Muscle Mass and Protein Metabolism

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Physiological Regulation of Muscle Protein Kinetics

Muscle protein content is regulated acutely (minutes to hours) by modulation of the rates of protein synthesis and degradation. In physiological conditions, a small fraction of muscle protein content is lost in the postabsorptive state, whereas it is immediately regained with the following meal. Thus, the efficiency of the mechanisms responsible for the regulation of protein synthesis and degradation in the postabsorptive and fed states appears to be crucial for maintaining skeletal muscle mass throughout the day, thereby avoiding protein wasting. The hydrolysis protein to their constituent amino acids is a highly regulated process. The adenosine triphosphate (ATP)-independent lysosomal proteases, Ca\textsuperscript{2+}-dependent proteases and an ATP-dependent pathway involving the ubiquitin-proteasome complex have been identified in skeletal muscle. Under normal physiological conditions, the lysosomes are predominantly involved in the degradation of extracellular and membrane-associated proteins. In contrast, the ubiquitin-dependent system is quantitatively the most important degradative system of myofibrillar proteins in skeletal muscle. Anabolic and catabolic hormones, such as insulin and cortisol, may inhibit or stimulate the activity of the ubiquitin-proteasome system. The synthesis of myofibrillar proteins in skeletal muscle requires the presence of physiological levels of insulin [1]. Nonetheless the importance of amino acid availability in the postprandial stimulation of muscle protein synthesis should be emphasized. Following amino acid administration, muscle protein synthesis increases proportionally to the amount of amino acids administered, up to 3 times the basal postabsorptive value. Amino acids are more efficiently utilized when given in divided doses (as occurs with meal feeding) rather than with continuous administration (as often occurs in artificial nutrition).
rate of myofibrillar protein synthesis is also proportional to the level of physical activity. Exercise training is associated with increased muscle protein turnover, whereas during prolonged bed rest or in a microgravity environment the rate of muscle protein turnover is decreased. Furthermore, the anabolic action of hyperaminoacidemia is enhanced by previous performance of physical activity [2], whereas it is inhibited during muscle inactivity [3].

**Mechanisms of Muscle Protein Wasting**

The physiological regulation of muscle protein synthesis and degradation is often altered in disease states. Depletion of skeletal muscle proteins may adversely affect the morbidity and mortality of patients. Weakness of respiratory muscles may be so great as to impair pulmonary ventilation and contribute to the respiratory insufficiency often associated with severe illness. Muscle wasting may also lead to impaired immune response and gut function through decreased muscle ability to synthesize glutamine. Finally, muscle wasting may delay the recovery from illness and increase the disability of patients leading to poor quality of life. In severe trauma, sepsis, burn injuries or in other critical illnesses an activation of the ubiquitin-proteasome proteolytic system leads to an acute, often-dramatic muscle protein loss. In contrast, chronic disease states are characterized by more subtle alterations in protein metabolism. Protein loss may proceed at such a slow rate that it is often undetectable by the common in vivo methods (e.g., nitrogen balance or isotopically determined protein balance) but may lead to severe protein wasting within months or years. Several mechanisms may contribute to changes in muscle protein kinetics in acute and chronic disease states. Protein loss or protein gain may result from different combinations of changes in rates of protein synthesis and degradation. Alterations in hormone secretion, tissue perfusion, oxygen availability, energy-protein intake, free amino acid pattern, hydration state, acid-base balance as well as activation of the systemic inflammatory response, may interact to change in different directions the rates of protein synthesis and degradation in human diseases.

