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Anabolic Resistance: An Uncomfortable Truth for Clinical Trials in Preventing Intensive Care–acquired Weakness and Physical Functional Impairment

Acute muscle wasting occurs rapidly in critically ill patients and results in long-lasting physical functional impairment, at substantial physical, emotional, and economic cost to patients, families, and society. After critical illness, patients struggle to regain muscle mass, and rehabilitation strategies have yet to be demonstrated to be successful, emphasizing the need for primary prevention to minimize muscle loss during the acute phase. Loss of muscle mass is the result of altered protein homeostasis, which is in turn underpinned by intramuscular inflammation and bioenergetic failure from altered substrate use (1, 2). Given the scale of the clinical problem, and the lack of therapeutic options, maintaining muscle mass and associated physical function is of increasing interest to clinical trialists and funding bodies (3). One frequently discussed possibility is to increase protein intake to prevent the loss of muscle protein, but trials have in general not been successful. Designing appropriate interventional studies requires additional physiological and mechanistic knowledge, such as the ability of skeletal muscle to both receive and respond to such interventions. The recent study by Chapple and colleagues (pp. 740–749) in this issue of the *Journal* supplies exactly this (4).

Dynamic measurements of physiological processes are challenging to both observe and quantify. Molecular medicine remains an imperfect window, with multiple competing and interacting intracellular pathways to account for, in addition to the entropic requirements of these processes. Stable isotope tracer methodology has existed for almost eight decades and has over time become increasingly sophisticated as a summative measure of physiological processes (5). This technology, which uses stable isotope–labeled metabolites, is the only method available to quantify the flux or rate of metabolic and physiological pathways *in vivo* in humans, without any risk for the subjects because of the use of nonradioactive isotopes that are already naturally occurring. Challenges with this technology are the relatively high costs for material and analyses and the required expertise in mass spectrometry and kinetic modeling. Chapple and colleagues (4) have used this technology by combining different stable isotope tracers of amino acid and protein metabolism in an innovative way, quantifying several components of protein metabolism at the same time.

Chapple and colleagues (4) offer a unique physiological observational study filling two important gaps in knowledge of relevance to current trials of nutritional protein supplementation in critically ill patients. First, is amino acid absorption impaired as measured by gut lumen to central circulation flux? Second, is the dynamic capacity of skeletal muscle to respond to nutritional amino acids impaired? Stable isotope infusions into two compartments (luminal and central circulation) were performed, and incorporation of amino acids into a third compartment (skeletal muscle) was measured, encompassing the entirety of the nutritional amino acid supplementation pathway and its potential downstream impact.

Three distinct but related observations were made. First, duodenum-administered protein absorption into the central circulation was not impaired in critically ill patients compared with healthy control subjects over 6 hours. Second, the response of the whole-body protein balance to an enteral protein feed was similar in patients and control subjects, despite overall higher whole-body protein turnover (protein breakdown and synthesis) in the patients. Last, although fasting muscle protein synthesis rates did not differ between groups, a blunted response in muscle protein synthesis was seen in critically ill patients after intraduodenal protein administration. This resulted in 60% less nutritional protein being incorporated into skeletal muscle in critically ill patients compared with healthy control subjects,

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in keeping with the presence of anabolic resistance. The convergence of data from different isotopes offers confidence in the observation of this phenomenon, unwelcome as it might be.

The impact of these data on routine clinical practice is likely to be minimal, though one might reasonably hypothesize that if anabolic resistance occurs in bolus feeding, then it is likely to occur in continuous feeding or even be more marked (6). This challenges current practice guidelines in addition to challenging current recommendations of increasing protein delivery to prevent muscle wasting, as this is likely to result in diminishing returns. However, a normal effect on whole-body protein balance has been observed in this and other studies, which could have beneficial effects for patients (7).

The impact of these data on the design of current and future clinical trials is, however, quite significant and potentially disheartening. Three multicenter randomized trials of increased protein delivery are currently ongoing: the EFFORT (Effect of Higher Protein Dosing in Critically Ill Patients) trial, the PRECISe (Protein Provision in Critical Illness) trial, and TARGET-PROTEIN (Augmented versus Routine Approach to Giving Energy-PROTEIN) trial. These data suggest that the idea that we may maintain muscle mass in critically ill patients by stimulating muscle protein synthesis with nutritional protein should be reconsidered. The scale of anabolic resistance seen suggests that the effect size of the intervention would be quite small (8). Possibly, higher protein doses will overcome this problem, but this is not guaranteed, and higher doses may even be harmful. Anabolic resistance in elderly patients can be overcome by increasing protein intake or by combining it with resistance exercise (9), but whether this will work in acutely critically ill patients needs to be studied. Age-related anabolic resistance may compound this further, as the average age in Chapple and colleagues' study was 50 years, a decade or so younger than the average critically ill patient. Worryingly, these data suggest that the synergistic interaction between exercise and nutrition may also be blunted in the acute phase.

These data do offer a clear steer in the field of intervention development for the prevention and treatment of muscle wasting in critically ill patients. Undifferentiated hydrolyzed protein formulae are likely to offer little benefit in terms of amino acid absorption. In devising strategies, researchers should perhaps consider focusing on underpinning abnormal physiology and metabolism of altered protein homeostasis: that of intramuscular inflammation and altered substrate use leading to bioenergetic failure (10). Immunomodulation, substrate switching, and altering peripheral insulin sensitivity are some of the more promising mechanisms to target, which may then reduce anabolic resistance and allow muscle mass maintenance from nutritional protein delivery and/or exercise. Muscle protein breakdown is the other side of the protein homeostasis equation that is significantly affected in critically ill patients (1, 11–13) and perhaps needs to be examined as a therapeutic target in critically ill patients. This has not been an approach taken in the field of muscle wasting generally, as muscle protein synthesis is the dominant or facilitative process in humans (14). Nevertheless, in the face of compelling evidence for anabolic resistance, altering muscle protein breakdown may be an alternative therapeutic option. These alternative approaches to maintaining muscle mass are ones that the field is less comfortable with, but data remain data regardless of our comfort zones. ■

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