Optimization of Dietary Protein Intake during Aging

Bernard Beaufrère

Unité du Métabolisme Protéino-Energétique, Université d’Auvergne/INRA, CRNH, Clermont-Ferrand, France

Body protein homeostasis primarily depends on protein intake, even if other dietary factors, such as the energy content of the diet also play a role. However, protein intake can affect protein homeostasis in a variety of ways.

First and obviously, the quantity of dietary proteins plays a major role. During short-term adaptation, an increased protein intake results in a temporarily higher nitrogen balance. However, over the long term, nitrogen balance stabilized itself, unless an excess energy intake is associated with the increased protein intake.

The amino acid composition is the second classical and important factor. The amount of indispensable amino acids ingested should meet the amino acid requirements. These amino acids will be utilized for protein synthesis, but also as precursors of metabolically active compounds or for regulatory purposes. Digestibility is the other factor affecting the ‘quality’ of dietary proteins. It is classically lower for vegetal than for animal proteins, although recent data show that many plant proteins are highly digestible [1]. The overall quality of a protein can be assessed by global approaches such as the measurement of postprandial nitrogen utilization, using $^{15}$N-labeled proteins.

More recently a third factor modulating protein retention has been identified. The bioavailability of dietary amino acids over time can be modified by two different means: the pattern of feeding, and the rate of digestion. The influence of the pattern of feeding has been studied for years, for example in the setting of parenteral nutrition. However, it was demonstrated only recently that modifying the repartition of the daily protein intake over a day modulates protein retention [2]. With respect to the influence of the rate of digestion, we recently proposed the concept of ‘slow and fast’ dietary proteins [3] and...
showed that the postprandial utilization of different milk protein fractions varies according to their rates of absorption. Collectively, these new data strongly support the potential importance of kinetic factors in dietary protein utilization.

Therefore, a tentative optimization of protein utilization may rely on a modification of one (or more) of the following factors: quantity of proteins ingested; quality of these proteins, this including not only their amino acid composition and digestibility, but also their rate of absorption, and finally the pattern of feeding. The efficacy of a given approach will also depend on the alteration of protein metabolism, which has to be corrected or prevented. Thus, we will first briefly review what is known about the abnormalities of protein homeostasis associated with aging.

**Modifications of Protein Metabolism with Aging**

The body protein content (i.e. the lean body mass) depends on an equilibrium between protein synthesis and breakdown (Fig. 1). There is a continuous loss of lean body mass with aging. It is accompanied by a reduction in protein turnover (i.e. whole body synthesis and breakdown), when expressed per kilogram of body weight. However, for most authors [4], when turnover is normalized per lean body mass unit, it remains constant with age. This loss of body proteins is not evenly distributed. It mostly concerns skeletal muscle (sarcopenia) while ‘central’ proteins (e.g. constitutive and exported liver proteins, or gut proteins) are little affected. The prevalence of sarcopenia depends of course on its definition. When considering a cutoff value of – 2 SDs below the values of young adults, 50% of all persons over 80 years of age meet the definition [5]. There is a great interindividual variability in sarcopenia, and some data, e.g. those obtained from twin studies, suggest an influence of genetic factors [6]. Sarcopenia has major functional consequences and contributes to disability, falls and loss of autonomy [7] (Fig. 2).

This progressive loss of skeletal muscle proteins could be associated with a reduction in fractional mixed (i.e. total) muscle protein synthesis rate. However, such a reduction was not reported by all authors [for review see 4]. In fact, Volpi et al. [8] very recently reported an absence of modification of the basal (i.e. post-absorptive) muscle protein synthesis rate in a relatively large series of healthy elderly subjects. The discrepancies between the studies are certainly due in part to confounding factors, such as variable levels of training. It is also now known that the various protein fractions of muscle are not altered to the same extent: for example, the syntheses of myosin and of mitochondrial proteins are more affected than the synthesis of the sarcoplasmic proteins [9]. The particular sensitivity of mitochondrial protein synthesis to aging is put in relation with the mitochondrial theory of aging [10]. Finally, and as considered below, the post-absorptive state may not be the most appropriate circumstance
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Fig. 1. Protein turnover and its regulation.