**Cytokines**

Several lines of evidence indicate a potential link between proinflammatory cytokines, the most important being tumor necrosis factor-α (TNFα), interleukin (IL)-1 and IL-6, and muscle protein catabolism. Epidemiological studies in chronic wasting diseases indicate that circulating levels of inflammatory cytokines correlate with the degree of malnutrition, severity and outcome of the disease [4]. In addition to proinflammatory cytokines, soluble cytokine receptors, cytokine receptor antagonists and anti-inflammatory cytokines are produced in the same settings, the role of which has still to be clearly defined. The exposure of human myoblasts or myocytes to TNFα, results in a decrease in protein synthesis in differentiated cells [5]. TNFα also prevents the
increase in protein synthesis induced by insulin-like growth factor-1, suggesting that the anabolic actions of insulin-like growth factor-1 on muscle protein synthesis may be impaired during catabolic conditions in which TNFα is overexpressed. In animals, TNFα infusion downregulates protein synthesis in muscle and other tissues [6]. Regarding muscle proteolysis, results are conflicting. TNFα has been shown to either activate or suppress components of the ubiquitin-dependent proteolytic system in skeletal muscles. In vivo, modulation of TNFα by xanthine-derived phosphodiesterase inhibitor, decreased proteolysis [7]. In addition, TNFα may influence protein turnover by reducing food intake. Cachexia is a common feature of most chronic inflammatory states. Although TNFα was originally discovered and named ‘cachetin’ because of its role in cachexia, also IL-6 and interferon-γ have been proposed as main mediators of tissue wasting. In experimental systems, muscle protein loss is prevented by the administration of anti-TNFα and anti-interferon-γ antibodies, confirming that humoral mediation of cachexia is not confined to a single cytokine. Not all features of cachexia can be accounted for by classical cytokines, however, which suggests that other mediators probably play a role as well. In the case of cancer cachexia, the tumor itself may produce mediators that influence normal host metabolism. One of these is a glycoprotein produced by human tumors, named proteolysis-inducing factor, which has been shown to initiate muscle protein degradation directly through activation of the ubiquitin-proteasome pathways [8]. In regard to other cytokines, a prolonged exposure to IL-1 has been reported to cause anorexia, weight loss and negative nitrogen balance, suggesting that IL-1 could play a role in the metabolic alterations associated with these pathological conditions. Chronic administration of TNFα or IL-8 was not as effective as IL-1 in the induction of anorexia. IL-6 is also increased in acute and chronic inflammatory states and may specifically affect muscle wasting. It is important to underline that IL-6 is a primary regulator of the acute phase response of liver protein synthesis. Cytokines could also be involved in muscle protein anabolism following resistance exercise training. Physical exercise induces the release of a cascade of cytokines. Nonetheless, in response to exercise, the plasma concentration of IL-6 increases more than that of any other cytokine examined. Recent evidence indicates that physiological concentrations of IL-6 induce an anti-inflammatory rather than an inflammatory response in humans possibly mediated by stimulation of IL-10 secretion and subsequent downregulation of other pro-inflammatory cytokines. Therefore this mechanism could explain the decrease in muscle TNFα gene expression following resistance exercise training in frail elderly individuals [8].

**Hormones**

Hormones play a key role in the regulation of muscle protein synthesis and degradation. Cortisol and catecholamines play a key role in the hypermetabolic response to critical illness. Cortisol is the main catabolic hormone, and directly stimulates the ubiquitin-proteasome proteolytic system. Cortisol
infusion in normal volunteers accelerates muscle protein degradation [9]. Results on catecholamine effects on protein kinetics are conflicting. The activation of the $\beta_2$ receptor in skeletal muscle has the potential to stimulate protein synthesis and inhibit proteolytic pathways [10, 11]. In contrast, a recent study in burned children shows that treatment with the non-selective $\beta_1 \beta_2$ blocker propranolol reverses muscle protein catabolism by increasing protein synthesis [12]. In addition, prolonged $\beta$-blocker therapy in patients with cardiac failure was associated with sparing of lean body mass. Insulin has the potential to stimulate synthesis of several individual muscle proteins including myosin heavy chain [13] as well as mixed muscle [1] and mitochondrial [14] proteins. In addition, insulin inhibits the activities of proteolytic systems including the cathepsins and the ubiquitin-proteasome complex [15]. The essential role of insulin in maintaining normal protein balance is well described by the dramatic muscle wasting observed in patients with insulin-deficient type-1 diabetes mellitus. Resistance to insulin actions with particular regard to glucose metabolism is often described in many chronic diseases (obesity, type-2 diabetes, hypertension, chronic liver disease, chronic renal failure, cancer, etc.). Nonetheless, the degree of resistance to protein anabolic actions of insulin in these conditions remains to be fully elucidated. Growth hormone and insulin-like growth factor-1 are protein-anabolic hormones with muscle-specific actions that may increase muscle protein synthesis under several physiological and pathological conditions [16] and may potentially inhibit proteolysis in other specific situations. Testosterone is also a protein-anabolic hormone whose secretion is often reduced in elderly men. Replacement doses of testosterone significantly increased mixed muscle protein synthesis as well as strength in a group of elderly males [17]. Interestingly, skeletal muscle insulin-like growth factor-1 mRNA was significantly increased by testosterone in this study [17], thus indicating that insulin-like growth factor-1 may be an important mediator of the anabolic effects of testosterone in this tissue. Thyroid hormone deficiency and excess are both associated with muscle wasting. However, the mechanisms of protein catabolism appear to be substantially different in these two conditions. Hypothyroidism with thyroxin deficiency is in fact associated with reduced isotopically measured protein turnover, whereas hyperthyroidism is associated with accelerated protein turnover. Hyperthyroidism is also characterized by increased metabolic rate and oxygen consumption. Increased uncoupling protein expression in hyperthyroidism may impair the efficiency of mitochondrial energy production and therefore contribute to tissue catabolism.

