrients attenuated the post-prandial rise in blood amino acid concentrations."

However, in contrast to what the authors state, as I alluded above, I do feel that we cannot extrapolate the findings in the above quote to all fats and carbohydrates such as maltodextrin. For, as I guess we would all agree, ingestion of sucrose and hydrogenated coconut oil could induce adverse effects on general metabolism that affect blood amino acid levels in ways that have little or nothing to do with the relatively simple issues that relate to intestinal uptake. More will be stated on the controversy about the wisdom of ingesting other macronutrients along with protein when attempting to optimize MPS and anabolic function when I review the Leenders and van Loon (2) study towards the end of this newsletter.

In concluding their paper, Churchward-Venne et al (1) emphasize how leucine co-administration can make a relatively low dose of whey protein much more effective in terms of stimulating MPS:

"In conclusion, our results show that, when a suboptimal dose of protein (6.25 g) is supplemented with a relatively high dose of leucine (W6+High-Leu), rates of MPS are equivalent in both magnitude and duration to those observed after ingestion of an energy-matched beverage containing a…25 g dose of protein. These findings show that, within the context of mixed macronutrient intake, suboptimal protein doses can be made more effective in stimulating MPS through the addition of a high proportion of free leucine. This effect may be of importance in the development of nutritional formulations designed to promote skeletal muscle metabolism, which may be of particular significance to individuals in whom total protein intake is restricted or inadequate."

Before moving on to another study, please recall again that benefits reported in the Churchward-Venne et al (1) concerning MPS occurred in young men engaging in resistance exercise and ingesting leucine as a supplement to a protein powder. The reason I am emphasizing this point again is to set up the discussion that follows on another study that considers young people engaging in endurance exercise and ingesting an essential amino acid supplement enriched with leucine. Will leucine supplementation in this context still have a positive impact?

<u>The impact of essential amino acid (EAA) supplementation enriched with additional leucine in relationship to endurance exercise</u>

When added to an EAA supplement with endurance exercisers, could additional leucine have the same impact on MPS as when leucine is added to a whey protein supplement with weight-bearing exercisers? This question was answered by the paper "Leucine-enriched essential amino acid supplementation during moderate steady state exercise enhances postexercise muscle protein synthesis" by Pasiakos SM et al (3).

The first quote I would like to feature from this paper addresses why results from research on supplementation and weight bearing exercise cannot be extrapolated to research on supplementation and endurance exercise:

"In contrast with resistance exercise, sustained endurance exercise is mainly catabolic, yielding simultaneous reductions in MPS and plasma leucine concentrations during exercise, which may be attributed to the metabolic demand for BCAAs in exercising skeletal muscle."

Given the traditional heavy focus in our society on endurance exercise as being the preferred and most common form of exercise, I feel the information in this quote, without question, warrants major emphasis. As I have noted in several newsletters and presentations, the primary, overriding goal with our chronically ill patients is to change the anabolic/catabolic balance from an emphasis on catabolic physiology, which promotes chronic inflammation, insulin resistance, sarcopenia, and a whole host of chronic signs and symptoms to an emphasis on anabolic physiology, which promotes a balance of inflammatory mediators, optimal insulin sensitivity, increases in muscle mass, and resolution of signs and symptoms. While there is certainly a place for traditional endurance exercise (such as walking, jogging or swimming) because of its positive impact on aerobic capacity and cardiovascular function; excessive amounts (which happens with alarming frequency with many endurance exercisers) can, as suggested in the quote above, actually <u>retard</u> our efforts to create emphasis on anabolic physiology and exacerbate signs and symptoms. With this in

mind, the Pasiakos et al (3) study addresses an important question as to whether leucine supplementation can retard the catabolic effects of excessive endurance exercise.

What can be stated about the participants in the study? The authors point out:

> **"The volunteers were free-living, active-duty military personnel who participated regularly in a combination of endurance (ie, running/marching) and resistance-type exercise (ie, calisthenics/free weights) 3-4d/wk as part of their standard military physical training regimens."**

The final report included results on 7 men and 1 woman aged 24 ± 2 years.

