## Discussion

**Leader:** Tracy R. Smith, PhD, RD, Abbott Nutrition, Columbus, OH

**Dr Lanza:** Dr Suetta, when you measure specific strength in humans, you could understand how specific strength would decrease because of neural factors and maybe even an increase in the noncontractile tissue in the muscle, if you did not account for that with your physiological cross-sectional area. The production of force depends on adequate neural drive to the muscle. If neural drive is lower, the apparent specific tension may be lower for reasons other than the amount of contractile tissue. But with the isolated fibers, I guess that is ruled out, because you have essentially removed the nervous system. What is it about the contractile proteins themselves (they are something that is intrinsic to the muscle) in the absence of a nervous system that decreases the force per cross-sectional area?

**Dr Suetta:** Interestingly, the loss of muscle fibers, as observed with aging, predominantly occurs in type 2 fibers. After immobilization, we also see decrease in specific tension, predominantly in type 2 fibers, and they seem to be more insensitive to calcium after immobilization, and the type 2 fibers of old individuals get more affected than those of the young. Then we speculated that it could be because of the difference observed in the crossbridge circles between type 1 and type 2 fibers. However, it also could be because of a smaller myosin content in old myofibers, as nicely demonstrated by Bottinelli's group [D'Antona G et al: *J Physiol* 2003;552(Pt 2):499-511, Fig 7].

**Dr Lanza:** If you were to dunk these fibers in a calcium bath to cause them to generate tension, would those differences in specific strength go away? I assume they were electrically stimulated.

**Dr Suetta:** We do not stimulate the fibers electrically. They are chemically skinned and then put in different concentrations of calcium, where we can measure isometric-specific force at different fiber levels. After immobilization, specific force decreased in both young and old, but still the type 2 fibers of the old individuals were affected the most. We are going to look more into the possible reasons for that.

**Dr Reid:** We have been interested in these same sorts of myofilament changes with a variety of insults. We do not look at aging, but colleagues down the hall have been looking at rodent muscle. What they find in rodent diaphragm, at least, is that the mitochondrial volume density is higher. So for a given cross section of the fiber you may have more mitochondria and fewer myofilaments.

That would not account for the change in calcium sensitivity, but it would contribute to the decline in stress. I do not know if that applies to your fibers. Have you looked at mitochondrial content?

**Dr Suetta:** Unfortunately, no.

**Dr Reid:** One group of researchers has shown, at least in rodents, that there is a preferential dropout in thin filaments. They have done cross sections with electron microscopy, and the thin filaments drop out and the thick filaments persist, suggesting a different mechanism for this loss in specific force.

**Dr Supinski:** You can have oxidative stress that will specifically knock down specific force, and caspase and calpain also can specifically knock it down. A multitude of things could account for her Dr Suetta's findings. She is going to have to do much work to sort it all out, but I am sure it will be interesting when she is finished.

**Dr Schols:** Dr Paddon-Jones, you show nicely the importance of high-protein intake spread out over the day. Obviously you were referring to the elderly. One of the problems in cachexia, which we will discuss later, also can be a decreased appetite, and obviously you want the patients to eat as much as possible. What about potential effects of the protein on satiety of these patients and ultimately then on their overall dietary intake?

**Dr Paddon-Jones:** That is one of the primary practical obstacles we face every day. In elderly patients, we have issues when we give any sort of supplement. In our ACE (acute care for the elderly) unit, we cannot get them to take in enough food, and I think that is amplified with women who have advanced cervical cancer. It is hard to get them to eat any sort of food when we add supplements, and it often leads to nausea. Finding a strategy to get them some nutrition almost requires one-on-one negotiation.

**Dr Schols:** What is your point of view then? We already discussed nutrition and exercise combination. Both require effort from the elderly, which is good, I think, because you consider long-term strategies.

What do you do if you know that is difficult for the elderly to maintain a high-protein intake, which seems to be needed according to all the available studies? What do you think about combined nutritional and pharmacological approaches to maintain or enhance the muscle mass?

**Dr Paddon-Jones:** Some of our colleagues are using combined nutrition and testosterone in hypogonadal men, and as we discussed earlier, it does seem to work. If we have a severely compromised population, we need to look at a combination of therapies to try to bring them close to normal. We tend to focus on using nutrition first, as more of a catchall strategy that needs to be in place before we can hope anything like testosterone will work.