Alterations in Plasma and Muscle Amino Acid Profile
Disease states are often characterized by altered plasma and cellular free amino acid profile. Free leucine levels were often found decreased in liver cirrhosis, chronic uremia and chronic obstructive pulmonary disease. This abnormality may contribute to decreased protein synthesis in these pathological
conditions. Aromatic amino acids are increased in liver cirrhosis, whereas tyrosine may be selectively decreased in chronic uremia because of impaired phenylalanine hydroxylation in the kidney [18]. In skeletal muscle of critically ill patients free glutamine pool is dramatically decreased. In addition, other conditions are characterized by moderate glutamine depletion, such as exhausting exercise and overtraining, liver cirrhosis, starvation and cancer.

**Tissue Perfusion and Oxygen Availability**

The vascular endothelium regulates vascular tone and tissue perfusion by the production of endothelium-derived relaxation factors. Endothelium-dependent vasorelaxation is abnormal in several disease states including atherosclerosis, chronic uremia, hypertension, diabetes, obesity, etc. This abnormality may be due to different factors including decreased nitric oxide generation. Atherosclerosis may also directly reduce appropriate blood flow to various tissues. In addition, heart failure may be associated with tissue hypoperfusion due to decreased cardiac output. Thus, part of the chronic morbidity associated with vascular disease may be due to the metabolic changes which occur in the presence of reduced blood supply, which can potentially inhibit protein synthesis and/or increase protein degradation by reducing nutrient, hormone and oxygen delivery. Ischemia has been reported to inhibit protein synthesis. A recent study demonstrated that regulation of nitric oxide production in skeletal muscle may affect the protein synthesis rate [19]. Furthermore, tissue hypoxia may increase the production of lactate, with consequent acidosis and stimulation of proteolysis [20]. On the other hand, increased skeletal muscle perfusion may in part mediate the anabolic action of exercise [2], insulin [1], growth hormone and catecholamines.

Tissue protein synthesis is one of the most important components of whole-body energy expenditure. Tissue and cell energy status may therefore have a substantial impact on protein turnover rates. In most tissues, and particularly in skeletal muscle, mitochondria represent the major quantitative site of high-energy phosphates (ATP) synthesis. Altered mitochondrial function and oxidative capacity have been reported in selected catabolic conditions and in aging [21]. The efficiency of mitochondrial ATP production at any given oxygen concentration and oxidative capacity is also an important issue. Uncoupling proteins are the recently described mitochondrial proteins with the potential to uncouple mitochondrial respiration from ATP production, thereby reducing mitochondrial efficiency. Increased uncoupling protein-2 mRNA and protein levels have been reported in aging muscle [22]. These changes may reduce ATP production capacity and ATP availability, thus also potentially affecting protein synthesis and turnover.

**Hydration State and Acid-Base Balance**

In 1993 Haussinger et al. [23] postulated that a decrease in cellular hydration might lead to tissue protein catabolism. Evidence indicates that cell
shrinkage is a catabolic signal, whereas cell swelling is anabolic. Cellular hydration is regulated by the intracellular concentrations of ions and metabolites. Intramuscular glutamine levels are often severely depleted in critical illness. This abnormality may contribute to cell dehydration by decreasing the osmotically active glutamine gradient between the intracellular and extracellular space. Thus, it has been hypothesized that modification of cellular hydration may be the link between intracellular glutamine content and protein catabolism in disease states. The importance of metabolic acidosis as a specific stimulus to protein degradation was demonstrated by a number of studies. Acidosis stimulates protein catabolism by increasing branched-chain amino acid oxidation and catabolic hormone secretion (e.g., cortisol), and promoting proteolytic enzyme synthesis (e.g., the ubiquitin system). In chronically uremic patients with metabolic acidosis the rate of protein degradation directly correlated with blood bicarbonate concentrations. Correction of acidosis with alkali therapy, which achieved normalization of blood bicarbonate, normalized the rate of protein degradation.

