

THE ROLE OF MUSCLE & HMB IN CLINICAL PRACTICE TO IMPROVE OUTCOMES

Featuring :: Dr Laura Matarese (PHD RDN, LDN, CNSC, FADA, FASPEN, FAND), Dr Gerry Mullin (MD, MS), Dr Refaat Hegazi (MD, PhD, MS, MPH, MBA)

TRANSCRIPT

Maura: You know, even in normal times outside of this Covid-19 pandemic, muscle plays a central role in immunity, recovery and overall health. Because really, many patients are at risk for muscle loss, especially those with advancing age or acute and chronic conditions. And, often, a person's lean body mass is an important factor that can have a strong influence on quality of life and physical function—especially when struggling with an illness or working toward recovery.

Maura: And that's in normal times. But let's face it, we're still in the middle of a pandemic. Things aren't normal yet, and maybe they won't be for a while. And so our focus on Covid-19 continues. We're talking today about the role muscle can play in *clinical practice*, with Covid-19 as our context. And we have a lot to cover.

Maura: So, with me today are three experts on this topic:

- **Dr Laura Matarese** (PHD, RDN, LDN, CNSC, FADA, FASPEN, FAND), professor of medicine, gastroenterology, hepatology and nutrition at East Carolina University
- **Dr Gerry Mullin** (MD, MS), a board-certified internist and associate professor of medicine, who serves as the director of integrative GI nutrition services at The Johns Hopkins Hospital
- **Dr Refaat Hegazi** (MD, PhD, MS, MPH, MBA), the head of global medical affairs and director of Scientific and Medical External Engagement at Abbott

Maura: That's a mouthful. <<laughs>> Welcome to you all today, and we are so grateful that you're here.

Dr Matarese: Well hello everyone! It really is a pleasure and a privilege for me to be here and to share this virtual podium with such distinguished faculty. I think this will be a very interesting discussion.

Dr Mullin: Yes, likewise. It's very exciting to be here and I'm looking forward to the discussion as well.

Dr Hegazi: And I'd say exactly the same. Thanks so much for connecting us, Maura, with two esteemed experts and leaders in the field.

Maura: One thing to note for our listeners: This podcast recording may sound a little different than you're used to hearing. We're all still social distancing, so Dr Matarese, Dr Mullin, Dr Hegazi and I are all dialing in for today's discussion rather than sitting in the studio.

Maura: Alright. With all that said, I'm hoping I can talk you all into telling us a little bit about yourselves—your current role, and what brought you to where you are in your career currently? Dr Matarese, would you like to start?

Dr Matarese: I'm a professor at the Brody School of Medicine at East Carolina University in Greenville, North

Carolina. I've held a number of positions beginning at the University of Cincinnati, and then the Cleveland Clinic, then the Starzl Transplantation Institute at the University of Pittsburgh. All of that before moving to Greenville.

Dr Matarese: The bulk of my career has been in nutrition support. I've been moved into the area of intestinal rehabilitation and intestinal transplant. In addition to my GI practice here, my current position has allowed me to expand my practice and research efforts into obesity and exercise physiology, as well as care of patients with HIV.

Dr Mullin: It's an interesting story, because I started out in a laboratory at the NIH doing basic immunology, and then when I moved to New York, I became more of a faculty, which was more geared toward inflammatory bowel disease basic research. But from there I had a personal interest in nutrition, and I pursued a master's-level education. After a good year-and-a-half of education in that direction, I took it back to my hospital in New York, and actually applied it in the clinical setting, and also in the hospital setting, and eventually led a nutrition support team, developed a nutrition committee.

Dr Mullin: And at that point back in the late 90s I had an interest in mitigating malnutrition when it wasn't really en vogue, and carried that over to John's Hopkins. It was a unique experience both in complementary integrative medicine nutrition, but also again looking at malnutrition and mitigating malnutrition in the hospital setting. Now, and for the last 10 years, I chair the nutrition advisory committee there.

Dr Hegazi: Yes, I'm a physician scientist by training. I graduated from Mansoura University in Egypt 1989. I started my clinical career as a surgery resident, but I discovered very soon that I was into reading and writing manuscripts and publications and doing clinical research, so I switched that. And I got a Master of Occupational Medicine at the University of Mansura before I went to the University of Pittsburgh in 1996, where I had my Master of Public Health and PhD studying nutrition and epidemiology. I stayed in Pittsburgh and did my post-doctoral fellowship in GI immunology at the GI division at the University of Pittsburgh School of Medicine. I then joined the clinical faculty in Pittsburgh as an attending staff overseeing the GI nutrition consult. And very interestingly, I did work with Dr Matarese, seeing patients of hers, and she saw patients of mine.

