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

INTRODUCTION

In part I one of this series I reviewed three papers that presented in great detail the hypothesis that anabolic resistance in aging populations is a major underlying factor in the ever increasing prevalence of probably the most important cause of loss of quality of life in this group, loss of muscle mass, or sarcopenia. Now I would like to present updated information on what we can do to assist our many patients experiencing this chronic condition. Actually, "updated" may not be the correct word to describe what follows. For, it is, in reality, a continuation of a major theme of **Entry Level Clinical Nutrition™ (ELCN)** that I have been discussing since the inception of ELCN approximately four years ago. With regard to sarcopenic patients experiencing anabolic resistance, part I of this series emphasized the importance of addressing metabolic imbalances such as insulin resistance and chronic inflammation with modalities such as life style modification and fish oil. Yet, there is still little question that the major foundation of any high quality treatment program has been and continues to be protein intake and resistance exercise. Why is this? While I could probably suggest several complicated, biochemically and metabolically complex answers to this question, the real answer, as with many aspects of clinical nutrition, is the most simple. As I have stated in several different forums over the years, dietary changes and supplementation always work best from an efficacy standpoint when repletion of significant deficiencies is occurring. As discussed in the paper "Malnutrition in the elderly: A narrative review" by Agarwal et al (1), gross protein deficiency is not just an issue seen in starving children in third-world countries:

> **"Multicentre studies that have evaluated protein-energy malnutrition (PEM) prevalence in the acute care setting report that 23-60% of elderly patients are malnourished and an estimated 22-28% are at nutritional risk."**

Of course, the above quote only refers to patients who are probably hospitalized for acute ailments. What about the elderly individuals who are the most likely candidates for becoming patients in our practices, those living in an outpatient or assisted care environment? Agarwal et al (1) state:

> **"In comparison to other healthcare settings, there is limited literature on the prevalence of PEM in community-dwelling older adults. However, the reported prevalence indicates a range of 5-30%. In the residential aged care setting, the reported PEM prevalence ranges from 16% to 70% depending on the assessment tool used and the level of care required. In general it is known that the prevalence of PEM increases as the level of care increases."**

Thus, it appears, sadly so, that the more your elderly patients are experiencing care in a traditional medical environment, the more likely they are to be existing in a state of protein-energy malnutrition.

Concerning the sarcopenia that is so common in this population, the authors are very clear on the best way that we can provide assistance:

> **"Dietary management should provide adequate energy and protein intake. However, this alone would be unlikely to address weight loss as sarcopenia is thought to occur regardless of energy balance. Recent evidence indicates that the most effective intervention thus far is a combination of nutrition and resistance training."**

IS DIETARY PROTEIN AND RESISTANCE EXERCISE THE FOUNDATION TO ANY EFFORT TO INCREASE MUSCLE MASS?

Hopefully, I have made it clear over the last few years that my answer to this question is an emphatic "Yes!!" As suggested above by Agarwal et al (1), increases in dietary protein alone will not be enough for many, if not most, sarcopenic patients who desire to optimize muscle mass, an opinion that has been echoed in the many papers I have reviewed in this forum that have discussed the benefits of resistance exercise. However, I do not believe I have reviewed any papers that considered the combination of diet and resistance exercise in depth. Therefore, I would like to review "Effect of whey protein isolate on strength, body composition and muscle hypertrophy during resistance training" by Alan Hayes and Paul J Cribb (2), a paper that does just that.

Hayes and Cribb (2) begin their paper by pointing out that the desire to increase muscle mass goes way beyond the popular misconception that it only matters to body-builders and athletes:

> **"Athletic performance and vanity aside, there are many important reasons for needing to know more about how to build muscle mass (hypertrophy), not the least being the underestimated role of muscle mass in healthy aging. Aside from the negative impact on health, functional ability and lifestyle quality, age-related decline in muscle mass is thought to underlie conditions that shorten lifespan such as type 2 diabetes and cardiovascular disease."**

They go on to point out another key, often misunderstood point. While resistance exercise is, by nature, an anabolic phenomenon, it only leads to increases in muscle mass when combined with protein ingestion:

