Discussion

Leader: Neile K. Edens, PhD, Abbott Nutrition, Columbus, OH

Dr Edens: In our last session, I would like to turn our attention to clinical science. We have heard over the course of the conference various priorities in clinical investigation. We have heard a need for larger trials, for longer interventions, and for trials in particularly vulnerable populations.

As a nutrition company, we are going to have to make choices and set priorities. So I would like the participants to talk about nutrition intervention questions to address in sarcopenia and cachexia. In particular, as we move nutrition beyond just provision of basic macronutrients and micronutrients into more experimental ingredients such as EPA for management of inflammation and HMB for management of protein degradation, how would you address how new ingredients factor into what you would like to see in the next wave of clinical innovation?

Dr Wheeler: First, we need to address what the role of nutrition can be vs drug therapy or vs no nutrition. In some of the trials we are involved with all over the world, especially in emerging markets, we are learning a great deal about patient care. People in some areas strongly believe that nutrition can play a role in health care. In those areas, the specific nutrients we have discussed here can have a role. But in other areas, people refuse to consider such a role for nutrition.

So we have to address people's beliefs about what role nutrition plays in health care and when it plays that role, and then decide how we feed patients who are in these circumstances where nutrition is not valued as a valid therapy. And we have to address what important outcomes nutrition interventions can produce working synergistically with drug interventions.

Dr Paddon-Jones: From our vast clinical experience, we have a ton of data on protein metabolism, specifically in young, healthy populations and older populations, but we really do not know how that translates to clinical groups. Our first charge is to see whether we get similar response to protein supplementation in these clinical populations. Theoretically, from a practical point of view, we could make a huge difference, if these effects carry over to those groups. But in reality, we really need to look at more of a minimal, feasible approach. Can we get some improvement with a low-volume supplement, something these patients will actually take, rather than the traditional, high-volume supplements we give to younger, healthier subjects?

Dr Guttridge: When I come to meetings like this, I always try to leave with some new insight into our cancer studies and whether some common mechanisms exist between cancer and others conditions related to cachexia such as COPD. I do not think we spend enough time trying to understand the commonalities or the differences between these conditions.

If you at Abbott Nutrition do see improvement in a particular cachexia state with one of your products, I hope that you would try to understand what the markers are that are being affected. Then hopefully, if we see improvement in another cachexia condition, we can see whether those same markers are affected and be able to understand where the overlap is or what the distinctive features are from one condition to another.

Dr Baracos: We need to ask whether we can transform somebody who is sarcopenic to someone who is no longer sarcopenic. Dr Morley stated earlier that you would not have believed that it was possible to put muscle back on people with lung cancer.

The fundamental question is, do they have anabolic potential? We do not know the answer to it. If they have no exploitable anabolic potential, which they might not have if they had been treated with sorafenib, they might well have under some conditions. When we can answer that, we will take a group of people and push them back up the scale, so that they are no longer sarcopenic. We need to do trials that have outcomes that are really clinically important. For instance, can the patients tolerate their chemotherapy, or live longer, or be discharged from an interim weaning ventilator unit—something that matters materially to their outcome. You cannot impress people with a mere promise of a few kilograms of lean body mass.

Dr Lanza: I will continue to harp on the idea that there is more than just muscle mass and muscle strength. I would like to see some more functional outcomes related to mitochondria. One thing that intrigues me, which I think is not well understood, is the

role of some things such as EPA on mitochondrial function. Dr Schols, you described some interesting data on how EPA can be a peroxisome proliferator-activated receptor (PPAR) agonist and possibly affect some intrinsic mitochondrial properties, such as mitochondrial coupling and the process of mitochondrial biogenesis.

Dr Cederholm: I have been thinking about resistance training in the elderly, because we know that resistance training is probably the strongest anabolic stimuli we can use. So why do we not use that much more, even in the elderly population? We know a great deal about the beneficial effects of nutritional supplementation, and we know a great deal about exercise effects, but I think we need to address the combination of strength training and supplementation. Of course, as has been discussed, we then have to try to find the best combinations of amino acids, EPA, or other nutrients. I think we should stress strength training more in the elderly, because we rarely prescribe it in that population. I would also prescribe it for cancer patients and for ARDS patients

Dr Johnson: I agree with Dr Cederholm that after we stabilize a patient after hospital admission, we need to continue the recovery with nutritionals and a rehabilitation component, and then look at morbidity, mortality, and 1-year survival. Because inpatients are still in the acute phase of illness, when designing a trial, we would need to identify the particular clinical conditions that would or would not respond to nutrition therapy.