Dr Hegazi: I moved to Abbott as a medical director before I now assumed the responsibility of the head of global medical affairs and the external engagement team, really working on developing new products and for patients that address the nutritional needs for a variety of patients, from disease-related malnutrition to diabetes and metabolic syndrome. I'm very involved in education, as well, definitely working with the Abbott Nutrition Health Institute, trying to promote best practices and superb nutrition education for our peers of physicians and dietitians and other healthcare professionals as well.

Maura: Great—thanks so much for sharing your backgrounds. So: As we all know, we are in the middle of a pandemic with COVID-19. How is this impacting your clinical practice and the way you care for patients?

Dr Matarese: Well, these certainly are challenging times. As far as research, all of my clinical research trials have been suspended, at least temporarily. The patient care has become more complex—at least in my opinion it has. We're trying to do most of it via telemedicine, but clearly there are some patients that I must see in person in the clinics. We're trying to screen those patients and really limit this as much as possible and move more toward telemedicine. So, I'll be interested to hear what Dr Mullin is doing, as well.

Dr Mullin: Yes, we've also moved much of our clinical operation to telemedicine, but we still have a front-line presence in the hospital. At Hopkins, we've become a bit overwhelmed with Covid. We've become more of a Covid hospital. And although not as bad as what you've seen in New York, we do have a convention center that we use for patients much like the convention center in New York has done for their patients. And here it's been a good question about whether—these patients come in particularly malnourished, and if there's a way we can mitigate that, has been on my radar of late.

Maura: In terms of the nutrition care being provided to patients, how is COVID-19 impacting how we provide optimal nutrition support?

Dr Mullin: Well, that's a good question. I would say that there are some challenges that we'll likely discuss around the table, and that is that there are limitations with appetite. People are coming in malnourished from not only lack of intake, from and lack of appetite, but also there is enteropathy associated with Covid-19. We're seeing more and more of an emerging theme that those with GI symptoms do worse. And they present later in the course, and they actually have a higher mortality with complications. So it's raising questions, and we know that SARS-Cov-2 does involve the gut and other organs, is there a way we can mitigate again the enteropathy associated with SARS-Cov-2 or Covid-19.

Dr Mullin: There's also challenges with feeding in the ICU—with proning—we know that the ventilation down to the lower bases of the lungs improved when patients are prone, and feeding these patients can be challenging because of that, at least enterally. So we have two challenges. One: That patients are coming into the with what appears to be a higher prevalence of malnutrition, which we have not seen papers quite at this point, to my knowledge. But we're considering that. Two: What can we do to really circumvent the limitations and challenges in feeding patients because of proning, and also because of the enteropathy associated with this condition.

Dr Matarese: We're looking at our Covid patient data on a regular basis. Most of our patients—about 80%--are African American. They're obese, with an average body mass index of 33. The average age is 60. And a very high-risk population for malnutrition. I think the biggest problem is that we have very little data regarding the safety and efficacy of nutrition interventions for Covid-19. In addition, I think there are likely three phases of nutrition intervention. The acute ICU phase, the non-acute Covid-positive patients, and then the post-ICU hospital discharge phase, and that's where our rehabilitation efforts are going to be required.

Dr Matarese: There are various protocols that have been proposed, including the use of vitamin D, Zinc, ascorbic acid, but the data are limited, basically non-existent. There are a number of trials that are underway. You can go to clinicaltrials.gov to look at them. The last time I checked there were around 20 underway or at least registered. But at the moment, the exact way to see these patients, the timing, the duration, are still unknown.

Maura: With so many patients still in the ICU, on ventilators and being bed-ridden for extended periods of time, is this impacting their overall muscle mass and muscle health?

Dr Matarese: We know that prolonged ICU stays and hospitalizations are associated with loss of body weight and in particular lean body mass. And many of these patients continue to lose weight after discharge with a progressive loss of function. And we've already seen reports of extreme weight loss and muscle loss in the Covid patient post-discharge from the hospital, especially if they've had a prolonged hospitalization where they've been bed-ridden for any length of time. So I think these issues will have to be addressed in the Covid-19 population. Dr Mullin, what have you seen?