> **"Although resistance exercise is fundamentally anabolic, a net gain in muscle mass is only possible via an interaction with protein-containing meals."**

Hayes and Cribb (2) go on to discuss research that supports this important yet under appreciated relationship:

> **"Data from both acute response studies and longer-term (6-12 weeks) investigations provide a foundation that suggests the strategic use of protein supplements can play a vital role in the development of muscle hypertrophy during resistance exercise training. In fact, supplementation may be vital to restoring the diminished acute response to anabolic stimuli (such as resistance exercise or meal consumption) that is characteristic of aging. Additionally, the strategic consumption of a supplement containing whole proteins or essential amino acids close to resistance exercise is consistently shown to dramatically enhance the acute anabolic response to this activity by providing a higher stimulation of protein synthesis and net protein balance compared to placebo treatments. Recent data also suggest that supplementation between regular meals may provide an additive effect on net protein accretion due to a more frequent stimulation of muscle protein synthesis."**

Specifically, how does protein supplementation increase muscle mass? The authors point out three ways:

> **"…protein supplementation appears to have at least three prominent roles in augmenting muscle protein accretion and promoting hypertrophy. First, by supplementing close to resistance exercise to ensure a greater stimulation of muscle anabolism in response to this activity. Second, some data suggest that supplementation between meals may promote more frequent stimulation of muscle protein synthesis, thereby promoting a higher net gain in muscle protein on a daily basis. Finally, strategic supplementation with protein that is rich in essential amino acids, particularly leucine, may help restore the acute anabolic response to meals which characteristically diminishes aging."**

<u>**Types of whey protein**</u>

Next, the authors discuss the different types of whey protein that are available commercially:

> **"The type of protein consumed may influence results from resistance exercise training due to variable speeds of absorption, differences in amino acid profiles, unique hormonal response or positive effects on antioxidant defense. Whey protein is the collective term for the soluble protein fractions extracted from dairy milk. Whey protein supplements, i.e. above 80% proteins concentrates (WPC**

80) or about 90% protein isolates (WPI 90), have become popular among athletes and others interested in gaining muscle mass."

Beyond its protein content, what are the benefits of whey protein?

"Rather than merely increasing the quantity of protein in the diet, these particular proteins may also provide some unique nutritional advantages. Characteristically, these whey protein supplements contain a very high concentration of essential amino acids (45-55 g/100 g of protein) with minimal fat, carbohydrate and lactose. They are also the richest known source of branched-chain amino acids, particularly leucine (up to 14 g/100 g protein).

What else can be stated about whey protein other than the fact it is a good protein source? Hayes and Cribb (2) point out:

Aside from strategic supplementation after exercise, regularly incorporating whey protein supplements into the daily diet may also promote the maintenance of lean body mass (LBM). Whey protein supplements are a rich rare source of cyst(e)ine residues; up to four-fold higher than other high-quality proteins such as casein and soy."

Why is cyst(e)ine important? The authors continue:

"Briefly, an abundant supply of cyst(e)ine in the blood is necessary for hepatic catabolism of this amino acid into sulfate and protons; a process that downregulates urea production, promotes glutathione synthesis and shifts whole-body nitrogen disposal in favor of preserving the muscle amino acid pool (which is synonymous with muscle anabolism). Whey protein supplementation (up to 1 g/kg/day) is the only protein source shown to augment this pathway of protein metabolism and it may do so possibly in a dose-dependent manner."

Still more benefits of whey protein revolve around its absorption properties:

"What is more relevant is that when whey protein supplements are consumed as part of a mixed-macronutrient meal, this protein's rapid absorption kinetics and ability to stimulate a very high rate of muscle protein synthesis is unaltered, but the result is a more prolonged state of anabolism and inhibition of protein degradation as well as a higher net gain in whole body protein."

With the above in mind, the authors conclude:

"Due to its amino acid profile and ability to promote higher net protein accretion, the incorporation of whey protein into the diet may enhance the development of muscle hypertrophy and improve body composition during resistance exercise training."

What about timing of supplement ingestion in relation to resistance exercise?