Changes in Muscle Protein Kinetics in Acute Critical Illness

Severely ill patients may lose up to 20% of body protein, much of which originates from skeletal muscle. Although catabolism of muscle protein may be useful in the acute phase to provide substrates for protein synthesis in visceral tissues (i.e., liver, gut, immune cells, wound tissue, etc.), severe depletion of body proteins may adversely affect the morbidity and mortality of patients [24, 25]. Evidence indicates that loss of lean body mass in severe stress conditions results mainly from a sustained increase in the rate of protein breakdown in skeletal muscle mediated by the ubiquitin-proteasome system [25, 26]. Depressed protein synthesis may also contribute to the catabolic response. However, despite the fact that both total muscle RNA and specific myofibrillar protein mRNA levels were drastically reduced in trauma and sepsis, studies utilizing stable isotopes have reported increased rates of muscle protein synthesis in patients [25]. It may be hypothesized that increased availability of intracellular amino acids derived from proteolysis may directly stimulate protein synthesis, possibly with a post-transcriptional mechanism. We have recently determined the transmembrane transport of amino acids in the skeletal muscle of patients with large burn injuries [25]. We found that transport in the outward direction was accelerated in order to facilitate the export of amino acids from muscle to other tissues. In contrast, the rates of inward amino acid transport from the bloodstream into skeletal muscle were normal in absolute terms but decreased relatively either to arterial amino acid delivery or to intracellular amino acid turnover. This may explain the relative inefficiency of protein-amino acid administration in preventing muscle protein loss in the critically ill patients.
Changes in Muscle Protein Kinetics in Chronic Diseases

Chronic disease states are preferentially characterized by either suppressed protein synthesis or increased proteolysis. Thus, in most chronic pathological conditions, alterations in protein metabolism are associated with either a decrease or an increase in the overall rate of turnover of muscle proteins. A moderately accelerated protein turnover has been observed in some chronic catabolic disease states, as hyperthyroidism, cancer, sickle cell anemia, Crohn’s disease, AIDS, celiac disease and congestive heart failure as well as in advanced liver cirrhosis, chronic renal failure and chronic obstructive pulmonary disease. Some of these diseases are characterized by an excessive systemic cytokine production typical of chronic inflammatory conditions. Isotopic studies indicate that these chronic catabolic conditions are usually associated with small accelerations in protein degradation at the whole body level or in skeletal muscle with no changes in the rate of synthesis.

A decreased protein turnover can be observed in some chronic catabolic conditions. A reduced or absent protein-energy intake is the most common pathophysiological mechanism leading to decreased rates of protein turnover. Either short-term or prolonged starvation decreased protein turnover at the whole body level and in muscle tissue [27, 28]. In addition, the presence of preexisting malnutrition in acutely ill patients may blunt the expected increase in the rate of protein turnover typical of the acute phase response [29]. Another common clinical condition characterized by decreased protein turnover is immobilization or low physical activity. Most pathological conditions are associated with reduced physical activity. Therefore, to define the effects of reduced muscle
contraction per se, normal volunteers were studied after a period of bed rest. In these experimental conditions the rates of protein synthesis and degradation exhibited parallel decreases both at the whole body level and in skeletal muscle [30]. Such a decrease in protein degradation in vivo appears to be in contrast with the upregulation of proteolytic pathways observed at the molecular level following immobilization or muscle denervation. With regard to specific pathological conditions, a decreased protein turnover rate has been observed in disease states in which reduced muscle function is the prevalent pathological mechanisms, as in myotonic dystrophy. Other mechanisms may lead to a decreased protein turnover. Chronic hypoxemia in pulmonary emphysema can decrease whole body protein synthesis. Some hormonal deficiencies such as hypothyroidism and low growth hormone secretion decrease whole-body protein turnover by suppressing both protein synthesis and degradation. Hormone-replacement therapy with thyroxin and growth hormone normalized protein turnover. Hypoalbuminemia in nephrotic syndrome can decrease whole body protein synthesis. Chronic conditions with muscle wasting in chronic diseases [3–6, 8, 9, 20, 21, 23, 27, 28, 30].