Fig. 2. Regulation of muscle protein metabolism and muscle functions.

to detect an alteration in protein synthesis. In contrast with the numerous data on protein synthesis, there are very few reports on muscle protein breakdown, particularly in humans, due to methodological difficulties.

The etiology of sarcopenia remains unknown, but is certainly multifactorial. The following factors could be involved: disuse due to the progressive loss of motoneuron α and to reduced exercise; intrinsic alterations in the protein synthetic machinery; impairment of anabolic hormone production and/or resistance to these hormones; repeated or chronic inflammatory challenges resulting in uncompensated protein losses, and alterations in the regulation of protein metabolism by its substrates (e.g. amino acids; Table 1).
Table 1. Possible causes of sarcopenia

- Disuse
- Loss of motoneuron α
- Decreased growth factors (GH/IGF-1), decreased sex steroids, insulin resistance
- Chronic (or repeated acute) inflammation
- Reduced synthesis or altered structure of (specific) muscle proteins
- Abnormal postprandial regulation of muscle protein synthesis

In the context of this review, the latter factor deserves some comments. Protein homeostasis depends on an equilibrium between periods of protein losses (i.e., the post-absorptive state, between meals) and periods of protein replenishment (i.e., the postprandial, or fed state). It seems that aging particularly affects the regulation of the postprandial period. The postprandial stimulation of protein synthesis, as well as the simultaneous inhibition of breakdown, necessitates a complex interplay between numerous factors, including increased amino acid availability and insulin secretion. In old rats, the stimulation of postprandial muscle protein synthesis is impaired [11]. However, when the amino acids are intravenously infused at high doses, muscle protein synthesis responds normally in old rats and humans suggesting that the defect of stimulation of synthesis is specific to the oral route [12, 13]. This is to be related to the demonstration by Boirie et al. [14] of a higher splanchnic extraction of dietary leucine in elderly humans (splanchnic extraction is the fraction of orally administered amino acids, which is taken up by the gut and liver). Recently, Volpi et al. [15] confirmed this observation for another amino acid, i.e., phenylalanine. Thus, one might speculate that a similar oral amino acid intake would be less well delivered to the peripheral tissues (including muscle) in the elderly than in the young. However, Volpi et al. [15] also noticed that the postprandial delivery of amino acids to the muscle of the leg increased to the same extent in the elderly and in the young.

Insulin resistance of protein metabolism might also be important. Although the role of insulin in the stimulation of muscle protein synthesis remains a matter of debate, it was recently demonstrated that the response of muscle protein anabolism to combined hyperaminoacidemia and glucose induced hyperinsulinemia is impaired in the elderly [16]. A resistance to insulin of the inhibition of whole body protein breakdown also exists in the elderly [17], a feature consistent with the lesser postprandial inhibition of protein breakdown observed after a mixed meal in old subjects [14, 18].

Finally, there might be a role for specific amino acids and in particular for leucine, even if the clinical trials with branched amino acids have been rather disappointing. Following the initial work of May and Buse [19], it is now well
admitted that branched chain amino acids, and particularly leucine, exert a specific stimulating effect on muscle protein anabolism, not shared by other amino acids. Some mechanisms of the regulatory role of leucine on protein synthesis were unraveled by Anthony et al. [20]. Briefly, leucine modulates the translation/initiation via the phosphorylation/dephosphorylation of key signaling proteins such as the ribosomal protein S6 kinase (p70S6K) and the translational repressor 4E-BP1. Interestingly, Dardevet et al. [21] recently demonstrated that, in old rats, the sensitivity of muscle protein synthesis to leucine was lower than in adults, with a shift to the right of the dose-response curve. This paralleled the lesser ability of leucine to stimulate the rapamycin sensitive pathway (mTOR pathway), which is believed to be the signaling pathway linking amino acids with the control of p70S6K.