As I have been reporting in previous newsletters, there has been some controversy as to whether ingestion of a protein-based supplement functions best in terms of optimization of muscle mass when ingested either before or after a resistance exercise workout. Interestingly, the position taken by Hayes and Cribb (2) is that ingestion before or after does not matter as much as the idea that ingestion occurs as close as possible to the time the workout occurs. The authors state:

"Supplement timing (i.e. the strategic consumption of a protein supplement before and/or after each workout) is thought to be the ideal strategy for promoting muscle hypertrophy from resistance exercise."

These findings were based on research conducted by the authors:

"In this study, the resistance-trained males were randomly matched for strength, completed a fully supervised 10-week resistance exercise program and consumed their supplement (1/kg/body weight containing whey protein isolate and creatine monohydrate) immediately before and after resistance exercise (PRE-POST). The second group (MOR-EVE) consumed the same dose of the same supplement in the morning and late evening (times that were at least 4-5 h outside training). No other supplementation was permitted and the athletes followed their regular eating patterns. Results showed that the group who performed the supplement-timing strategy (PRE-POST) demonstrated a gain in lean body mass (LBM) that was almost double the MOR-EVE group. This group also demonstrated greater improvements in one-repetition maximum strength, which were supported by a greater increase in hypertrophy of the type II fibers and

muscle contractile protein content of this group."

Of course, you may wonder, after reading the above quote, given that the study group was composed of athletes, would similar results be seen in your patients who are not trained, healthy athletes but, most often, older individuals suffering from varying degrees of ill-health. In answer to this concern, consider the following quote:

> **"This protocol may however, also have important implications for populations that require improvements in strength and body composition, but have a reduced capacity for exercise, such as the frail elderly, cardiac rehabilitation patients or other living with conditions that compromise health, such as HIV, cancer and the various muscular dystrophies."**

In particular, concerning aging populations:

> **"Importantly, aged individuals showed the same significant elevation in amino acid levels within 2h of ingesting a protein-rich meal as their young counterparts and also displayed the same elevation in acute protein synthesis. Thus, it is likely that supplementing the diet with essential amino acids surrounding a resistance training session would similarly augment the effects of training in elderly individuals, although further work is required in this area."**

Therefore, based on this paper, it appears that ingestion before or after an resistance exercise workout is not nearly as important as ingesting protein-based supplements in close proximity to the workout. Beyond the science, I feel this information is reassuring in terms of patient compliance since many patients will have a strong bias for ingestion either before or after their resistance exercise workout.

WHICH IS BEST – WHEY PROTEIN CONCENTRATE OR ISOLATE?

As was mentioned above, whey protein concentrate is at least 80% whey and whey protein isolate is at least 90% whey. With the assumption that a 90% whey product is better for your patients, you may be wondering why many whey protein products are whey protein concentrates containing at least 80% whey? An interesting paper by Hoffman and Falvo (3) entitled "Protein – which is best?" answers this question in ways you might not intuitively expect. First, in discussing whey protein concentrate, the authors state:

> **"The processing of whey concentrate removes the water, lactose, ash, and some minerals. In addition, compared to whey isolates whey concentrate typically contains more biologically active components and proteins make them a very attractive supplement for the athlete."**

Before continuing, please notice again that, based on the above quote, even though whey protein concentrates contain less whey protein than isolates, they are more biologically active. Why is this? Hoffman and Falvo (3) elaborate:

> **"Although the concentration of protein in this form [isolate] is the highest, it often contains proteins that have become denatured due to the manufacturing process. The denaturation of proteins involves breaking down their structure and losing peptide bonds and reducing the effectiveness of the protein."**

Therefore, as you can see, even though whey protein isolate contains more whey than whey protein concentrate, contrary to common intuitive thinking, whey protein concentrate will be the more clinically effective form.

Before leaving this paper, please note the informative chart from this paper that follows the text in this newsletter on page 8. It provides a succinct description of protein quality rankings of different proteins, with whey protein ranking the highest, even higher than an egg.

LEUCINE – THE MOST IMPORTANT PART OF WHEY PROTEIN?