**Fig. 2.** Mechanisms of muscle protein wasting in chronic diseases [3–6, 8, 9, 20, 21, 23, 27, 28, 30].
increased. These apparent discrepancies stem from the fact that the pathogenesis of the abnormalities of protein metabolism in chronic disease states is multifactorial. The different metabolic and hormonal complications have often opposite effects on the regulation of protein synthesis and degradation. Low protein-energy intake secondary to anorexia or excessively restricted diets, low physical activity, insulin and growth hormone resistance and reduced substrate and oxygen delivery tend to decrease protein synthesis. In contrast, metabolic acidosis, increased cortisol secretion, infections, and increased cytokine levels tend to increase proteolysis and overall protein turnover.

References

Protein Metabolism in Wasting Diseases


Discussion

Dr. Basu: Those were excellent data. A few comments and questions regarding the role of insulin and protein breakdown. You are familiar with the study by Halvatsiotis et al. [1] in which type-1 diabetics were taken off insulin and then given insulin. It was shown that on insulin therapy their protein degradation came down significantly, coupled with your observations that people with poorly controlled type-1 diabetes have significant muscle wasting, and when you give them insulin the muscle wasting improves. The other comment that I have is with regard to amino acid infusions. Did they also stimulate insulin secretion; did insulin levels also increase when you infused the amino acids? I am suggesting that perhaps insulin and amino acids together have an overall anabolic effect on protein turnover.

Dr. Biolo: Of course it is known that the insulin–amino acid interaction on protein synthesis is a really golden story. The effect of insulin on muscle protein synthesis is really dependent on amino acid levels. When the amino acid level is maintained, insulins has been shown to have a potentially stimulatory effect on protein synthesis, we agree on that. If amino acids are not maintained, then insulin does not have any effect on the stimulation of protein synthesis. When insulin is given systemically the aminoacidemia drops and no anabolic effect of insulin is seen on muscle protein synthesis. In this study we gave amino acids without clamping insulin with somatostatin, then an increase was also observed in the insulin concentration from an average of 10 to an average of 20, which is mild stimulation but probably significant in this context. However, when we performed another study giving just insulin locally with maintenance of aminoacidemia, we did not observe such a large stimulation of protein synthesis. Therefore there is definitely an interaction between insulin and amino acids and we are convinced that the major regulator of protein synthesis is amino
acids. In the study performed by Bohe et al. [2] a few years ago and published in the *Journal of Physiology*, you can see that there is a dose response of aminoacidemia and protein synthesis and you can double protein synthesis by multiplying aminoacidemia by 3.

**Dr. Komindr:** We have been taking care of many chronically ill patients, most of them bedridden. What do you think about giving them passive exercise, the effect on the protein–nitrogen balance in these cases?

**Dr. Biolo:** The effect of bed rest in critically ill patients is probably relevant but quantitatively it is not as important as the activation of hormones and cytokines. Then in critically ill patients we observe an acceleration in protein turnover mediated by cytokines and hormones. When normal subjects are kept in bed, a decrease in protein turnover is seen; the effects of exercise are in the opposite direction. Anabolic agents stimulate protein turnover, growth hormones and β-blockers, and we know that this is probably another good way to intervene on our patients. Performing exercise in this setting probably would further accelerate protein turnover. But I hypothesize that it is not as important and useful in this clinical setting. This is of course just a hypothesis.

**Dr. Kijboonchoo:** Can I just continue with this question? Are you saying that in the unconscious vegetative patient, for example, who cannot be moved, it is not important that they have passive exercise?

**Dr. Biolo:** I am speaking about the critically ill patient, that is a patient with acute trauma or sepsis. You are talking about a different situation with chronic immobility. In chronic immobility it is crucial to activate, to initiate that exercise program, absolutely.

**Dr. Tantibhaedhyangkul:** What is the effect of ketone body infusion on muscle catabolism in the normal or sick patient? We know that by infusing ketone bodies you can inhibit muscle breakdown.

**Dr. Biolo:** You are right, and there are old studies on the direct effect of ketone bodies on muscle protein metabolism, and if I remember there is an anabolic effect of ketone bodies. Of course we have to differentiate the direct effect of ketone bodies from the effect of acidosis. Acidosis has a direct stimulatory effect on the ubiquitin system and patients with metabolic acidosis exhibit a rapid protein degradation, protein catabolism. If you talk about the direct effect of ketone bodies, this is anabolic.