Thus, the metabolic abnormalities leading to an impaired postprandial protein replenishment could be a combination of reduced delivery of dietary amino acids to the peripheral tissues, e.g. muscle, and of a decreased sensitivity of protein anabolism (via a decreased synthesis and a lesser inhibition of breakdown) to both insulin and specific regulatory amino acids. Such changes are potentially accessible to dietary manipulations, which have the advantage of being a priori safe and applicable to a wide population. This stands in contrast with the pharmacological interventions using either growth hormone (GH) or testosterone: numerous trials have been conducted in humans with these two hormones [22]. While their positive effects on muscle mass (if not muscle function) are generally accepted, the high costs (for GH) and side effects of such treatment preclude their generalized utilization in the elderly.

**Dietary Protein Requirements in the Elderly: How Much Protein and Amino Acids Are Needed?**

There has been some controversy over the protein requirements of healthy aging humans over the last 10–15 years. However, this controversy was fueled by a very limited number of new data, due to the methodological difficulties of such studies. The current protein requirements (safe level of intake of the 1985 FAO/WHO/UNU [23]) are set at 0.75 g proteins/kg-day, which corresponds to an average protein intake of 0.6 g/kg-day to achieve a neutral nitrogen balance.

After revisiting old studies, and adding some new data, some authors now believe that the average protein intake needed to achieve a neutral balance is closer to 0.8 g/kg-day, which translates into a safe intake of approximately 1.1 g/kg-d for the elderly [24–27]. This is 30–40% higher than previously believed, and also 30% higher than in adults, in whom there is a general agreement that the safe level of intake is still 0.8 g/kg-day. Other authors challenge such an increase. In an extensive review, Millward and Roberts [28] concluded in 1996 that an increased protein requirement for the elderly has not been demonstrated unequivocally. Furthermore, a series of experiments
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conducted by Millward et al. [29] and Fereday et al. [30] and based on a
$^{13}$C-leucine method (the so-called ‘postprandial protein utilization’ method)
concluded that a lower apparent protein requirement was necessary in the
elderly [29, 30].

Obviously both methods (nitrogen balance and tracers) are opened to
criticism on both conceptual and technical grounds. Even though further
studies would be needed before an ‘official’ recommendation can be made,
it appears that advocating a safe level of protein intake of 1–1.2 g/kg-day
may be beneficial to the elderly. It is consistent with the theory of a need
for a sufficient – or even increased – amino acid delivery to the peripheral
tissues. Most importantly, it constitutes a simple nutritional message in
a population, which is prone to protein energy malnutrition. It certainly
does not have any harmful consequences. Renal side effects of high chronic
protein intakes are not a concern in healthy subjects [31]. The problem
raised by the relationship between bone health and protein intake is more
complex and more specific to old persons. The calciuric effect of high protein
intakes has been known for decades. Its generally accepted mechanism is
the following: high protein intakes, rich in sulfur amino acids, generate
sulfates and a mild chronic acidosis, which is counteracted by the release
of various buffers from the bones (mostly calcium carbonates). While the
experimental data are rather straightforward [32], the evidence from long-
term population studies is far less convincing. For example, an increased risk
of hip fracture (relative risk of 3.7) was recently reported in a large cohort of
elderly women consuming high amounts of animal proteins [33]. But, in fact,
two other recent large trials found an inverse relationship between protein
intake and bone loss or hip fractures [34, 35]. One might also remember
the beneficial effects of protein energy supplements on the outcome of
old patients with hip fractures [36]. These apparently contradictory results
underline that the problem is far more complex than a simple acid-base
equation: a possible detrimental effect of dietary proteins on bone loss in
the elderly depends not only on the quantity and quality of the proteins
but also on the buffering power of the diet (fruits and vegetables), on the
calcium intake, on the initial bone status, not to mention genetic factors.
At present, and given the risk of malnutrition in the elderly, it would be
unwise to advocate a reduction in protein intake with aging on the basis of a
calciuric effect.