Dr Boseaus: Two things come to mind. First, selection and classification of subjects is crucial, because with respect to nutritional issues we are not talking about a single

mechanism, a single target, a single outcome, but a multitude of them. Some are obviously more important than others. For instance, if we recruit patients for a cachexia trial, we should go for patients in the early phases of the condition rather than trying to restore something that has broken down, and ensure that they are not hypogonadal and that they are comparable in terms of physical activity. You also will need some measures of the inflammatory response.

The second thing is determining what outcomes are of interest, because there could be a multitude. I advocate function and survival as primary outcomes, and to use other outcomes as proxy indicators along the line.

Dr Reid: What are the most important questions to address first? I want to echo what my colleagues have been saying repeatedly—the importance of a functional measurement. That is not to dismiss the importance of muscle mass. I think maintaining or increasing muscle mass is valuable, but mass alone is not enough. Functional measures are more physiologically relevant to the patient's life, and therefore a more valuable outcome.

Which trials will have the most impact? The ones that get positive results. It is tough to do that in a diverse population of people over long periods of time in slow-moving processes.

I like the Dr Paddon-Jones's model of the saw-toothed wave form, showing catabolic crises that occur from which people recover slowly, if at all. Those crises make a great

opportunity for intervention, because they happen abruptly. We can predict that they are going to happen. We could find clinical or community settings in which we could predict and be prepared to intervene, and we could see an outcome in a fairly short time in a way that would be feasible. What would have the broadest applicability? This depends on what happens most commonly. Infections offer one opportunity, but I think unloading is perhaps a more available crisis in which to intervene. We might find a targeted, specific condition with which we could get positive results in a big population of people—people who get bed rest for 2 weeks, for example, or older people who break their leg and get a cast.

Dr Schols: I think three issues should be addressed. First, there is much exciting experimental research ongoing on trying to unravel mechanisms involved in muscle maintenance. I think we also should invest in translating these studies to specific groups of patients that are phenotypes with respect to their body composition and functional capacity. I think this is more important than just discussing all the definitions for sarcopenia or cachexia.

As Dr Reid said, when we are interested in seeing whether specific nutrients or novel compounds can modulate these processes, we have to go to more acute models, patient situations such as acute exacerbations in chronic diseases such as COPD, and in cancer, maybe when patients have controlled interventions which we know will affect their muscle maintenance because of upregulation of many processes that may adversely affect

the muscle. Then we have this patient situation plus an important process—the recovery from an acute intervention.

Last, I want to stress intervening earlier with sarcopenic patients, particularly when you are dealing with chronic patients.

Abbott Nutrition should not focus only on what supplements should be given, but also on how they are positioned within the total diet, because glucose can be good for muscle maintenance or improvement of function. The general diet of these patients, which provides most of their calories, has a composition that can interfere with ongoing inflammatory processes.

Dr Volek: I think the successful nutrition interventions will be targeted interventions. As I heard today, when the various patient populations with metabolic stress were described, the common thread was inflammation, chronic constitutive inflammation, and acute inflammation. Therefore, nutrition interventions that focus on the inflammatory process, in particular, should be promising. I am a little concerned, however, that much nutrition support pushes high-carbohydrate intake and dextrose, even in total parenteral nutrition solutions. Some evidence shows that such nutrition can exacerbate the inflammatory process.

I like the EPA research for a variety of diseases beyond those described today. However, I would point out the need to protect that EPA, especially with high-dose EPA

supplementation, as it gets incorporated into the phospholipid membrane. Combining EPA with antioxidants and tocopherols, in particular gamma-tocopherol, which is actually anti-inflammatory itself, could be promising. Trials with EPA will have a good chance of showing some efficacy.