**Dr Schols:** Nutrition first or exercise first?

**Dr Paddon-Jones:** Nutrition first, because of the types of patient populations we get. I showed you the step activity count on some of these inpatients. They are in the hospital because they cannot exercise, so we tend to focus on nutrition first. Then anything else is almost a bonus. We know we will have a positive synergistic effect if we can add exercise and if we can add hormonal therapy.

**Dr Schols:** With creative exercise, you can try to stimulate muscle. But what about electrical stimulation? Do you see that as an alternative for those patients?

**Dr Paddon-Jones:** Yes. We are going to trial that. We know that we cannot get many of our patients to do anything. They are bed bound for maybe a few days, so we are going to try some electrical stimulation while they are in bed to provide a minimal amount of muscle contraction.

For some patients, we left the bed boards on the bottom of the bed. The patients rested their feet against it and just tapped—a minimal amount of activity, but it preserved much of the functional characteristics in isolated single fibers.

In terms of function, it takes a minimal amount of exercise to offset some of the decrements that we saw. Electrical stimulation and minimal amount of exercise are better than nothing.

**Dr Morley:** Our group looked at supplements, protein, carbohydrate, and fat separately. We did not get an anorectic effect in not-very-healthy older people with between-meal protein, but it has to be given about 2 hours before the meal. When protein is given closer to the meal than that, we got an anorectic effect. So if you space out the protein, it works, and you will not see the anorectic effect.

Exercise is a big problem because we deal with exercise theoretically in the hospital. It is called physical therapy. We deal with it theoretically in nursing homes, and the amount of exercise they do does not, in my mind, reach the minimal level of exercise.

There seems to be no concept among physical therapists of how much exercise we really need, and we know minimal is better than none. I am totally convinced we could get people out of a nursing home 10 to 15 days earlier if we actually tried to exercise them, because we do not. It is about timing and how much time the physical therapist has.

The question around now is, what about vibration exercise such as that used by the National Aeronautics and Space Administration? Research in older people shows some improvement by just putting them on a vibration stair, which is doable for almost anyone because they are strapped in. Some people have done the same thing with stroke patients, and 3 to 4 years post-stroke these patients suddenly improve dramatically.

I think there is no question that we grossly underexercise. We should be doing basic research on innovative ways to get patients to exercise. Otherwise nutrition is the only choice we have.

**Dr Suetta:** I have a comment on electrical stimulation. We performed a study some years ago in which we compared electrical stimulation with normal physiotherapy and resistance training in postoperative hip replacement patients. We saw that with conventional physical therapy, patients had a further drop in muscle mass 5 weeks after

the surgery, while the electrical stimulation could maintain their muscle mass, although they had a diminished level compared to the healthy leg. With resistance training, muscle mass actually increased. My point is that resistance training in most conditions is the optimal way of training, but if for some reason it is not possible, it seems to be a good idea to apply electrical stimulation.

**Dr Schols:** That is an important message from a hospitalization point of view. We are glad if we can maintain muscle mass in hospitalized patients. We so not think of improving it.

**Dr Supinski:** There is no doubt that we should try to move the majority of patients around and exercise them. But some research has shown that in those with infections, exercise can break down the subsarcolemmal support structure, the spectrin in muscle. Then when it contracts, it breaks. You get holes in muscle.

These same researchers found that they could reduce the amount of diaphragmatic injury during an infection by putting the patients on a ventilator for 24 hours. So there may be some circumstances in which a patient is so sick, with activated caspases and calpains throughout the body, that exercise actually might be harmful and break muscle down for the first day or two right after some event such as pneumonia.

**Dr Schols:** I can imagine if you want someone to walk or cycle or whatever, that is not possible, but if you perform resistance type of exercise, you are not challenging the diaphragm that much.

**Dr Supinski:** I am not saying this is always the case. In fact, I may be the only one here who sees these patients, but in the first day or two after they come in, the spectrin is unstable. We have seen this in the leg, as well as the diaphragm. We want to do a study to see what exercise actually does in these circumstances, because we hypothesize that if we exercise animals too soon after they are infected, their condition will get worse.

**Dr Schols:** Obviously then, you are talking about a different issue, because then you are interfering, and maybe should not interfere, with the normal acute phase response that occurs during acute disease.