**Dr. Tantibhaedhyangkul:** Ketosis is not high enough to produce acidosis.

**Dr. Biolo:** Definitely, probably the ketone bodies per se have an anabolic effect, a positive effect.

**Dr. Tantibhaedhyangkul:** The reason I am asking this question is that if ketosis can reduce muscle breakdown, then a high-fat diet would be better than a low-fat diet because a high-fat diet can produce ketosis.

**Dr. Biolo:** Nobody has compared the anabolic effect of the ketone bodies per se on low-insulin levels with the effect of hyperinsulinemia on the ketone bodies. This is a study which should be performed of course. We don’t know if it is more anabolic just having ketone bodies with low insulin or having enough insulin with no ketone bodies, that is the question. I don’t know the answer; a study must be performed on that.

**Dr. Schiffrin:** I would like to ask you how oxidative stress overlaps in the picture of sarcopenia, acute and chronic sarcopenia? Are the glutathione stores in the different cell compartments differently affected by acute and chronic sarcopenia, and does this therefore become a target for a nutritional intervention? Another question regards the proteosome ubiquitin proteolytic activation pathway in the proteolysis of the muscle: is this ubiquitination of I-κB also happening and thereby promoting NF-κB gene activation of proinflammatory cytokines, and then does the muscle become a source of proinflammatory cytokines and a positive feedback loop for the continuation of a catabolism? My last question is if in the cytokine network, that you explained, would you like to see their TGF-β-like negative, side by side with IL-10 as an inhibitory cytokine for proinflammatory cytokines?
Dr. Biolo: These are very complicated questions for a clinical scientist, I am not a basic scientist. We know that the glutathione stores are decreasing in acutely ill patients, glutathione stores are mildly decreasing in chronic disease, we know that nutrition is probably not as effective in restoring glutathione stores. I am not an expert on glutathione, but I think that giving precursors is not as effective in restoring glutathione. Regarding the second question, we know for sure that muscle can express TNF-α. I showed a slide showing that exercise may downregulate TNF-α expression in skeletal muscle. We know that anabolism may upregulate insulin-like growth factor expression in skeletal muscle. Then we know that when the pathway is open muscle may regulate itself locally. I am not a basic scientist so I am not an expert on these things, but potentially this is a mechanism that can play a role in this system. The last question: so far our method involved measuring only what we said, the main pro- and anti-inflammatory cytokines, TNF-α, IL-6 and IL-10, but we are of course ready to measure the others in the future.

Dr. Allison: Can I ask you and perhaps Dr. James to comment on the recommended protein intakes, particularly in relation to muscle activity? If we look at the low-protein intake of a rural farmer with a low-muscle mass who is capable of working all day in the fields, what is the minimum protein intake? Is this because he is young and using the protein very efficiently? On the other hand if we look at the studies from Toulouse [3], which suggest that elderly patients probably require a higher protein intake, is this because their muscle is more resistant to maintaining itself? We are talking about levels of perhaps 1 g/kg/day as opposed to the WHO recommendation of 0.7 g/kg/day. Is this recommendation influenced by aging and muscle resistance to its maintenance, or what is the kind of minimum level that we couldn’t survive on?

Dr. Biolo: Traditionally a high level of physical activity is associated with a higher protein requirement. Actually our studies and also studies from other groups have shown that a high level of physical activity may require a lower protein intake because proteins are used more efficiently. On the other hand our group and others are going to show the same thing, that bed rest or immobility is associated with a higher protein requirement.

Dr. Allison: I am volunteer.

Dr. Biolo: And actually we don’t know about the effect of bed rest or immobility in old subjects. I am not an expert on the minimum protein requirement and I would like to have a comment from Dr. James on that topic.