In addition to (possibly) higher protein requirements, the elderly might
also have particular indispensable amino acids requirements. For example, it
is conceivable that an increased demand of sulfur amino acids could exist, due
to an increased synthesis of glutathione, in response to an increased oxidative
stress and/or frequent inflammation or infections [37]. In fact, earlier nitrogen
studies by Tuttle et al. [38] concluded that higher requirements for methionine
(and also for lysine) were necessary in older individuals. The question was
re-evaluated by Fukagawa et al. [39] using tracer techniques. They found no
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evidence for increased methionine requirements, which was similar to that of adults. They reported, however, that methionine balance was not achieved in the elderly, when half of the total sulfur amino acids were given as cystine. In any case, it should be remembered that the current FAO/WHO/UNU pattern for adults will probably be increased in the near future and that the future values will be close to the so-called ‘Massachusetts Institute of Technology indispensable amino acids pattern’, derived from tracer techniques [40]. This increase will likely concern both adults and the elderly. Still, for healthy older individuals there are currently no objective data to propose amino acid requirements different from those of adults.

In summary, it is reasonable to advocate in healthy elderly the maintenance of a high enough level of daily protein intake of approximately 1–1.2 g/kg·day, which is safe and might help to prevent malnutrition. The requirements of malnourished and/or sick elderly people are beyond the scope of this review. However, it is well known that protein-energy malnutrition due to inadequate intake and/or intercurrent diseases is highly prevalent in hospitalized or institutionalized elderly. In such patients, protein (energy) supplements have demonstrated a short-term anabolic response [41]; furthermore, despite some inconsistencies between the studies, it is very likely that supplementation reduces mortality and improves nutritional status [for a meta-analysis see 42].

Is It Possible to Improve Protein Retention by Modifying the Pattern of Intake and/or the Rate of Digestion of Proteins?

The major rationale behind this question is to increase amino acid availability in order to simulate protein synthesis during the postprandial period. Indeed, as said above, amino acid delivery – as assessed by the plasma/intracellular amino acid levels – is a potent stimulus of protein synthesis. However, increasing amino acid delivery also stimulates amino acid oxidation and thus, net loss of amino acids might counterbalance the favorable effect on protein synthesis. Delivery of branched chain amino acids to the peripheral tissues might be a particularly worthwhile target, given the low splanchnic extraction of these amino acids (20% for leucine vs. 40–80% for other amino acids, thus resulting in particularly high postprandial levels) and, given the potential specific effects of leucine, as discussed above.

If we consider a fixed value for the daily protein intake, an increased postprandial amino acid delivery might be obtained either by changing the repartition of protein intake over the day or by modifying the rate of digestion of the dietary proteins.

For the latter approach, we hypothesized that a rapidly hydrolyzed and absorbed protein would result in a fast, high but transient amino acid increase, while a slowly absorbed protein would induce a prolonged but moderate hyperaminoacidemia, somehow similar to what happens during continuous
feeding. Thus in young healthy adults we compared leucine kinetics after ingestion of single meals containing either milk whey proteins or caseins, taken as paradigms for fast and slow proteins, respectively. Whey proteins are in fact a mixture of dozens of soluble proteins that share a common characteristic of not precipitating at low pH. In contrast, caseins coagulate into the stomach and are known to exhibit a delayed gastric emptying. In order to assess the time course of appearance of the ingested amino acids, an oral tracer given together with the meal was needed. We first demonstrated that a free labelled amino acid added to a protein meal does not reflect the behavior of the amino acids bound into the protein [43]. Thus, we used an intrinsically labelled protein, in which labelled leucines are inserted into the peptide chain. This was obtained by infusing lactating cows for 24–48 hrs with large amounts of tracer, then collecting the milk and separating by membrane techniques the micellar native caseins from the whey proteins [44]. Initially, we had been using [1-13C]leucine as a tracer because of cost constraints. The drawback of this tracer is that, if the 13C-leucine-labelled protein is given orally, this precludes the simultaneous use of free 13C-leucine as the intravenous tracer, which is needed for measurement of classic leucine kinetics including leucine oxidation. Therefore, in our first experiments, each meal was tested in the same subject by two separate experiments: one with the oral 13C-leucine tracer (for assessment of the rate of digestion), and one with intravenous 13C-leucine. In our more recent studies, we used 2H3-leucine-labelled protein fractions together with intravenous 13C-leucine, which allows obtaining all the parameters in a single experiment.