**Dr Supinski:** Perhaps, but I think there is a period during which exercise might be dangerous, say the first 24 or 48 hours.

The same thing may be true with some muscular dystrophy patients. When they get acutely ill, their muscle breaks down, and then they have impaired repair responses. So they go through a period of cycles where they get sicker and sicker. During those acute phases it might be best to prevent infection in them or have some other approach to treatment. But exercising muscular dystrophy patients when they are acutely ill might be bad for them.

**Dr Tisdale:** Do you have any thoughts about the world of reactive oxygen species? As we heard from Dr Reid earlier, reactive oxygen species are thought to be important in muscle protein loss. Some experiments in animals have knocked out copper-zinc superoxide dismutase, resulting in changes in muscle reminiscent of those in older animals. The animals lose muscle mass and force contraction.

It is probably not a coincidence that type 2 fibers are more sensitive to oxidative stress than type 1 fibers. It may explain the serum effect from older people—why the satellite cells are not propagating properly. I wonder whether anybody has looked at this in humans or just in animal studies of experimental scientists.

**Dr Reid:** I think the lab that is doing the best work on oxidative stress in aged muscle is a group near Liverpool. They have shown that oxidative stress contributes to both the loss of muscle mass and the loss in specific force seen at least in aged rodents. They have not done nearly as much work in humans as they have in rodents, but the work that they have done in rodents has been instructive.

**Dr Tisdale:** I agree about the rodent studies. The question is, is anybody going to look at this in humans to see whether they can alter the situation that we see in older adults? If you do experiments in humans, do not use vitamin E, tocopherol, as an antioxidant, because that can act as a pro-oxidant. The reason we see these anomalous results using

so-called antioxidants is because they are not true antioxidants. They actually can propagate a chain reaction.

**Dr Supinski:** Conley et al has written about this [*Curr Opin Clin Nutr Metab Care* 2007;10:688-692]. He has postulated that reactive oxygen species may play a role in producing mitochondrial dysfunction in his older patients.

**Dr Tisdale:** As we talk about various forms of treatment, maybe that should be factored in as well.

**Dr Reid:** The paper to which Dr Tisdale refers has to do with adaptation to exercise, and the subjects were sort of normal healthy people who were given antioxidants. It was found that the antioxidants inhibited the adaptation to training.

The response in sick people or the response in aged people may be qualitatively different in the sense that you are giving antioxidants in an environment in which oxidative stress is tonic. So there can be phasic oxidative stimuli to which we adapt, and then there are baseline shifts in redox status in tissue. People with chronic oxidative stress such as the elderly may benefit from antioxidant therapy, whereas healthy young people might not. I think it is a worthwhile experiment to do.

**Dr Wheeler:** If we have muscle mass and show retention of muscle mass, but they do not convert into functionality, what have we gained for these patients? We know that muscle

mass alone is not going to necessarily translate into functionality, unless the patients use the muscle and develop the strength and power. If we go back to research that shows things like gait speed being related to mortality (ie, the lower the gait speed, the slower the individual and the higher the rate of mortality or risk for mortality), then muscle without functionality conversion becomes what?

I pose this as a general question: Are we really saying that the muscle mass is the thing we are going for? Or is it muscle mass plus functionality? Are both not critical to the patient populations we are speaking of?

**Dr Lanza:** A related question is, is there any evidence that doing things to decrease protein breakdown preserves lean mass such as essential amino acids? The essential amino acids stimulate protein synthesis, but by decreasing protein breakdown do we end up with muscle mass that contains proteins that may be modified in certain ways that inhibit their function? Doing that, we are not accomplishing anything functional; we are just increasing mass that does not function the way it should.

**Dr Hegazi:** Back to the point about whether patients like the protein. We know that they need a protein supplement or even basic nutrition. That is a great point for clinical practice. All the time, we see patients and provide them with nutrition support, for instance, by prescribing a nutritional supplement. However, we find that the patients have not touched the supplements. I think we should be aggressive in these cases. We could do

this by counting calories, and if intake did not meet 50% of caloric needs, we would place a nasogastric tube and start feeding the patients.

My question to the whole panel is, is there a correlation between protein synthesis, skeletal protein synthesis, and visceral protein synthesis?