Dr Suetta: I agree with Dr Cederholm about how we should be more specific about how and when we apply exercise in our studies, because it is just as variable as nutrient supplementation. If we do that in trials, we should have no problem seeing an effect, especially if we apply both resistance training and supplementation.

I have a comment on focusing on unloading instead of on sarcopenia. I think two different mechanisms are involved. The response we see after an injury or an unloading type of procedure is much faster than what we normally see. We may have to look at this as two different models, but it is not a problem to rebuild muscle, even in patients from the ICU. We just have to do it right.

Dr Supinski: I look at the cells as a factory, making protein instead of, say, cars. If a car factory is not making enough cars, we need more raw materials. Maybe we do not have enough steel. Maybe we do not have enough glass for windshields. Sometimes one of the machines inside the factory breaks or a worker gets sick. Many of these illnesses we are talking about not only have insufficient factory parts, but they have specific workers who are not doing their job. I think we need to use biopharmaceuticals to fix those workers,

get them back to work, and then they will be able to use those supplies that they get more efficiently, and you will get more cars.

I think the answer is a combination of good nutrition, plus for specific diseases for which we know specific targets, biopharmaceuticals that reverse those specific injuries.

Dr Morley: This is a complex question, and you can take it many ways. First, we have to decide what to give. Do we give just a leucine-enriched amino acid supplement a couple of times a day to get our peaks? Would that be enough? Do we need to add creatine? HMB? Do we add EPA? Finally, should we use an oligopolysaccharide? We have shown that decreases inflammation, at least in the elderly in nursing homes. We have to decide what to study. Abbott Nutrition cannot do 40 studies over a year with 40 different things. Maybe you could, but then your bosses would want to know where the profit went. It would be nice, but we are not going to see it. So, you have to find one product that combines what, in your best guess, works.

When you have that product, there are a couple of things to consider. The one I just want to get out of the way is that somebody should study giving protein to everybody who comes into a hospital. Dr Paddon-Jones' literature shows that we can stop much of this muscle loss just by giving people protein from the start for bed rest. If we were doing that, we would make a huge difference.

Otherwise, I would look at a preventive approach. Because I am a geriatrician, I probably would look at COPD. There are many patient models, but I would look at people who exhibit the Fried criteria for frailty or prefrailty, and I would study those living in the community, not in institutions, similar to the study that Chapman and I did.

I would not intervene at first, then I would consider use of a supplement. The supplement would not be given more than twice a day in small amounts, most probably no more than about 300 kcal maximum. Finally, I would look at use of an anabolic stimulus. We know the best anabolic stimulus is resistance exercise. So, I would look at resistance exercise alone first, then add testosterone as another anabolic stimulus and examine the effects of the combination. We have to show that an addition of a supplement to resistance exercise improves outcomes.

The data Chapman and I got show that hospitalizations decrease, and power improves in the population. These are incredible outcomes. I think we would need 1000 to 1500 people to be able to clearly show it, because we need four groups, and at least 250 in a group. If you did that work with an Abbott Nutrition supplement, you would be able to say nobody could give any other supplement but yours.

Of course, I forgot that the supplement has to provide 2000 IUs of vitamin D per day. It is a pain in the neck to give vitamin D. We forget. I am obsessed about vitamin D, and I forget to give it to my patients. I suddenly find that they are now vitamin-D deficient again, because I gave them their 50,000 IUs and then forgot to continue it.

I think you have to put that sort of product together and do one big study instead of multiple little studies. Do a multinational study so you make everybody happy. That would basically give you the product, and it is going to work. Resistance exercise plus a good protein product certainly will work.

Dr Wheeler: Thank all of you for contributing to this conference. We appreciate your taking time out of your busy days, your busy schedules, and your busy jobs to spend this few days with us to bring this important topic to life.

We hope that some of the information we discussed here will stimulate other thoughts and other research programs in this important area for months and years to come. We have learned a great deal and had great discussions about lean body mass. We have talked about how muscle mass is related to overall health and that loss of muscle mass can lead to serious problems, loss of health, and possibly worsening of certain diseases.

Finally, we have learned of various nutrition and exercise therapies that not only help maintain muscle mass, but also help make it more functional as it relates to strength and power.