We first compared two meals made of 30 g of whey and 43 g of caseins, containing exactly the same amount of leucine (i.e. 380 µmol/kg) but of course not isonitrogenous. No source of energy was added. The whey proteins were indeed rapidly absorbed with a peak of plasma amino acids (and in particular of leucine) reaching 3–4 times the basal values at 60–80 min. Absorption of the dietary amino acids was completed by 180 min. By contrast, after casein ingestion, no peak was noticeable, plasma amino acids increased by a factor of only 1.5–2, and remained at plateau for 360 min. The pattern of appearance in the plasma of the oral tracer was very similar to the one of the amino acid concentrations. Whole body protein breakdown was unaffected after the whey meal and was durably inhibited by about 30% after the casein meal. Whole body protein synthesis was stimulated after both meals, but less so after the casein meal. Most importantly, leucine oxidation was increased sharply after the whey meal and its increase over baseline made up for the leucine intake of the meal, resulting in a postprandial leucine balance close to zero. By contrast, leucine oxidation was less stimulated after the casein meal, which resulted in a positive leucine balance significantly better than the one observed with whey [45].

As mentioned earlier, the two meals were, however, not isonitrogenous: the leucine content is higher in whey (11% w/w) than in casein (8% w/w),
and in this first experiment, we had deliberately elected to have the same leucine content in both meals. Therefore, we conducted a second series of experiments, in which the ‘fast’ and ‘slow’ meals were both isonitrogenous and of identical leucine content [46]. A single whey meal (i.e. ‘fast’) was compared with the same amount of whey given over 5 hrs, thus mimicking a ‘slow’ meal. A single casein meal (i.e. ‘slow’) was compared with a meal made of free amino acids mimicking the casein composition, but behaving as a fast meal. As expected, this set of experiments fully confirmed the initial results. Recently, Metges et al. [47] also published a comparison of leucine kinetics during meals made of intrinsically labelled casein (from goat milk) or from free amino acids. They used the frequent, small and equal meal design that has been applied in most of the amino acid kinetic/requirement studies. Therefore, their data are not directly comparable to ours: however, they also demonstrate a higher leucine oxidation with the free amino acids than with the labelled casein, thus confirming our findings. In the same respect, we had previously compared leucine oxidation during continuous enteral feeding with either short-chain peptides or casein and also found a higher oxidation with the peptides [48]. Thus, even under conditions of continuous feeding, the rate of absorption by the gut of the dietary amino acids affects their future metabolic fate.

In summary, a slowly absorbed protein promotes a higher postprandial deposition than a rapidly absorbed one, in young healthy adults. As said above, it is likely that delayed gastric emptying is the rate-limiting step that explains the slower digestion of caseins. By contrast, the whey proteins are rapidly emptied from the stomach, then hydrolyzed and the amino acids absorbed; then, the dietary amino acids literally flood the systemic pool and strongly stimulate leucine oxidation, even if protein synthesis is also stimulated. This difference between the fast and slow proteins might, however, be blunted, when the proteins are given in more complex meals. Carbohydrates and lipids could act either by affecting the rate of gastric emptying or via metabolic regulation (glucose-induced insulin secretion). Indeed, addition of carbohydrates or fat to whey proteins slows down its rate of digestion and improves postprandial leucine balance [49]. Nevertheless, we now have evidence that when the whey and caseins are given within mixed meals, their rates of digestion are still different, but less so than when given alone; most importantly, the postprandial leucine balance remains higher with casein than with whey in young adults [Dangin, unpublished data].

