Discussion

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Dr Tisdale: Dr Bosaeus, you suggested that the drive to synthesize acute-phase proteins by the liver was actually driving the breakdown of skeletal muscle. However, several years ago experiments in mice suggested this was not the case. In that experiment, researchers gave interleukin 6 (IL-6) to mice, and they showed that it indeed induced acute-phase response, but it had no effect whatsoever on skeletal muscle protein or body weight. In contrast, another member of the IL-6 family, ciliary neurotrophic factor, actually produced both. It produced an acute-phase response and a depletion of muscle protein. So although there might be a correlation between the two, I do not think there is a direct linkage between the drive to synthesize acute-phase protein and the loss of skeletal muscle.

Dr Boseaus: I hope I did not imply a direct link there, because I am quite ignorant of all the details. I was trying to illustrate a shift in interorgan metabolism, in which there is a shift to acute-phase proteins in the liver, driven by IL-6 and other cytokine signals. The fuel for that must come from somewhere, and skeletal muscle is probably the best candidate for that. Somehow there has to be a signal, but it does not have to be the same to produce these things. I am not aware of the role of specific cytokines or other signals in orchestrating this, but this is obviously something of interest.

Dr Tisdale: Acute phase proteins can be produced without any loss of skeletal muscle.

Dr Baracos: Skeletal muscle protein is the most likely precursor and fuel to support the acute-phase response; there is not much in the way of alternative resources to commit to the acute-phase response. Theoretically, we could provide more protein intake to drive the acute-phase response in the liver without muscle mobilization. However, as far as I know, the data so far do not show any great reduction in protein breakdown in skeletal muscle by feeding extra protein.

Dr Boseaus, I told my good friend and colleague, Neal McDonald, that I had a patient who had lost 5 units of body mass index in the last 6 months, and who was extremely sarcopenic and cachexic. Noting that I would reasonably expect this person to die within 1 to 2 weeks, I asked him what anticachexia therapy he would propose. His response: "Are you nuts? I do not propose any anticachexia therapy for this person. He or she has no reasonable expectation to benefit from it." If this is indeed a clinically appropriate response, then why is it that in many randomized clinical trials of anticachexia therapy and nutritional support, so many patients very close to death are included?

It may be in the best interest of research done in this area to find a way to exclude such people from trials or analyses of data, because there is indeed no expectation of a treatment response. Benefit of nutritional support is not expected immediately preceding death, like it might well be in longer-surviving cancer patients or COPD patients who are not imminently dying. Is approximately 12 weeks of treatment required to produce a quantifiable benefit? What do you think about this issue?

Dr Boseaus: I agree. But the main criterion in the studies I described has been expected survival of more than 6 months in the mind of the attending physician. In practice, this measure ends up a mean of 8 months ±130 days. This is crude, but it is one way to go. Perhaps we could find better features than the clinical judgment of the attending physician for identifying those people at an earlier stage.

Another crude measure we have tried is to be on the alert for small changes in weight. So for instance, when initiating an insulin trial, it was on the premise of when weight loss started. In practice, we were able to clinically detect, with the help of the patient, about a 2% weight loss from the stabilization plateau.

Dr Baracos: Another conundrum that strikes me every day as I go into the cancer center worried about cachexia is that there are more new patients diagnosed with metastatic disease who are so fat that they cannot fit in the magnetic resonance imaging (MRI) machine than there are people who are clinically underweight. This may be a leading-edge North American phenomenon, but I do not have an honest answer to what the nutritional strategy should be for a patient who is sarcopenic obese.

Dr Boseaus: I do not have that answer either. But if a patient has a large fat reserve, which is energy reserve, we could focus less on energy balance and more on muscle. What that would reflect in practice, I would not speculate on now.

Dr Morley: Dr Boseaus, I liked your approach to cancer cachexia, but the question that now has to arise with the GTx Ostarine™ study in cancer is whether catabolism actually matters. Those researchers used an anabolic agent with minimal anticatabolic effects and showed improved power in a sick group of cancer patients over 6 months to 1 year. I thought the study would fail, so I was surprised at the outcome. We have to recognize the possibility that if we can actually drive protein into muscle, we will build muscle even in the presence of a catabolic stimulus, which all of these patients had. This turns everything upside down from the way I have thought of it before.