Dr Mullin: I agree with you about the rehabilitation being a challenge and not really getting enough attention, quite honestly, because those that do survive are quite beat up, physically, psychologically, mentally and nutritionally. And that type of rehabilitation really takes a concerted effort. And I don't see that being done at this point.

Dr Hegazi: I think the fact that any inflammation-associated diseases put patients under a tremendous amount of risk for muscle loss, and the intricate association between acute and/or chronic inflammation and muscle loss, have been really highlighted in probably one of the major events that has happened in our field in the last few years. And you start to see inflammation as a requirement of diagnosing malnutrition in both ESPEN and AND guidelines and the GLIM criteria for diagnosing undernutrition. So, for Covid-19 patients, definitely there are tremendous amounts of inflammatory stress and cytokine storm that could lead to severe muscle wasting that probably will not be addressed within the first few days of nutrition intervention. It's actually a long period of recovery that requires

intensive nutritional therapy.

Maura: And why does this loss of muscle matter so much? We know it complicates their care and recovery—can you describe how?

Dr Matarese: First of all there is no disease or clinical condition that actually benefits from a malnourished state, but many that can benefit from the appropriate nutrition interventions. I know that loss of lean body mass is a particular concern. It's difficult to replenish muscle once it's lost. And this reduced muscle mass is associated with impaired physical function and frailty, and that's related to increased morbidity and mortality.

Dr Matarese: I've already seen a few photographs on cable news networks and social media of patients who are discharge after prolonged hospitalization—these are Covid patients—and the loss of not only body weight and lean body mass is impressive. So, I think we're going to have some challenges in the repletion phase.

Dr Hegazi: We know that muscle is a structural organ that supports the maintenance of the structure of the body. But muscle is much more than that. Muscle is an important metabolically active and homeostatic organ. It is the source of all the amino acids we depend on in acute illness and critical illness to support our metabolism. All these amino acids are actually a fuel source for immune cells. So it's considered muscle as a reservoir of amino acids that are stored there to help when conditions become critically ill, and that's why we get the loss of muscle mass associated with acute illness. But also it's a major endocrinological organ; it's very important in glucose homeostasis, and insulin resistance, for example, because it's a major fuel for blood glucose and the more we know about the muscle quality and its association with insulin resistance, the more we realize how important muscle is.

Dr Mullin: It's interesting that muscle is a physiological contributor to an anti-inflammatory process, and that when we optimize we know from exercise physiology we can actually help attenuate inflammatory attacks, so in the setting of loss of lean body mass, you're less apt to contribute to that process, and also you're more susceptible to an inflammatory attack as well. So that's why when we see the elderly who are incredibly sarcopenic, their outcomes are much poorer because of their decreased ability to really take a hit from any infectious entity, particularly an aggressive virus like this.

Maura: So for patients with COVID-19 who have lost muscle mass, what can we do for them nutritionally? For instance, are there specific nutritional interventions or specific nutrients or ingredients that can benefit them both early during ICU admission and post-discharge?

Dr Mullin: Well, I think we all would agree that an HMB supplement would make a lot of sense, for those who are particularly sarcopenic to preserve the lean body mass that's available. And, you know, we're seeing more and more attention paid to the GI issues, so it's more than just respiratory that may be contributing.

Dr Matarese: I agree with what Dr Mullin just stated, and as a dietitian, I certainly would say that I think food is best, but when patients can't eat enough for repletion, which I think is the case for many of these Covid patients, then we need to do something extra, and oral nutrition supplementation may be of benefit. And I know Dr Mullin and I have discussed this: I'm intrigued by the idea of providing an oral supplement with HMB to try to increase the muscle mass and function in these patients. I think there's enough data out there to suggest that with HMB—and good nutrition—that we can probably increase muscle mass function.

Dr Hegazi: Yes, I totally concur with what Dr Matarese and Dr Mullin have alluded to—that for us to decrease the degradation that happens with acute illness, high protein first, and then high protein oral nutritional supplementation especially in the early phases, or high protein enteral feeding formulation, and then there are the specific nutrients like HMB for example. Those are actually all intervention that helps decrease the impact on the muscle, especially with the acute illness.

Dr Hegazi: I just want to highlight that yes, food is best—I totally agree with Laura—but what those patients especially with infection, there's something very well known in the medical community called anorexia of infection, and that means the appetite suppression of patients with infectious diseases. So, I think there's now in 2020 more science that alludes to the fact we have certain ingredients that can help with this illness. And I totally agree on HMB, in addition to high protein.