In parallel with this approach, another pathway was explored by Arnal et al. [2]. They elegantly demonstrated in elderly women that the increase in protein retention due to an increase in daily protein intake from 0.75 to 1.05 g protein/kg·day was modulated by the protein-feeding pattern. Indeed, when 80% of the daily protein intake was consumed at lunch (a ‘pulse’ pattern), the increase in nitrogen balance was higher than when the same intake was evenly distributed over 4 meals (a ‘spread’ pattern). The better efficacy of the pulse pattern was attributed to the improvement in the responsiveness of
protein synthesis to feeding but also to a better protein-sparing effect in the post-absorptive state. In other words, the fact that the evening meal of the pulse pattern contained little protein was probably responsible for the lower post-absorptive losses during the night following this meal. Therefore, both the high-protein lunch and the low-protein dinner participated in the global protein-sparing effect [18].

These interesting results were apparently inconsistent with the data obtained with the slow/fast proteins, since one might equate a ‘fast’ protein with a pulse condition. But Arnal et al. [50] then reported that the positive effect of the pulse pattern did not exist in young women. In fact, in this age group, there was a strong trend ($p = 0.16$) for a better (+50%) nitrogen balance with the ‘spread’ pattern than with the ‘pulse’ one. These results are in keeping with older results from the literature. Furthermore, we very recently completed short-term studies with slow/fast proteins in elderly subjects. Our preliminary results confirm that, contrary to what we had observed in young people, a fast protein (i.e. whey) induced a better postprandial leucine balance than a slow one [51].

Thus, the effects of modification of the kinetics of delivery of dietary amino acids, whether they are achieved by modifying the pattern of intake or by using ‘slow’ or ‘fast’ proteins, are clearly age-dependent. In adults, a rapid and strong increase in postprandial amino acids promotes oxidation rather than synthesis, while the stimulation of synthesis predominates in older subjects. As discussed above, other mechanisms are also involved in the post-absorptive state.

Collectively, this series of studies strongly suggests that, in healthy elderly people, short-term optimization of protein retention could be achieved by changing the pattern of protein feeding and/or the rate of absorption of the proteins. Further studies are obviously needed to confirm this possibility over longer periods and in frail subjects.

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References


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Discussion

Dr. Trakulhoon: Why do you get better results with the pulse feeding in elderly people, and does it work with parenteral amino acids as well?

Dr. Beaufrère: I have two explanations. The first is a higher postprandial delivery of amino acids right after the meal. Muscle protein synthesis needs a boost and this boost can only be achieved by pulse feeding; it can never be achieved by spread feeding. The second explanation is that if you give all your proteins at lunch you have less protein at dinner and thus there is a relative protein fast for the next 16 or 18 hrs with reduced amino acid oxidation, which continues to the next day. There are nice studies by Millward’s group on that [1]. I am not sure of the mechanism of course, but those are two possible explanations. The situation with parenteral nutrition is controversial. I know of at least two studies showing opposite results [2, 3]. In one there was better nitrogen retention with pulsed parenteral nutrition, and in the other worse! At present I don’t see any clear pattern emerging from the total parenteral nutrition data.

Dr. Grimble: How do your findings on insulin sensitivity and protein turnover fit in with Roubenoff’s [4] idea that aging is a low-grade inflammatory condition? Is there a consistency between these two messages?

Dr. Beaufrère: In a sense one of the drawbacks of our studies was that all the subjects were very fit and healthy, though they were 70 years old. We checked very carefully that none of them had any kind of disease or inflammation. In my opinion inflammation is probably very relevant with respect to the need for specific amino acids with aging. In our studies, I only considered the quantity of protein and the way we gave it. I have not considered, whether healthy elderly people need specific amino acids – I’m thinking of course of cysteine. As you know, there are 40-year-old data suggesting an increased cysteine and possibly lysine requirement in old people, though these data were not confirmed in a recent report by Fukagawa and Young [5]. My view at present is that we have no good evidence for specific amino acid needs in healthy elderly people, though I don’t know whether the same is true for people with low-grade inflammation. I agree that similar alterations occur in the two situations, but I don’t think they can all be attributed to insulin resistance.

Dr. Grimble: As I understand it, whey protein is much richer in sulfur amino acids than casein. I know your study was an acute one, but could that have had an impact on the results?

Dr. Beaufrère: That’s a good point. These were acute studies, as you say, and we hope shortly to have the results of longer term studies.