The design of the experiment was as follows:

> **"This 13 d randomized, crossover study included 2 identical assessments of protein turnover and intracellular signaling (days 8 and 13). The only variation on protocol days was the randomly assigned EAA supplement consumed during exercise, either an EAA or a leucine(L)-EAA drink."**

What about the baseline diet? As you may recall from part II of this series, I had some concerns about the studies I reviewed concerning the possibility that dietary intake of protein was too low. In this study, in contrast, daily dietary protein intake was within ideal ranges based on the research discussed in past newsletters:

> **"Macronutrient distribution was consistent with the study design; mean protein intake was 1.2 ± 0.1 g per kg^{-1}, with the remaining energy derived from carbohydrate (55 ± 3%) and fat (32 ± 2%)."**

The next quote discusses the specifics of the exercise regimen and its timing in relation to the time of ingestion of the amino acid supplement:

> **"After resting for 30 min, the volunteers began a 60-min bout of moderate steady state (ie, endurance) exercise (60 ± 5% VO_2 peak) on a cycle ergometer (Lode BV). Intensity was verified at 3 time points by using indirect calorimetry, and the workload was adjusted accordingly for accuracy. Throughout the exercise bout, the volunteers consumed equal volumes (~125 mL) of either the L-EAA or EAA supplement in 20-min intervals to minimize potential disturbances in isotopic steady state, beginning immediately after exercise initiation and ending at the completion of the exercise bout."**

What was the amino acid content of each type drink? The authors note:

> **"Isonitrogenous L-EAA and EAA drinks were dissolved in water (500 mL) with artificial sweetener. The experimental drink (L-EAA) provided 3.5 g leucine, whereas the control EAA supplement provided 1.87 g leucine. The percentage of leucine provided in the L-EAA and EAA drinks was based on earlier reports indicating changes in protein turnover and intracellular signaling when similar EAA supplements were consumed."**

What were the results of this study? Pasiakos et al (3) point out:

> **"The major finding from this applied human trial was that consumption of an EAA supplement enriched with leucine throughout moderate steady state exercise enhanced postexercise MPS by 33% when compared with an isonitrogenous EAA control. To the best of our knowledge, this was the first study to assess whether increasing leucine provision during endurance-type exercise by dietary supplementation enhances muscle protein anabolism in recovery. Until now, studies assessing the skeletal muscle anabolic response to increased leucine concentrations of an EAA- or protein-containing supplement have been performed at rest and after resistance exercise."**

Before continuing, please keep in mind that both formulas stimulated MPS. However, the L-EAA blend performed the task 33% better. Why was this positive MPS response seen? The authors comment:

> **"The MPS responses observed after L-EAA and EAA supplementation may be attributed in part to alterations in whole-body protein turnover. We suspect that increasing leucine availability during endurance-type exercise with L-EAA supplementation spared endogenous protein stores to a greater extent than did EAA alone, which contributed to the greater stimulation of MPS."**

Pasiakos et al (3) then further comment on why the L-EAA blend performed better:

"In the current study, observed differences in MPS may have been influenced by plasma amino acid availability. Although fluctuations in EAA and BCAA concentrations were similar between L-EAA and EAA trials, plasma leucine concentrations were higher with the consumption of L-EAA than of EAA and remained elevated throughout recovery."

In addition, it appears that the combination of L-EAA and endurance exercise enhanced intracellular amino acid metabolism. Why is this important to note? The authors state:

"…recent publications suggest that intracellular amino acid transport and subsequent amino acid concentrations are critical rate-limiting steps in amino acid metabolism that modulate MPS."

With this important point in mind, the authors hypothesize about the findings of their study:

"…our findings do suggest that increasing plasma EAA concentrations, particularly with leucine, combined with endurance-type exercise may upregulate muscle intracellular amino acid kinetics, resulting in greater MPS during recovery."