Now I would like to focus more intently on an aspect of protein supplementation that I have touched on repeatedly in past discussions on protein supplementation, muscle mass, and sarcopenia, leucine. Of all the key factors in whey protein that play a role in the optimization of muscle mass, could leucine content be the most important? According to Hulmi et al (4), as stated in their paper "Effect of protein/essential amino acids and resistance training on skeletal muscle hypertrophy: A case for whey protein," the answer is yes:

> **"It is probable that the most important component in whey, for increasing protein synthesis and skeletal muscle size is its high concentration of the BCAA, leucine."**

Why is this so? The authors state:

> **"Leucine, acting as a signaling molecule in the mTOR cascade, has been shown to be a critical amino acid for increasing skeletal muscle synthesis, both *in vitro* and *in vivo***

in humans and rats. Leucine may also be involved in suppressing muscle protein degradation, according to investigations *in vitro* and *in vivo* in humans."

How does the concentration of leucine, as well as other essential amino acids, in whey protein compare with other forms of supplemental proteins? To answer this question, please see the chart on page 8 of this newsletter from the Hulmi et al (4) paper.

Clinical studies on leucine supplementation

The first study I would like to review on the impact of leucine clinically is "Leucine supplementation chronically improves muscle protein synthesis in older adults consuming the RDA for protein" by Casperson et al (5). It begins by pointing out the minimum amount of protein per meal needed in aging adults to maintain protein synthetic response:

"It is generally accepted that aging is associated with a blunted protein synthetic response to meals containing less than approximately 15-20 g of protein or the equivalent essential amino acid content."

In the quotes that follow, the authors point out an exceedingly important, highly clinically relevant problem with many studies, where protein and/or amino acid supplementation is being evaluated for its ability to increase muscle mass and function in the elderly. The length of the study, often only a few hours or a day, is often too short to lead to reliable extrapolations about that which interests us the most, long-term effects from chronic, long-term intake:

"…in controlled metabolic studies it is easy to demonstrate acute increases in muscle protein synthesis or markers of anabolism following ingestion of a protein or amino acid supplement. However, in practice, there is a risk that acute responses will not translate into positive chronic adaptations in muscle mass or function. The reasons for a lack of success are varied, but we suspect they more often reflect compliance-related issues or consumer choice, rather than a temporally diminished physiological capacity. To this end, we propose that an effective supplement should produce a robust anabolic response, and be i) low-volume and easily incorporated into existing menu plans, ii) palatable, and iii) cost effective."

As I hope you can see from this quote, this paper should be particularly valuable to those of us "in the trenches" because it is one of the few written by researchers who truly appreciate the hurdles we face with patient care beyond those relating to biochemistry and physiology.

With issues relating not only to biochemistry and physiology but practicality in mind, Casperson et al (5) discuss leucine:

"From a practical and mechanistic perspective, the branch chain amino acid leucine is an attractive supplement. Leucine has many well described effects on the regulatory mechanisms controlling translation initiation and muscle protein synthesis."

Furthermore:

"Several studies in both animals and humans suggest that increasing the leucine content of regular mixed nutrient meals may normalize or even increase protein synthesis in older populations."

However, even these positive studies need to be considered "with a grain of salt." Why? In the quote that follows, Casperson et al (5) make an exceedingly important point that I have been emphasizing for years – nutrient supplements are ***not*** drugs. In other words, unlike a drug, they do not have a universal effect regardless of sometimes subtle variables unique to each patient. In contrast, clinically evident benefit tends to be seen only when ingestion of supplements is repleting a suboptimal or grossly deficient state. Where do we tend to see protein and, specifically, protein deficiencies most often? In aging populations. The authors state:

"While the headline result from the leucine studies mentioned above are encouraging, an important emerging caveat is that leucine supplementation is not unconditionally effective. Specifically, ingestion of supplemental leucine appears to be of little benefit to: i) younger adults, and/or, ii) individuals who habitually consume a protein/leucine-sufficient diet."

With the above in mind, Casperson et al (5) conducted a study on eight healthy but sedentary older adults with a daily protein intake of 0.75 – 0.85g protein per kilogram body weight per day, which is near the current RDA. Why is this amount significant in relation to this study? As I have pointed out in several newsletters, very often elderly populations will need protein ingestion anywhere from 1.2 – 1.5 g/kg/per day to optimize muscle mass (6). Therefore, the authors classified the meals ingested by the study subjects as "low protein." The study was fairly long-term as these studies go (15 days), with the subjects ingesting 4 grams of supplemental leucine with each of three meals per day for days 2-14.