Dr. Wagenmakers: Can you speculate on the importance of lack of exercise? I assume that the older subjects were less active than younger people. If they were to do more exercise, would that increase the synthesis rate in the mitochondria or restore the ability to respond to a normal meal?

Dr. Beaufrère: There are two issues here I think. First, the lack of homogeneity within groups of healthy elderly people partly explains the discrepancies in basal protein synthesis. We need to be more careful in selecting our subjects. We excluded
highly trained people or very lazy people but there is still considerable variation. Second, is there any possibility of combining amino acid intervention and exercise? It is clear that the avidity of the muscle for amino acids depends on the timing of their administration in relation to exercise, so I could speculate that it would be an advantage to combine fast proteins and exercise.

Dr. Leverve: I was fascinated by your data on splanchnic extraction, because that is a very well-regulated process and it is insulin-dependent. Insulin resistance may affect organs differently. Was the insulin concentration the same in both your groups (the elderly subjects and the young ones), and do you have any idea about the portal concentration of amino acids?

Dr. Beaufrère: We have no idea what the portal concentration of amino acids is. However, there is a clear decrease in insulin clearance with aging. In other words, when you infuse insulin in young and old people at the same rate, the plasma insulin concentrations are about twice as high in the older people. This could be good news as it might be seen as a protective mechanism against insulin resistance. Anyway, it is clear that there is reduced insulin clearance and a higher insulin level in elderly people.

Dr. Leverve: Were body composition and body weight similar in the two populations?

Dr. Beaufrère: There is always the problem of whether you should match your subjects for lean body mass or for total body weight. I don’t know the answer to that. In this case as far as I remember we matched them for lean body mass.

Dr. Haschke: The data you presented on fast and slow proteins are interesting for the food industry, because a couple of years ago it was vice versa – we were looking at slow proteins, with animal models and data from healthy young volunteers. What you have shown today seems rather different. Do you think your data are sound enough to recommend whey-enriched supplements or meal replacements for this target group, or would you recommend waiting for longer term outcome studies?

Dr. Beaufrère: I think it is still too early. When we came up with the idea of slow and fast proteins 6 years ago it seemed very simple and clear cut: slow proteins when you need to reduce oxidation, for example in patients with kidney disease; fast proteins when you need to increase amino acid delivery. But the more we work on this subject the more complex it appears. I believe we will end up by saying that fast proteins are probably better for elderly people, but I’m not yet 100% sure. There are many other problems. How do we give it? Do we give it with energy? What should the timing be with respect to exercise? What should the timing be with respect to other meals? For example, if you give all your proteins at lunch it means you will have less protein at dinner, and the effect of this low protein intake at dinner may be part of the explanation for the effect of the pulse diet. So there is still much work to do.

Dr. Labadarios: In relation to the meal pattern – pulse versus spread, and the concept of insulin insensitivity: have you measured lipid profiles in these people, and what did you find? Secondly, why should we be concerned about sarcopenia and want to reverse it? Is it not part of aging and to be accepted as such, or has it got other clinical significance?

Dr. Beaufrère: By lipid profile I presume you mean cholesterol and so on. I cannot give you comparative figures, but we excluded subjects with hypercholesterolemia or hypertriglyceridemia. As for sarcopenia, this is an interesting point. I said that sarcopenia is common, but it depends on your definition. If you define it as a body weight of –3 SD from the mean, then about 50% of people over 70 years old have sarcopenia. The consequences are very variable. There are studies relating sarcopenia to strength, walking performance, climbing stairs, rising from a chair, and so on, and a longitudinal study published in 1995 showed that lower extremity function is a good
predictor of subsequent disability [6]. So while it is not a pathological process, it clearly has implications for daily life activities in old people.

Dr. Soeters: I am puzzled by your finding that splanchnic extraction in older people is increased, and that pulse feeding in these people gives improved nitrogen balance. Am I right in thinking that the proteins you give as a pulse are not digested, absorbed, and transferred to the liver in the normal way, because then you would have enormous urea production, but rather that that protein stays somewhere in the gut or the liver? If you agree with that, what is its biological destination? Does it become bacterial protein, enzymes, enterocytes, liver protein, or what?