Dr. James: Dr. Young was involved in sharing this still unpublished new version of the protein requirement report, and I confess I have read everything except that piece of it. The debate is simply that in terms of protein requirement, what proportion of the requirement has to come from good quality proteins, and if you don’t get good quality proteins, for example in a society that doesn’t eat meat or animal protein, then how much more or can you really get away with an appropriate mix of different proteins; the old story about amino acid balance. Dr. Young of course has produced a huge number of very elegant amino acid turnover studies to propose that actually we have underestimated the fundamental needs for the essential amino acids by virtue of having bizarre early experimental studies with an excess of energy, and the manipulation therefore to minimize absolutely the actual amino acid requirements of the volunteers. If you are going to the real world then you need a rather higher amino acid intake consistent with that found in babies or even young children. Therefore we should not be saying that adults need far lower essential amino acids. As I understand, it is pretty clear that Dr. Young’s proposition has huge implications. The original data, if I remember going back 20–30 years when we were doing these early protein turnover studies, were certainly in animals, and I think we also had some in humans. We had data from Jamaica compared with the UK and elsewhere, where in this chronic highly active, relatively poor rural population the adaptive drop was seen, but not in protein turnover.
if you are talking about whole body protein turnover. This might imply that you could get away with somewhat less, but I think this 0.7 g/kg is consistent with what is currently being proposed. Now in terms of the increased protein intake in the elderly, I am not sure. I think it is back to your point about physical activity, and if I remember correctly the proposition that as you get older you need a higher intake is not actually born out by the evidence. But this whole business of protein requirement seems to be maintained until you get into two different questions. One, the patient care issue when it is critical, and secondly if you are actually saying that people need a higher quality protein to sustain something more than simple crude protein balance, then that actually has huge agricultural policy and economic implications.

Dr. Sitges-Serra: Is there a different meaning between acute and chronic sarcopenia? I think most of you will agree that chronic sarcopenia is associated with more morbidity and is really bad for people, whereas those who care for acute patients have felt traditionally that acute sarcopenia is associated with more morbidity and is really bad for people, whereas those who care for acute patients have felt traditionally that acute sarcopenia may have a logical mechanism whereby muscle offers amino acids to the so-called visceral protein compartment to support the immune system or wound healing. It is interesting that in acute sarcopenia no strategies have had limited success in improving the skeletal muscle protein anabolism and prognosis, probably because acute sarcopenia is not that relevant for acutely ill patients. So there may be some qualitative differences between the loss of muscle in these two circumstances, and in fact to a certain extent it may be helpful for acute patients to lose some muscle protein in benefit of the visceral protein compartment. What is your view on this?

Dr. Biolo: I completely agree with you. I have shown that minimizing protein catabolism by growth hormone or β-blockers is not associated with improved outcome, and when we improve outcome with normal glycemia this is not associated with improved muscle balance. I think that it is not bad to minimize catabolism in the acutely stressed patients because of course it is better to spare muscle, but this is not the key to survival for this kind of patient.

Dr. Allison: It may be the key to the rate of recovery, rehabilitation, and there is a difference between improving survival and getting better more quickly, absolutely.

Dr. Biolo: Whereas it is one of the keys when we are dealing with chronic patients. Of course, maintaining muscle mass is probably beneficial for several things, for keeping normal insulin sensitivity, for maintaining a normal cytokine network, for improving mobility and ambulation.

Dr. Shenkin: Two questions about the cytokine data which you showed. I was struck by the difference between the proinflammatory cytokines in your severe exercise group where their IL-6 levels increased and in your resistance training in the elderly where the tumor necrosis factor (TNF) went down. I am just wondering if this is because with more severe exercise you get traumatic damage to muscles or to red cells which activate the inflammatory response, and therefore it is a bad thing to exercise too much. The second question is about the effects in your elderly subjects. I was struck again by the hazard of getting old as you seem to get more spontaneous TNF production. To what extent does that link with the risk of heart disease? Getting back to the other issue we were talking about earlier on, that heart disease appears to be at least partially linked to the activation of an inflammatory response, are those elderly people who have activation of the TNF more at risk of heart disease?

Dr. Biolo: About the direct effect of exercise on cytokines, they were not my observations but a summary of several papers from other groups. We know that strained exercise, like a marathon running, is associated with a large activation of cytokine expression, mainly IL-6. However, when we are not dealing with strained exercise but with continuous training, mild training, we observe a decrease in cytokine secretion, proinflammatory cytokines, probably through the activation of IL-10. This is what I was meaning. Then exercising regularly is an anti-inflammatory mechanism,
not a proinflammatory, but if we run a marathon that situation is proinflammatory. I forgot the second question.

Dr. Shenkin: Whether the elderly people who have activation of TNF are more at risk of heart disease?

Dr. Biolo: I am not so confident about those things because it is very difficult to separate old people and comorbidity because very old people, even if they look completely healthy, may have some comorbidity that cannot be detected clinically but can be detected by extensive methods. So far many studies have tried to select a population of healthy old people and may suggest that inflammation is something inevitable in aging, but I think that this is not a final conclusion. Of course if this is true, if inflammation is inevitable in aging, this may play an important role in mediating arteriosclerosis of in this age class.

References