Dr Boseaus: Perhaps I should have been clearer, but this imbalance with synthesis down, degradation up, probably varies in a single individual and perhaps also over time. If the main problem is on the synthesis side, yes, anabolic stimuli could be the agents of choice, but these would probably be less effective if at the same time degradation was up. I do not know what clinical markers that could be used to classify a patient in these terms, but if it became possible, I think it would be a help.

Dr Morley: I would have thought in a predominantly lung-cancer group, it would have been catabolic. That is what I believed before I saw the data. Our study in assisted living, coupled with other recent studies, suggest that if we provide some sort of protein supplement along with an anabolic stimulus, we may well make a major difference in this population.

A question we are left with in the ICU population is whether we should first give them vitamin D, then give everything else. Should we give essential amino acids and fish oil, as people come into the ICU, along with an anabolic stimulus, or should we wait? The insulin trials in the ICU are difficult to interpret. We have no idea what the right answer is anymore.

Dr Supinksi: I think these patients need to be fed early, and giving EPA when they first come in would be logical.

A characteristic of the ICU population that makes it different from the cancer patients is the ICU patients get acute respiratory distress syndrome (ARDS). The strange thing about ARDS is that procollagen 3 is a biomarker in the lung fluid that predicts bad outcomes. The higher the procollagen 3, the more fibrosis the patients get, the worse the outcome is.

One concern is that anabolic agents tend not to just be anabolic in legs, but they also may be anabolic in lungs. Testosterone, for example, activates procollagen 3 pathways. One marker in patients indicating a response to testosterone is procollagen 3 levels in their blood. We have had that experience when we tried to give anabolic agents such as oxandrolone to patients in the ICU; lung function actually gets worse in response to the anabolic agent. I am concerned about the really critically ill patient population—people who have fibrosis in their lungs or some sort of ongoing pulmonary inflammation. Is there an anabolic agent that can help muscle without damaging the lung? I think that is a serious unanswered question. One controlled study by some surgeons who randomized

everybody in their ICU to oxandrolone vs a placebo found that length of stay on a ventilator increased and time in the ICU increased in the patients who got the anabolic agent [Bulger EM et al: *Ann Surg* 2004;240:472-478].

Dr Reid: Dr Supinski, I am stimulated by the discussions earlier about the effects of nutrition in cancer and in COPD, and by your repeated comments that in the ICU, patients often get very little nutrition and nutrition is not a high priority. Do you think that protein or nutrition per se would fall in the same category, and you would want to be cautious about providing it? Or if you would be willing to give nutrition, how do you go about changing the culture in the ICU to help people understand the importance of nutrition?

Dr Supinski: I am fairly crazy, but I am not so crazy that I think you should not feed patients. I worry about oxandrolone and androgens in general, but I would feed them. I complained this morning that patients are not being fed. I do not think that clinicians do not want to feed patients, but patients fail to receive nutrition because of procedural issues (eg, holding feedings to perform tests, to perform ventilator weaning trials, etc). Sometimes feeding is stopped for a procedure, and people do not get around to resuming it for 24-48 hours. How do you change that? This is a national problem in taking care of patients in ICUs. ICUs are chaotic, and we need to have better approaches that allow a more determined approach to feeding.

Dr Stephen DeMichelle [Abbott Nutrition]: Dr Supinski, I share with Dr Reid a philosophical question. Do you see antiproteolytic therapy being implemented with the new recommendation for lower tidal volume, lung strategies, and fluid therapy in ICU patients with a complex pathophysiology, or do you see it implemented more often in patients weaned off the ventilator and discharged from the hospital?

I am interested in acquired weakness and frailty once the patients leave the hospital, and in the new data coming 5-years later. Is this proteolytic pathway still turned on, or is the issue that patients are discharged, depressed, and delirious and not getting adequate care and good nutritional support?

Dr Supinksi: As I said, these patients should get some nutrition, and we should not wait to provide it. In fact, I do not think that we can wait until they are ready to wean from the ventilator. The data I presented show that by the time the physician gets around to weaning these patients, they are already weak. We need to give nutrients and anabolic agents such as EPA early. We have to set some better standards to feed these people earlier. Much of the delay is caused by the chaos in the ICU unit, but we have to figure out a way to get around that.