What were the results of the study? The authors state:

> **"Our data suggest that leucine supplementation may be an energetically efficient and practical means of chronically improving muscle protein synthesis in response to a low protein meal in older adults who habitually consume close to the RDA for protein."**

However, this newsletter series is not just about muscle mass and function. It is primarily designed to address the important issue of anabolic resistance. In this respect, what were the results of the study:

> **"…we demonstrated that supplementing regular daily meals with a relatively small amount of leucine improves both mixed-muscle protein synthesis and anabolic signaling in older adults."**

Of course, as I mentioned above, the value of this study is that it considered more than just biochemistry and physiology. From a practicality standpoint, were there any concerns? The authors state:

> **"No compliance issues were noted during the study."**

Concerning compliance, Casperson et al (5) also issued the following, more in depth comment:

> **"…while we did not conduct a specific assessment of practical issues such as longer duration compliance, ease of use or palatability, our low-volume approach is intuitively less likely to be burdensome than most traditional higher-volume amino acid supplement regimens."**

Why was the leucine supplementation effective? The authors reiterate what I stated above:

> **"The anabolic potential of leucine has been attributed to its capacity to stimulate translation initiation both dependently and independently of the mTOR signaling pathway."**

Furthermore:

> **"In addition to its effects on muscle protein synthesis, there is some evidence suggesting that leucine augments glucose-induced insulin secretion. In animal models, chronic leucine supplementation improved insulin sensitivity despite consumption of a high-fat diet."**

In concluding their discussion of their study, Casperson et al (5) first point out that this study demonstrated the same positive short term effects of other studies which examined short-term ingestion of protein/leucine combinations and its impact on muscle protein synthesis and function:

> **"Given the right circumstances it seems clear that leucine supplementation can acutely increase muscle protein synthesis."**

What makes this study somewhat unique is its duration. While two weeks is still not a long period of time to conduct a study, it is still much longer than the usual study on the effects of protein/leucine ingestion on muscle in the elderly, which sometimes only covers a span of a few hours. This enables us to learn about the issue that is probably, more often than not, the major limiting factor in successfully treating patients, compliance, which, in this case, was good.

While encouraging, though, two weeks is not two months or two years. Keeping in mind that the study above did not include resistance exercise, would the same positive results be seen in longer term studies conducted over a period of months? Unfortunately, no, as demonstrated in the following study by Leenders et al (7).

In the paper by Leenders et al (7) entitled "Prolonged leucine supplementation does not augment muscle mass or affect glycemic control in elderly type 2 diabetic men," the authors conducted the following experiment that is very relevant to what we typically see in our practices:

> **"Sixty elderly males with type 2 diabetes (age, 71 ± 1 y; BMI, 27.3 ± 0.4 kg/m^2) were administered 2.5 g L-leucine (n = 30) or a placebo (n = 30) with each main meal during 6 mo of nutritional intervention (7.5 g/d leucine or placebo). Body composition, muscle fiber characteristics, muscle strength, glucose homeostasis, and basal plasma amino acid and lipid concentrations were assessed prior to, during, and after intervention."**

Interestingly, this experiment was a follow-up to a similar experiment performed on healthy elderly males. What were the findings? The authors state:

> **"We recently reported the impact of 3 mo of leucine supplementation with each main meal on muscle mass and strength in healthy, elderly males. No changes in skeletal muscle mass or strength were observed over the 3-mo intervention period."**

(In case you are interested in reading this study, it is entitled "Long-term leucine supplementation does not increase muscle mass or strength in healthy elderly men" by Verhoeven et al (8).)

Because some critics stated that these results had nothing to do with leucine per se but the fact that the experiment was conducted on healthy individuals over a relatively short period of time, Leenders et al (7) decided to perform this follow-up experiment.