Dr. Beaufrère: I don’t know, though I believe you yourself have data suggesting that there may be protein storage within the splanchnic bed. What can happen to protein in the liver? It can be incorporated in the constitutive proteins, it can be oxidized, or it can be exported, for example as albumin. We have measured albumin synthesis in elderly people and it is normal. We cannot measure constitutive proteins. As for oxidation, the only answer I can give is that the total protein intake with the pulse protein feeding was only 1.4 g/kg/day, which is probably less than we eat normally and I wouldn’t expect that protein to be oxidized.

Dr. Soeters: Oxidation would be in urea production. It would result in very inefficient utilization and you could never have a better nitrogen balance under those circumstances.

Dr. Beaufrère: Exactly – we would see that in the nitrogen balance.

Dr. Soeters: So it has to be something different. Your suggestion of a liver export protein would escape detection by your measures and might be a possibility.

Dr. Beaufrère: We have not measured albumin synthesis during pulsed and spread diets.

Dr. Soeters: But albumin has such a slow fractional synthesis rate that it could never make much of an impact.

Dr. Beaufrère: That is true.

Dr. Soeters: It would have to be protein with a more rapid turnover – perhaps still in the gut? Maybe it is bacterial protein. What about gut motility in these patients. Isn’t motility decreased in old people?

Dr. Beaufrère: We have not noticed anything in terms of basic clinical variables such as stool frequency. That’s not an answer, it’s just a hint.

Dr. Segal: You mentioned the prevention of sarcopenia by resistance exercise. As I understand it, there is a difference between aerobic exercise and resistance exercise. It is recommended that one should have half an hour of aerobic exercise at least five times a week. I wonder how practical it is for elderly people to start doing weight training as well.

Dr. Beaufrère: To the best of my knowledge the positive effect of resistance exercise on sarcopenia has been clearly proven. The problem with resistance exercise is that it may be impracticable in everyday life. Second, in our experience, when you stop exercise the benefit disappears quite rapidly. Third, there is a risk of trauma. It is certainly much easier to use aerobic exercise – for example, bicycling. This has many effects on insulin resistance, fatty acid oxidation, well-being, and so on, but it does not necessarily have a major effect on muscle mass and strength. It is better but it is not fantastic.

Dr. Wagenmakers: I think it is easier for elderly people to do resistance exercise than endurance exercise. I agree you have to be a bit careful, so you need a greater number of repetitions with lighter weights, but many elderly people find it easy to do this kind of exercise.

Dr. Pichard: I have a problem with your interpretation of your results. At any age it has been shown that physical exercise improves not only muscle mass but also muscle
function. In addition to that, with aging you have a decrease in anabolic hormones, and I am sure you will agree that these two influences are very powerful in comparison with the importance of the protein profiles. If you look at space medicine results, the effect of aging is not part of the equation, only the effects of changes in the anabolic hormone profile and physical exercise. I believe you are misinterpreting your results and I think you probably have significant differences in physical activity and hormonal profile in your elderly subjects, which have completely distorted your analysis.

Dr. Beaufrère: Thank you for the kind comment! Most of these studies were crossover designs between the two types of feed pattern. We are also very careful about the problem of physical exercise. I admit that we have a certain heterogeneity within a given group, but there was no obvious difference using questionnaires, VO₂max, and so on between the groups. So I don’t think that could explain our results. Secondly, with respect to the growth factors, I certainly agree that IgF-1 decreases with aging and growth hormone has been shown to be efficient in preventing sarcopenia. Unfortunately we can’t modify the growth factors or give growth hormone to everyone as you well know. I accept that nutritional intervention is less efficient than growth hormone but it is at least applicable to everybody!

Dr. Heymsfield: This is a comment rather than a question. Most attention has been paid to muscle in studies of sarcopenia, but there are very striking changes in food intake regulation in elderly people. As you probably know, Susan Roberts [7] has shown that if you disturb body weight it returns to baseline much more slowly in the elderly than in younger people.

References