**Dr Paddon-Jones:** Yes.

**Dr Hegazi:** Question answered. My point is that if we are talking about patient undernutrition in the setting of stressed semi-starvation, coupled with immobilization for a couple of weeks, is there concomitant visceral or intestinal barrier protein depletion? In other words, is there visceral protein depletion in general and then organ dysfunction in association with skeletal muscle protein depletion?

**Dr Supinski:** Some literature argues that the gut epithelium requires glutamine for adequate function. One question is whether we need different amino acid supplements to make sure that we are maintaining protein synthesis and the integrity of the gut, and whether this differs from what is required for skeletal muscle? This may not be important for the average person walking around, but it is critically important for somebody who is very sick, because if the gut epithelium is not maintained, the patient will get bacterial translocation, and he or she can die from that.

**Dr Morley:** Some but not all literature suggests that glutamine does not improve outcomes, particularly in patients who are critically ill. Some people believe it does, but we concluded that while a little glutamine is good, a lot of glutamine, as has been used in ICU settings, does not seem to work.

**Dr Supinski:** There are some experimental data in animals, though.

**Dr Morley:** Animals are not humans.

**Dr Supinski:** No, I understand, but some people argue that if you are not sure, what is the harm of giving somebody a little bit of glutamine? Is what we see in skeletal muscle the same as in every other organ, or do some organs require a different nutrient mix?

**Dr Schols:** I want to follow up on Dr Wheeler's question regarding whether it is muscle mass or muscle function that is important. Obviously, when your outcome is physical functioning, quality of life, and being able to perform activities of daily living, then the translation of maintenance or improvement of muscle mass to muscle function is a logical one. We know that muscle mass is an independent predictor of survival in some chronic diseases and also in the elderly. The question is, why is this so?

In patients with COPD, it has been shown that quality of life is strongly determined by their exercise capacity and less by muscle mass per se. However, some studies have shown that low muscle mass or weight loss is an independent predictor of hospitalization

or acute exacerbations. We cannot yet say that, in disease, if an improvement in muscle mass does not immediately translate into one of the markers that we use to assess muscle strength or muscle function, that maintaining or increasing muscle mass is not important.

We can try to find the proof by performing longer-term intervention studies with survival as the end point, or in chronic diseases with exacerbations or hospitalization as the end point. The problem is that such studies may require a follow-up of 3 years. These are expensive, so we are searching for biomarkers. There are markers for sarcopenia, for instance, that are relatively simple to measure but that are not very sensitive, such as a handgrip strength. That is a bit of a challenge for all of us.

**Dr Rebecca Biga [Abbott Nutrition]:** Does anyone here have any thoughts on why the elderly, compared to young people, respond as they do and on the benefits of the way they respond?

**Dr Suetta:** My answer will be speculative, because my findings are different from those of Dr Paddon-Jones. I think the data show that when we just looked at young people, we saw strong correlations between initial muscle mass and how much they lost. There seems to be a generic potential—myogenic potential—both for how much you lose and how much you regain after a period of disuse, which might make some sense. If you do not have a lot of muscle mass, you are not going to lose it all after a period of disuse, indicating that there are some mechanisms that retain muscle mass.

However, knowing this I think counteracting muscle loss during hospitalization is even more important. A certain amount of muscle mass is needed to base the exercise on. We know that muscle strength is strongly correlated to muscle mass and maybe more important muscle function and disability.

**Dr Pereira:** Dr Paddon-Jones, you showed that aged muscles did not respond well to anabolic stimulus, say an amino acid, at a certain level. Michael Rennie thinks this has something to do with a dysfunctional S6 kinase [Cuthbertson D et al: *FASEB J* 10.1096/fj.04-2540fje. December 13, 2004]. Have you been looking at that mechanism?

**Dr Paddon-Jones:** In terms of the difference between young and older people, if we give the elderly adequate nutrition and exercise, it is hard to detect the difference in their responses compared to young people. It is only when something goes wrong that we put them in bed or we give them suboptimal amounts of protein. When we give them a less than adequate dose of protein, which may be 7 g of essential amino acids or the equivalent, we do see a blunted, diminished response in the elderly.

We just did an encouraging pilot study in which we gave a small amount of leucine, about 3 g/meal, to elderly patients and were able to restore basal and postabsorptive protein synthesis to what we think were youthful levels. In those cases, it did not take a large intervention to restore elderly back to a youthful response.