What were the findings on the second, longer term experiment in subjects who many of us would suspect are deficient in leucine? The authors state:

> **"The present study shows that 6 mo of leucine supplementation (a total of 7.5 g/d) with each main meal does not augment skeletal muscle mass and strength, modulate body composition, or improve glycemic control and blood lipid profile in elderly men with type 2 diabetes who habitually consume sufficient protein."**

It should also be noted that, for both the control and experimental groups, dietary protein intake per day was 0.94 ± 0.04 g/kg body weight. In their previous study performed on healthy elderly, the dietary protein intake per day was 0.99 ± 0.07 g/kg body weight in the leucine group and 0.99 ± 0.04 g/kg body in the control group.

Why were the results of the long term studies in stark contrast to the short term study? I have two theories. First, as I have pointed out in past newsletters, elderly populations tend to require a daily protein intake much higher than the RDA of 0.8 g/kg/day or even the somewhat higher amounts used in the Leenders et al (7) and Verhoeven et al (8) studies. Very often elderly populations will need protein ingestion anywhere from 1.2 – 1.5 g/kg/per day to optimize muscle mass (6). Second, none of the studies on leucine supplementation discussed above included a resistance exercise regimen. Therefore, from a long-term standpoint, my take away from the above studies is that, even when all the positive attributes of leucine supplementation are taken into account, as you might expect, they cannot compensate for suboptimal dietary protein intake and suboptimal exercise.

In part III of this series, I will explore still more clinical research on leucine and how we can use it clinically to optimize muscle mass and function. However, as I continue to expound on the benefits of leucine supplementation, again, please keep in mind the lessons taught by the clinical studies just discussed. While leucine supplementation with a minimally adequate diet and little or no resistance exercise may demonstrate benefit in the short term, it may be a poor investment in terms of time, money, and efficacy in the long term. Therefore, while I am a strong advocate of leucine supplementation in the elderly, sarcopenic patients, I feel it will only have value if it is combined with optimal dietary and/or supplemental protein intake and optimal resistance exercise.

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→ Two Charts on the next page →

Table 1. Protein quality rankings.

Protein Type	Protein Efficiency Ratio	Biological Value	Net Protein Utilization	Protein Digestibility Corrected Amino Acid Score
Beef	2.9	80	73	0.92
Black Beans	0		0	0.75
Casein	2.5	77	76	1.00
Egg	3.9	100	94	1.00
Milk	2.5	91	82	1.00
Peanuts	1.8			0.52
Soy protein	2.2	74	61	1.00
Wheat gluten	0.8	64	67	0.25
Whey protein	3.2	104	92	1.00

Adapted from: U.S Dairy Export Council, Reference Manual for U.S. Whey Products 2nd Edition, 1999 and Sarwar, 1997.

Table 1: Approximate Essential Amino Acid Profile of Various Protein Sources

ESSENTIAL AMINO ACID	MILK PROTEIN ISOLATE	WHEY PROTEIN ISOLATE	WHEY PROTEIN HYDROL.	CASEIN	SOY PROTEIN ISOLATE	EGG PROTEIN
Isoleucine	4.4	6.1	5.5	4.7	4.9	5.7
Leucine	10.3	12.2	14.2	8.9	8.2	8.4
Lysine	8.1	10.2	10.2	7.6	6.3	6.8
Methionine	3.3	3.3	2.4	3.0	1.3	3.4
Phenylalanine	5.0	3.0	3.8	5.1	5.2	5.8
Threonine	4.5	6.8	5.5	4.4	3.8	4.6
Tryptophan	1.4	1.8	2.3	1.2	1.3	1.2
Valine	5.7	5.9	5.9	5.9	5.0	6.4
Total BCAAs	**20.4**	**24.2**	**25.6**	**19.5**	**18.1**	**20.4**
Total EAAs	**42.7**	**49.2**	**49.8**	**40.7**	**36.0**	**42.3**

Approximate concentration of essential and branched chain amino acids (EAA and BCAA, respectively) present within various forms of commercially available protein (g/100 g). Adapted from [27]. Casein is the average of reported values for Calcium Caseinate, Sodium Caseinate, and Potassium Caseinate; Whey Protein Isolate is the average of reported values for Ion-Exchange and Cross-Flow Microfiltrated Whey Protein Isolates. Hydrol. is hydrolysate.