The cases for and against dietary protein for healthy aging

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To date, there is very little strong evidence on nutrition and aging, with perhaps the exception of protein consumption. Yet despite the many studies investigating the relationship between protein intake and aging, debate nevertheless continues to rage over whether dietary protein has a net positive or negative effect when it comes to *human* longevity. As many reading this will be aware, I am in favor of increasing protein intake well above the recommended dietary allowance, but advocates of low-protein diets cite concerning effects on the mammalian target of rapamycin (mTOR) and IGF-1. So what should we make of these data? And why do I still maintain that protein intake is an important part of nutrition for healthy aging?

Protein and mTOR

Perhaps the most popular argument against high-protein diets stems from its apparent effects on the mammalian target of rapamycin complex 1 (mTORC1) and its core enzyme component, mTOR.

mTORC1 is a protein complex with a central role in regulating anabolic processes, including the synthesis of nucleotides, lipids, and proteins, as well as other cellular functions such as autophagy. Anabolic processes are only possible if sufficient nutrients are available to provide the necessary building blocks and energy, and as such, the activation of mTORC1 depends on sensing nutrient availability – especially amino acids, the molecules that make up proteins. Eating a protein-rich meal increases levels of circulating amino acids and thus stimulates mTORC1, which is specifically activated by pathways that sense the amino acids leucine, arginine, glutamine, or homocysteine. This drives the anabolic processes associated with muscle protein synthesis. As I've recently described, I've changed my eating habits to consume several high-protein meals per day with the specific goal of maximizing muscle protein synthesis through the activation of mTORC1 pathways.

But as many low-protein advocates have pointed out, animal studies have shown that *inhibition* – rather than activation – of mTOR activity is associated with longer lifespans, possibly due to the relationship between mTOR activity and aging processes at the cellular level. Five of the nine proposed "hallmarks" of aging have relationships to mTOR. For instance, one of the most prominent among these hallmarks is mitochondrial dysfunction, which can result from impaired mitochondrial turnover and inadequate degradation of those that are damaged. Hyperactivation of mTORC1 reduces the rate of this turnover process. In addition to mitochondrial function, other hallmarks of aging potentially affected by mTORC1 include loss of protein homeostasis (proteostasis), aberrant nutrient sensing, cellular senescence, and stem cell exhaustion. Consistent with these findings, treating mice and other species with rapamycin – which inhibits mTOR activity – has been shown convincingly and repeatedly to extend lifespan and slow aging processes.

This has, not surprisingly, contributed to the hypothesis that protein *restriction* extends lifespan, as reduced amino acid availability would inhibit mTORC1, thus slowing the progression of the aging hallmarks associated with mTOR activation. In mice, protein restriction reduces mTORC1 activity, and since leucine is a potent stimulator of mTORC1, not surprisingly, mTORC1 activity is restored by supplementation with branched-chain amino acids.

However, this basic model of low protein intake → reduced mTOR activation → longer lifespan fails to account for the distinction between *chronic* mTOR activation (suppressed by rapamycin) and the *acute* mTOR activation that occurs in response to amino acids. While we have reasonable evidence to suggest that suppressing chronic mTOR activity may extend lifespan, we have no such evidence that suppressing acute protein-induced mTOR activity spikes would have the same effect – or indeed that they wouldn't have the *opposite* effect. (To illustrate this possibility, consider exercise. Acutely, exercise increases blood pressure and heart rate and so on, but chronically, exercise lowers these same metrics – and it's the chronic effect that matters for long-term health.)

Additionally, it's unclear how the *location* of mTOR activity impacts aging and lifespan. Amino acids disproportionately impact mTOR activity in muscles, whereas it's possible that the longevity benefits of rapamycin are due to its ability to suppress mTOR activity in other tissues, such as the liver.

Protein and IGF-1

Another oft-cited concern with dietary protein regards its effects on insulin-like growth factor 1 (IGF-1), a marker of growth hormone activity. IGF-1 levels correlate positively with protein intake, and specifically the consumption of essential amino acids. In meta-analyses, both high and low levels of IGF-1 have been associated with increased mortality compared to the median range, resulting in a "U-shaped" curve. However, low levels of IGF-1 in mice, usually achieved through genetic modifications, are associated with increased lifespan and a reduced risk of cancer. Likewise, a study of nonagenarians found increased rates of survival in women (not men) with low IGF-1. Many have pointed to these data as evidence that low-protein diets are preferable to high-protein diets in terms of promoting longevity.

This interpretation, however, is hardly justified. The nonagenarian study did not include any information about diet, and the apparent inverse correlation between IGF-1 and mortality was driven by increased survival of individuals with low IGF-1 who had a history of cancer diagnosis, a special circumstance in which lower concentrations of growth factors may be beneficial to survival by limiting tumor progression. Similar trends are observed in humans with Laron syndrome who have reduced incidences of cancer and diabetes thought to be caused by extremely low levels of IGF-1 due to a mutated growth hormone receptor. However, in humans without this mutation, low IGF-1 is associated with *higher* levels of cardiovascular disease, diabetes, and conditions of frailty (osteoporosis and sarcopenia).