Maura: I know there isn't much research on Covid-19 right now, so what evidence can clinicians turn to direct their care in terms of nutrition intervention for these patients?

Dr Matarese: Well, I'll start. There are at least two recent meta-analysis on HMB, and I think that's a good starting point. I think the most significant study is the Nourish trial with focused on malnourished patients with cardiopulmonary diseases. Obviously it's a different model, but I think it demonstrates that we can increase muscle mass function in other important parameters. I'll be interested in hearing what Dr Mullin and Dr Hegazi have to say on this point.

Dr Mullin: Actually, with the Nourish trial I feel that the cardiopulmonary disease is one of the main comorbidities with this disease in an elderly population so I think that if I were going to fashion a proposal to feed people, I would model it after the Nourish trial.

Dr Matarese: I agree with that. And these patients do have cardiopulmonary issues.

Dr Mullin: ...And worse outcomes, so I think that would be a target population using high-pro HMB.

Dr Matarese: Right. It wasn't Covid per se, but certainly there's a lot of overlap in terms of their disease processes.

Dr Hegazi: Yes. I totally agree. And if you recall, Dr Matarese—you were a co-author of the Nourish trial publication—those were elderly, malnourished patients with cardio pulmonary diseases. And if you look at the risk factors for acute Covid-19, it's actually all of these conditions in addition to malnutrition and low albumin that has been popping up in the literature now as an independent risk factor for the severity of the disease. So I think the process we're talking about is similar, which is inflammation associated with loss of muscle mass, which is really the main issue we're targeting here.

Maura: You've each mentioned HMB, or beta-hydroxy-beta-methylbutyrate. Can you tell us about its mechanism of action? How can HMB be used to help these patients in terms of muscle mass and outcomes?

Dr Hegazi: Sure. So HMB as you mentioned is a metabolite of the amino acid leucine and it has been in the literature for many decades. It started in the athletes showing that improved muscle mass and decreased degradation. It has a couple more mechanisms of action. For example, HMB is known to stimulate the mammalian target of rapamycin or mTOR, which leads to increase protein synthesis. So, the net effect of HMB is you probably stimulate muscle protein synthesis and decrease muscle protein degradation.

Maura: Since we have a combination of clinicians here today, how can physicians and dietitians work together to optimize care for these patients?

Dr Matarese: Well I'll start by saying communication is key, is absolutely essential, especially since at this point we really do not know the best way to nourish these patients. We have lots of ideas, and these ideas are based on sound hypotheses and biochemistry and physiology, but I think communicating with the physician and the whole healthcare team is really an important point.

Dr Mullin: For me I chair a nutrition advisory committee which is multidisciplinary, and we receive really tremendous input and make policy changes once we engage a number of different specialties on the table: speech pathology, physical therapy, and particularly dietitians. They are essential partners in patient care in particular this population with Covid-19. It takes a tremendous amount of resources to care for these patients, and the dietitians are really assets for us. I've found that since I was leading a nutrition support team back in the 90s and forward. And I think doctors and dietitians need to continue to partner to impact outcomes. And the one thing I'd like to say—maybe Refaat can speak to this—in our society we've seen a shift in the way gastrologists perceive and partner with the dietitian. And I think there's a number of people who really forwarded that or pushed that effort. Now we're seeing the fruition of that in terms of partnering with dietitians even in academia within our own field. That ultimately is going to lead to more communication as Laura said, and better outcomes for the patient because doctors are now more mindful of nutrition, and realize they need to partner with an expert in food-based therapies to impact these outcomes.

Dr Hegazi: I totally agree with Dr Matarese and Dr Mullin. It's a multidisciplinary effort. And I recall our days at the University of Pittsburgh Medical Center where we had the physician, the dietitian and the pharmacist, the nurse practitioner, the GI fellow—all part of one team addressing patients for nutritional intervention and the best nutrition therapy. And it's amazing how every one of those specialties bring a unique contribution to the team. At the end of the day, we're all for the best care for patients, and it's all this "Everybody chime in," you know. The pharmacist will lead the TPN formulation and the IV fluids; the dietitian can take care of the whole comprehensive nutritional care, the physician will tie into the medical specialty and disease of the patient. At the end of the day this team is needed to promote proper nutrition and intervention.