**Dr Boseaus:** I think we have been rightly focusing on muscle here, but at the same time I must expose my great ignorance in not knowing what factors contribute in an environment of systemic inflammation. The same thing that produces protein breakdown in muscle tends to increase or at least preserve protein synthesis in the liver and the inter-organ transport here also. There was a debate about this a number of years ago because the amino acid composition of the liver acute-phase protein synthesis and the muscle breakdown do not match. There is a mismatch about 2.1 to 2.6, if I remember correctly.

As you said, muscle mass in itself without function may not be a beneficial thing, but it could be a good proxy marker for how much metabolism is disturbed and at what pace it goes. But this is pure speculation.

**Dr Reid:** A simple reason we might want to maintain muscle mass is purely for metabolism. It is a glucose sink. In many conditions, not only is muscle contractile function compromised, but glucose regulation can be compromised. That is one reason that I would like to have more meat around patients.

Data from Galveston the last few years and the data that Dr Paddon-Jones showed about amino acid supplementation suggest that if the primary response is preservation of muscle mass, we might still have a deficit in specific force. Our observation in rodents is that antioxidants were pretty good at protecting specific force, but they did not do much for muscle mass. Perhaps we can devise a strategy by two different parallel mechanisms and preserve both components of the muscle, both force and mass.

**Dr Volek:** I think metabolic health is an important point with insulin sensitivity. I would add that muscle also is the main contributor to metabolic weight. We mainly are talking about muscle wasting here, but obesity is also a big problem. Maintaining metabolic rate is crucial for long-term success. Lean body mass accounts for about 80% of metabolic rate, another reason that muscle is important beyond its functional capacity.

One thing we have not discussed is the issue of variability among people. I think personalized or customized medicine and nutrition will be important advancements. Any of us who have done research and looked at the data sets know that nobody responds like the mean. Since we treat people, we must understand some of the factors that contribute to that variability.

We do not have many tools to do that now, but there is some precedent in the pharmaceutical world. For example, it is now possible to identify people who may have an adverse response to certain drugs, or to even titrate drugs such as warfarin based on the presence of specific single nucleotide polymorphisms in their genetic code. This is an exciting area. If we really want to be ahead of the curve, we will try to understand the variability rather than frowning upon it because we do not like it when we do our statistics.

**Dr Morley:** What I am about to say always gets me into trouble. It is feasible that muscle mass could be bad for you when you are really sick or malnourished. Studies of starving

African children, the only relatively clean model, show that when they start to eat, they put down fat. Why do they put down fat before they put down muscle? Because of resting metabolic rate. Muscle uses up energy. If we are putting down muscle and do not have a store of energy to feed our brain, my heart, and other organs, we can run into trouble. We have to be careful that we have adequate fat. People die when they have lost all their fat. It is important to have a store of energy that does not cost you anything.

I do not think muscle size alone is useful. The Osterman study showed that if we put back functional muscle in patients with cancer, we improve power. I think we have to have functional muscle, but we have to be careful about this muscle; if it is just there soaking up energy in a sick person, it may not be useful.

The other point was about why older people look different. First, despite everything we have heard, maybe they are different, but maybe they are not. Maybe at baseline they are not. The best weight lifters in the world by the time they are 80 years of age are 60% to 70% worse than at age 30. Clearly, muscle mass goes down dramatically with aging, and its function goes down as well. The question is why.

There is a rate of living theory that has many problems, but basically it says that the more energy we use up, the more rapidly we will die. We have only so much potential energy in our life, so we might as well moderate it. We need a lot when we are young because we have to go out to hunt and gather, at least our ancestors did. As we get older, we can sit and think, and we do not need as much energy.

Look at the decreases in hormonal levels, particularly those that occur at menopause and beyond—and men have their quasi-menopause around the same age. All these changes are trying to slow us down as we get older. Slowing down may not always be bad as long as we can function.

If I am really into muscle building, I would think that is an anathema, and I would not accept either of my two comments. However, the reality is somewhere in between. We never should believe that muscle does not go down dramatically with aging, because the real life experiment, the muscle builders and weight lifters, clearly shows that we have incredible loss of strength no matter how hard we train.

We have to be careful in the very sick. I do not think we should let them lose muscle, but I do not think we should be adding muscle in ICU patients.