In concluding their study, Pasiakos et al (3) summarize their findings:

"In summary, consumption of a 10-g dose of EAA enriched with leucine during moderate endurance-type exercise stimulated increased MPS when compared with an isonitrogenous EAA supplement with an amino acid profile consistent with high quality proteins. These data indicate that increasing leucine availability during steady state exercise promotes skeletal muscle protein anabolism and spares endogenous protein."

As you might imagine, these findings have significant clinical implications. The authors state:

"Our findings indicate that increasing the leucine content of protein supplements provided for those populations susceptible to muscle loss, including proteolytic conditions—such as cachexia, sarcopenia, and calorie deprivation—may warrant further exploration."

Furthermore, as I mentioned above, the findings of this paper make it clear that when we provide leucine enhanced supplementation of either a quality protein powder such as whey or a quality essential amino acid blend, we can give greater assurance of a positive anabolic outcome to those patients who are trying to do the right thing when engaging in endurance exercise but, for various reasons, are overdoing it a bit.

LEUCINE AND OPTIMIZATION OF INSULIN METABOLISM

As we all learned in our basic science classes, certain hormones tend to stimulate anabolic physiology and others tend to stimulate catabolic physiology. Specifically, two of the most prominent catabolic hormones are cortisol and glucagon. As I have noted in many newsletters and others have noted in hundreds of publications, Cortisol, in particular, is an especially potent catabolic hormone that appears to be involved in many of the symptom-causing catabolic phenomena we see in our chronically ill patients such as loss of muscle mass (sarcopenia) and chronic inflammation. Do these catabolic hormones have a specific impact on leucine metabolism? In the paper "Hormonal regulation of leucine metabolism in mammary epithelial cells" by Lei et al (4), the authors state the following about cortisol:

"…glucocorticoids stimulate whole-body leucine oxidation in adult humans…"

Concerning the impact of glucagon on leucine metabolism Lei et al (4) point out:

"…glucagon stimulates the uptake of leucine, isoleucine and valine by liver, while increasing intracellular proteolysis, leading to increased availability of these amino acids for catabolism."

In contrast to cortisol and glucagon, insulin is the primary anabolic hormone. Unfortunately, as we all well know, in chronic, catabolic illness poor functioning insulin or insulin resistance is an almost universal norm. Could supplementation of leucine improve insulin sensitivity and function, thus negating the catabolic effects of cortisol and, to a lesser extent, glucagon, that are so often seen in chronically ill patients? As you will see in the literature review that follows, I do believe that the answer to this question is a resounding yes.

As suggested in the title, "Insulinotropic and muscle protein synthetic effects of branched-chain amino acids: Potential therapy for type 2 diabetes and

sarcopenia" by Manders et al (5), leucine, a branched-chain amino acid, can have a major impact concerning the optimization of insulin metabolism. The first quote I'm going to feature from this paper provides a principal reason for this powerful impact. Like so many other nutrients, a main reason why supplementation works so well is that leucine, in particular, can be severely depleted in certain populations. The authors state:

> **"Splanchnic sequestration of leucine following feeding is 50% higher in older *vs.* younger adults and the rates of muscle protein synthesis are decreased with aging, termed 'anabolic resistance.' Therefore, older adults may require additional dietary protein with greater leucine concentration to counteract muscle wasting over time. Supplemental leucine ingestion has been shown to overcome resistance to the anabolic effects of amino acid consumption, providing evidence that leucine supplementation may be beneficial for preserving muscle mass with aging."**

The next few quotes I would like to feature discuss the results of several studies on the impact of leucine supplementation on insulin metabolism. The first states the following:

> **"These findings are in line with recent *in vivo* observations, showing co-ingestion of relatively small amounts of free leucine to further augment the insulin response following the combined ingestion of carbohydrate and protein in healthy men."**

Then the authors point out:

> **"As such, the insulinotropic properties of amino acids (and leucine in particular) can therefore be of great clinical relevance in the treatment of type 2 diabetes or any state where there is a certain level of insulin resistance (e.g., aging) or hyperglycemia. Increasing endogenous insulin secretion with amino acids could therefore accelerate blood glucose disposal resulting in better glycemic control."**