Maura: With all of that said, what advice can you give to front-line clinicians caring for patients nutritionally – what 1 or 2 things can they do to help their patients?

Dr Matarese: Nutrition is a critical component of the care of these patients, so start early. Use the gut whenever possible. Correct any nutrient deficiencies and make certain you have a plan for rehabilitation for these patients once they're discharged.

Dr Mullin: I think that Covid-19 is a very uniquely aggressive condition like we've never seen before, with a high mortality and a proclivity for what they call cytokine storm, and associated with that we're becoming more and more aware that the gut is a primary area of attack. And those individuals who unfortunately suffer a GI manifestation of this condition have worse outcomes. So I think it provides all of us opportunities to promote early enteral nutrition for these individuals with Covid-19 associated GI manifestations, most notably enteropathy, because unless you intervene early, you can have a run-away train situation, and once you have a cytokine storm, the mortality is particularly high. So we haven't seen early enteral nutrition on a clinical trial basis, I think you will see that happen, and I think you will see that there will be impacts on outcome, just like with the Abbott-sponsored ONS trial with NOURISH that Laura and Dr Hegazi have been speaking about with positive outcomes. In terms of impacts on 90-day mortality, I think you have a very similar population to intervene and with a very strategic intervention, I think we'll have positive outcomes.

Dr Hegazi: I totally support exactly what Dr Mullin and Dr Matarese have started. Early intervention is the key, early enteral nutrition is preferred because you're supporting the gut associated lymphoid tissue and all the gut function, and then optimizing protein and calories for those patients. And the EFFORT trial that was recently published in Lancet by Dr Philipp Schütz, informed us and actually supported what we've seen also with the NOURISH trial, that early intervention, achieving calorie and protein amounts required to support patient nutrition early in the disease during hospital admission is associated with both decreased 30-day mortality and 30-day readmission. They even published a meta-analysis in JAMA open-access very recently showing the same thing. So early enteral protein and probably in specific ingredients that can address muscle loss like HMB.

Maura: Alright, last question for you: You've talked a bit about resources—including the NOURISH study—to help

practitioners address this pandemic. Are there others you'd like to mention?

Dr Matarese: I would also add the ESPEN website has some guidelines as well. And even various societies like the AGA have posted some guidelines. And that's what they are—they're guidelines—because at this point we really don't have a lot of data. And to add to that, I always go to the primary literature to see what's out there, and in the absence of any data on nutrition intervention, I think anything you do needs to be based on sound biochemical and physiological principles. And the other thing I've done is I call colleagues to see what they're doing.

Dr Mullin: Yes, the ASPEN website does have broad-based strokes in terms of guidelines for feeding patients during the pandemic.

Dr Hegazi: I totally agree, especially these days when a plethora of information pops up every day, every minute, on the internet, and little evidence is probably supporting some of these claims or advice, so definitely a trusted resource—probably society guidelines, society websites, esteemed experts in the field. And I think I would add to that Abbott Nutrition Health Institute has also hosted a lot of the authors of the guidance that was published talking about nutritional management of Covid-19 patients. ANHI.org is a trusted resource that I would recommend until we have the evidence we have to rely on the expertise of our thought leaders.

Maura: Excellent insights from each of you. Thank you so much. We appreciate all you're doing to help build awareness for the important role nutrition has to play in the management of patients with this virus. So thank you all. And I hope you'll join us again sometime.

Maura: Now, for our listeners, if you're hoping for more podcast episodes on nutrition and immunity, we've developed a robust series of additional episodes to help support you—in fact, we have a host of Covid-19 related episodes already on our website, and we'll continue to add to the episode list each week until this virus begins to subside. You can find these recordings on anhi.org by clicking "RESOURCES" then "PODCASTS & VIDEOS." These recordings are incredibly insightful, so don't miss an episode: Become an anhi.org member today by clicking "REGISTER" at the top of our homepage, and by doing that, you'll receive regular nutrition science news updates from our team. You can also follow the Abbott Nutrition Health Institute on LinkedIn—we publish posts there every day.

Maura: And finally, our website, anhi.org, has a series of printable resources related to this topic—for instance, infographics on [nutrition and immunity](#), [dehydration](#), and [why maintaining muscle matters](#). You can find these resources on anhi.org by clicking "RESOURCES" and "PRINTABLE MATERIALS."

Maura: Thanks everyone. Stay healthy and safe.