In addition to the fact that there is no demonstration of disease causality by low levels of IGF-1, it is also unclear that modulating IGF-1 through protein restriction has beneficial effects on human lifespan. IGF-1 is sometimes used as a proxy for measuring protein consumption, but IGF-1 is affected by many factors and does not have a *direct* relationship with dietary protein. Acutely, consuming a high protein meal (42 g) raised levels of free IGF-1 in *young* adults by 17.5% 24 hours after meal consumption. (IGF-1 was not assessed beyond the 24-hour time point to determine when it returned to baseline.) But IGF-1 levels naturally decline with age and the association of dietary protein with IGF-1 disappeared *after age 65*. A large study from the UK Biobank demonstrated that both low and high levels of IGF-1 were associated with increased mortality and disease. However, the effects on mortality were far greater for low than high IGF-1 levels and the magnitude of the effects was greatest in midlife and further diminished with increased age. The increased mortality of both high and low concentrations of serum IGF-1 may be more indicative of other underlying diseases than the relationship to dietary protein, especially later in life.

Dietary protein and longevity in humans and mice

Both the mTOR and IGF-1 arguments against protein are largely based on mechanistic links that are partially hypothetical and haven't fully been shown experimentally. Ultimately, the most relevant question is not whether protein intake increases mTOR activity or if high IGF-1 raises mortality risk – the relevant question is whether protein intake modulates lifespan.

There are few human studies on overall protein intake and aging or longevity in healthy adults, as nutrition and aging are difficult topics to study individually, let alone together. Diet studies are often rife with confounds and assume a consistency in eating habits over long periods, and aging studies present challenges due to the duration over which they must be conducted and the fact that our environment is rapidly changing.

One of the few investigations on this topic in humans analyzed a subset of data from NHANES III, a large-scale health and lifestyle survey in the United States conducted between 1988-1994. This analysis suggested that protein intake should be low before age 65 and increased thereafter. In this study population, mortality risk from cancer and diabetes was higher with a high- compared to a low-protein diet for subjects ages 50-65, but for those over age 65, low-protein diets were associated with *increased* all-cause and cancer-related mortality. However, results from this older age group are far more reliable and relevant than those of the 50-65 age group because mortality rates in those over 65 is higher *in general* than it is in those aged 50-65. If we take these results at face value, we can conclude that it makes sense to prioritize an intake pattern that reduces risk over age 65 – that is, consuming higher levels of protein to reduce the higher level of mortality risk. However, the fact that absolute mortality risk is low among those under 65 also means that data from the 50-65 group are likely heavily biased, as those dying prior to age 65 are likely to be among the least healthy individuals in this age bracket at baseline, skewing results in a manner which may not reflect effects in a general population, just as we have seen above in the IGF-1 data.

Despite this major confound in the younger cohort, it's worth noting that the *positive* association between protein intake and longevity in the 65+ group makes biological sense. As we age, we develop anabolic resistance, a phenomenon in which muscle protein synthesis responses to anabolic stimuli become attenuated, and we therefore require greater quantities of protein to build and maintain muscle mass, a key factor in longevity.

Since human studies are difficult to implement, often the best data we have come from animal studies. Various studies in mice have shown that protein restriction is associated with extended lifespan, though many of these are complicated by protein restriction during developmental life stages or unequal total caloric intake. Still, while it's certainly possible to cherry-pick data showing that decreased dietary protein increases maximum lifespan in laboratory animals, there are several important differences between mice and humans that are crucial considerations for translating nutritional studies to humans.

The gap between mice and humans

There are several reasons to keep a healthy amount of skepticism that what works for mice in a laboratory isn't necessarily what's best for humans in the real world.

Laboratory mice are maintained in pathogen-free environments, but humans live in a world that regularly challenges our immune systems, which are compromised by protein malnutrition. Community-acquired pneumonia is the cause of over 1.5 million infections and 100,000 deaths annually in the U.S. Protein malnutrition is an independent risk factor for mortality and morbidity in viral forms of community-acquired pneumonia. Further, in patients hospitalized due to acute

illness, muscle mass has been shown to have prognostic value in predicting mortality because muscle serves as a protein reserve that greatly benefits the immune system, reducing disease severity and mortality.

Additionally, laboratory mice predominantly die of cancer, and any increases in lifespan on low-protein diets may be due to the restriction of tumor growth through mTORC1 inhibition. While cancer is one of the leading causes of death in humans, accidents and falls also pose a significant mortality risk, whereas these pose essentially zero threat to mice in controlled environments. Thus, frailty is far more likely to shorten lifespan in humans than in laboratory mice, and protein restriction greatly increases frailty risk due to both loss of muscle mass and strength and the accompanying loss of bone density.

The bottom line

The challenges of studying nutrition and aging are one of the reasons I've become more flexible in my beliefs around diet for optimizing health with age. What is clear from reviewing the current evidence is that most people would benefit from *increasing* their protein intake with age. Muscle protein synthesis via mTORC1 is necessary to avoid sarcopenia and increase the likelihood of surviving acute illness. Even though mTORC1 is activated upon sensing amino acids, what may be more important is inhibiting *chronic* activation of mTORC1 through other means, such as rapamycin. While there may be some exceptional circumstances, for many people, higher dietary protein would help maintain skeletal muscle, improve immune function, and reduce frailty – all of which translate to an increase in lifespan and healthspan.