The next quote provides detail on how leucine can improve insulin secretion:

> **"Leucine both induces and enhances pancreatic β-cell insulin secretion through oxidative decarboxylation and allosteric activation of glutamate dehydrogenase (GDH) increasing ATP/ADP. Leucine can also be transaminated to α-ketoisocaproate (KIC) that is converted into acetyl-CoA before entering the TCA cycle."**

Another excellent review of the literature provides still more evidence that leucine supplementation can be a powerful tool when making efforts to optimize insulin metabolism. In "Leucine as a pharmaconutrient to prevent and treat sarcopenia and type 2 diabetes" by Leenders and van Loon (2) the following is stated:

> **"…leucine has also been identified as a potent insulin secretagogue when administered in combination with carbohydrate and protein. Co-ingestion of additional leucine increases postprandial insulin release and stimulates blood glucose disposal. Several studies support the hypothesis that administration of protein and additional leucine represents an effective dietary strategy to improve glycemic control in patients with type 2 diabetes."**

Before continuing, I do want to emphasize an important point made in the previous quote. As I have stated in previous newsletters and presentations, for the beneficial impact of supplemental leucine to occur, whether it be optimization of insulin metabolism or optimization of muscle mass, it is important that it not be ingested as an isolated entity. In contrast, as I have also previously stated, it is important that supplemental leucine be ingested with carbohydrate and/or protein sources. These could certainly be quality whole foods. However, equally acceptable are protein powders and meal supplement/replacement powders.

Next, I would like to feature several quotes from the Leenders and van Loon (2) paper on the impact of leucine on insulin metabolism. First, consider the following:

> **"…co-ingestion of protein plus leucine represents an effective nutritional strategy to strongly stimulate post-prandial insulin release, augment glucose disposal, and attenuate the postprandial rise in blood glucose concentration in patients with type 2 diabetes. These findings imply that the insulin secretory capacity of the compromised β-cell remains highly functional when responding to stimuli other than glucose, like amino acids."**

This quote, in my mind, makes an important point that leucine is quite unique from other macronutrients in terms of its impact on insulin metabolism. For, if increasing insulin production is our only concern, we have many options as you know – most concentrated simple carbohydrates, which tend to be abundant in the average patient's diet, will do a very good job of raising insulin production. What's the problem with this aspect of concentrated simple carbohydrate physiology? As you all know, it does little to positively impact any other aspect of insulin metabolism, yielding a net result of insulin resistance and increased blood glucose concentrations. Leucine, in contrast, as is stated in the preceding quote, positively impacts virtually every aspect of insulin metabolism, yielding the beneficial net result of increased insulin sensitivity and optimization of blood glucose levels.

The next quote goes into great detail on how leucine optimally affects insulin metabolism:

> **"From both in vitro and in vivo studies in humans, it has become evident that leucine functions as a strong insulin secretagogue. Recent in vivo observations show a two- to four-fold increase in endogenous insulin release following ingestion of relatively small amounts of free leucine (3.75 g) with carbohydrate and protein. Leucine stimulates insulin release in the pancreas via its mitochondrial oxidative decarboxylation as well as by allosterically activating glutamate dehydrogenase in the β-cell. Besides the acute effects of leucine co-ingestion on β-cell function, Xu et al suggested that a more prolonged exposure to leucine might also contribute to enhanced β-cell function through improved maintenance of β-cell mass. In accordance, Zhang et al reported improvements in glycemic control by increases in insulin sensitivity (homeostasis model of insulin resistance [HOMA-IR] index was 50% lower) and approximately 50% lower glucagon levels following 14 weeks of leucine supplementation (via drinking water containing 1.5% leucine) in mice fed a high-fat diet. These findings support the hypothesis that leucine co-ingestion with each main meal, containing both carbohydrate and protein, might represent an effective nutritional strategy to increase postprandial insulin release and, as such, improve glycemic control."**

Could leucine's impact on insulin and glucose metabolism also yield a positive impact on serum lipid metabolism? The authors state:

> **"Generally, improvements in postprandial blood glucose homeostasis are accompanied by improvements in the blood lipid profile. Besides the improvements in glycemic control, Zhang et al reported a 27% decrease in plasma total cholesterol concentration and a 53% lower level of low-density lipoprotein cholesterol following 14 weeks of leucine supplementation in mice fed a high-fat diet."**

The last quote I would like to present from this discussion not only sums up the net positive impact of supplemental leucine on muscle and insulin but also discusses dosing recommendations:

> **"…increasing postprandial insulin release, e.g., by ingesting leucine (2-4 g) with a mixed meal, might represent an effective nutritional strategy to improve postprandial muscle protein synthesis and counteract the anabolic resistance to feeding in insulin-resistant muscle."**

Could leucine supplementation have a significant negative long-term impact on the metabolism of the other branched-chain amino acids, isoleucine and valine?

As you will recall, I briefly discussed this concern at the beginning of the newsletter. As noted in the following quote from the Leenders and van Loon (2) paper, the fact that you are providing leucine supplementation with protein ingestion alone or in combination with carbohydrate negates the possibility that leucine supplementation will have a major adverse impact on isoleucine and valine metabolism:

> **"Leucine supplementation generally induces a decline in the plasma concentration of other BCAAs, i.e., valine and isoleucine. It has been suggested that such a decline might negate the anabolic properties of leucine administration.**
>
> **However, it should be noted that lower plasma concentrations of valine and isoleucine are observed only in a postabsorptive resting condition and not in a postprandial situation, where large increases in the plasma concentrations of virtually all amino acids become apparent. Therefore, the stimulatory properties of the ingestion of**

leucine (2-3 g) with a mixed meal are unlikely to be attenuated by a relative lowering of the basal plasma concentration of valine or isoleucine. Furthermore, despite the observed decreases in basal fasting plasma concentrations of valine (approximately 10-20%) and isoleucine (approximately 0-10%), plasma levels still fall well within the normal physiological range. Consequently, there do not seem to be any major concerns associated with the lowering of the basal plasma concentration of valine or isoleucine following leucine supplementation with the main meals."

Therefore, as I have mentioned several times before, to gain the maximum anabolic impact of leucine supplementation while negating any adverse impacts, it is extremely important that leucine supplementation be ingested with quality macronutrient meals, protein powders such as whey, drinks containing other essential amino acids, or meal replacement/supplement powders.

CONCLUDING THOUGHTS

In concluding their paper, Leenders and van Loon (2) give an excellent summary of the key positive aspects of leucine supplementation:

"Leucine administration stimulates muscle protein synthesis and inhibits protein degradation via insulin-dependent and insulin-independent pathways. Recent studies report that increasing the leucine content of a meal to a level exceeding 3 g increases rates of postprandial muscle protein synthesis in vivo in elderly men, thereby normalizing the blunted response of muscle protein synthesis to food ingestion. Furthermore, due to its insulinotropic properties, free leucine (2-5 g) ingested with a mixed meal stimulates endogenous insulin release and attenuates the rise in postprandial blood glucose concentrations in patients with type 2 diabetes. Consequently, leucine supplementation has been suggested to represent an effective nutritional strategy to prevent and treat the loss of muscle mass with aging as well as to improve postprandial glycemic control in patients with type 2 diabetes."

To conclude this series, it is my hope that I have impressed upon you that muscle loss and "anabolic resistance" to regaining muscle mass from typical dietary measures can truly be an important "missing link" in explaining why chief complaints are not improving as expected in aging, chronically ill patients. In addition, I hope I have convinced you that, when adding a time efficient, cost-effective "back to basics" regimen that includes supplementation of leucine along with quality protein powder, meal replacement/supplement drinks, and/or essential amino acid formulas to your usual therapeutic repertoire, your success rates in even the most complicated chronically ill patients will increase dramatically.

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