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The protein paradox – how much dietary protein is good for health?

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In Germany, average intake of dietary protein is far above the recommended minimum daily intake, so in terms of adequate protein intake, we have nothing to worry about. However, protein intake has become a controversial topic of discussion in recent years. On the one hand, increasing protein intake is recommended in the context of calorie-restricted diets for weight loss, and it is recommended in general for older people, but on the other hand, there is the trend towards vegetarian and vegan diets, which contain less protein. In addition, epidemiological studies have shown that a protein-rich diet is associated with a higher risk of disease. This "protein paradox" was discussed at a meeting of leading scientists held by the German Institute of Human Nutrition (DIfE).

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Protein as a source of indispensable amino acids

Protein is an important macronutrient. This is because we are unable to synthesize some of the amino acids that make up proteins for ourselves. After water, protein is the substance that accounts for the largest proportion of body mass in adult humans, accounting for about 10 kg. The dry weight of many cells found in the body is made up of over 50% protein. Although protein is one of the energy contributing macronutrients, as are fats and carbohydrates, protein is special, because it is never used primarily as a store of energy

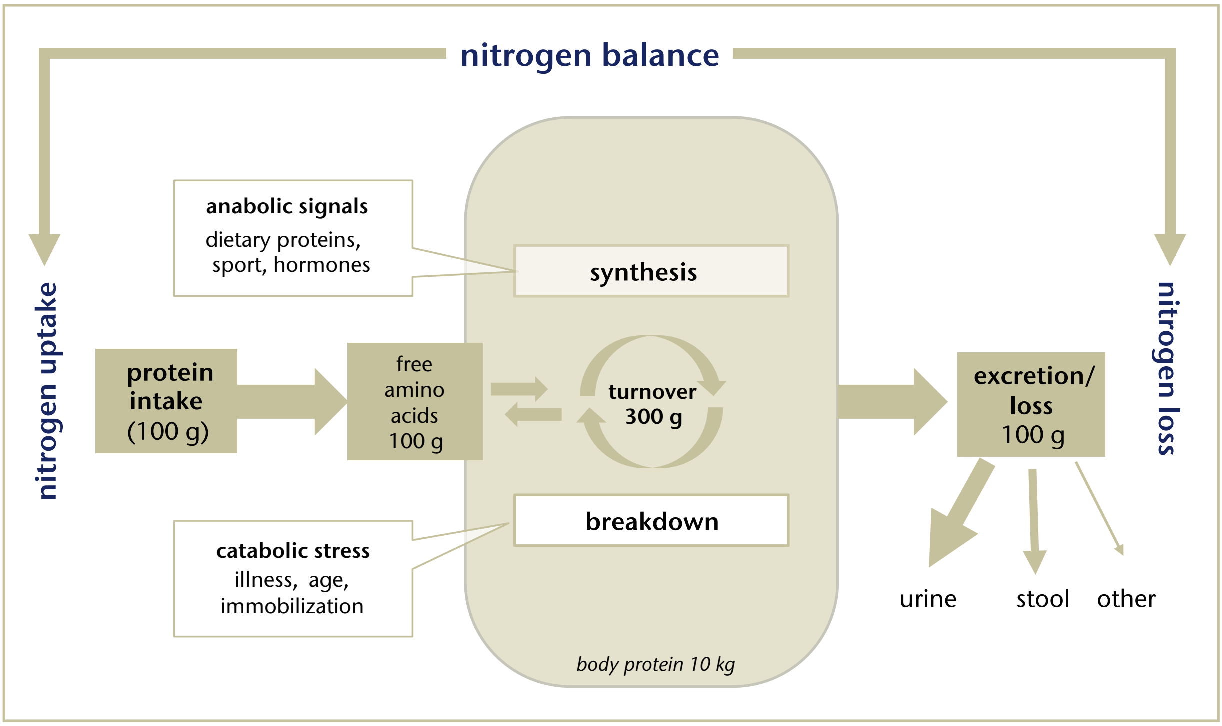

Fig. 1: **Daily protein turnover of an adult in nitrogen equilibrium**
The state of nitrogen equilibrium is characterized by the same amount of nitrogen being excreted from the body as is consumed in the form of protein/amino acids each day. Of the approximately 10 kg of protein in the body, a small portion is renewed every day, which is to say it undergoes protein turnover, and in this process, some nitrogen is always lost as a result of the breakdown of amino acids, and must be replaced through protein intake. Protein turnover is determined by synthesis and breakdown, which in turn are influenced by anabolic signals and catabolic stress. Protein turnover also increases with increased protein intake. Since the body does not have any dedicated protein store, surplus amino acids are oxidized to produce energy, and the nitrogen is then excreted, mainly in the form of urea. Conversely, protein turnover, and therefore also nitrogen excretion, may also be reduced in the case of reduced protein intake, for example when fasting. However, when fasting, a certain amount of body protein is always broken down as it is needed to supply the body with energy.

in the body. In contrast to fats, which are stored in fatty tissue, and carbohydrates, which are stored in the liver and muscle as glycogen, endogenous proteins always have a specific function: as structural elements (e.g. in the muscle), as catalysts for biochemical reactions in the form of enzymes, or as receptors and messengers for signal transmission and communication between organs and cells.

Protein turnover in the body is constant (◆ Figure 1) – about 300 g of the protein pool is renewed on a daily basis, and between 50 and 100 g of it is lost from the body and must therefore be replaced by dietary protein. As a result, the body appears to react very sensitively to any protein deficiency. According to the protein leverage hypothesis, the primary aim of the body's regulation of dietary intake (i.e. the appetite) is to ensure adequate consumption of protein. When foods are relatively low in protein, appetite increases and more food is consumed (meaning that more fat and carbohydrate is also consumed) than when foods are rich in protein [1]. This implies that a protein-rich diet is more satiating than a low-protein diet, which is ultimately why protein-rich diets are so successful when it comes to weight loss.

Recommended daily protein allowance

It is difficult to determine a minimum daily protein intake because requirements do of course vary drastically between individuals. In principle, the recommended daily allowance (RDA) of 0.8 g per kg of body weight should ensure a sufficient supply of protein for healthy adults aged 19 and over. This recommendation, which has been in place for many years, is based on studies on nitrogen balance. Amino acids – the building blocks of proteins – always contain nitrogen (N) within the amino group that gives them their name. When proteins and amino acids are broken down, only some of the nitrogen they contain can be recycled in the body. The rest is mostly excreted in the urine in the form of urea and ammonium. By measuring the amount of nitrogen that is excreted as accurately as possible, we can calculate how much nitrogen needs to be consumed in the form of protein in order to re-establish the nitrogen balance. Strictly speaking, the RDA is a safe, minimum intake amount. It does not necessarily advise against a higher protein intake (which is usual in industrialized countries). A proportion of 10–35% of daily energy intake (en%) in the form of protein is considered acceptable (acceptable macronutrient distribution range, ADMR). In the case of a man with a body weight of 80 kg, this would correspond to a protein intake of 65–228 g per day (assuming an energy turnover of 2,600 kcal), whereas the RDA would be 64 g. There is currently a heated debate about whether the RDA should be increased, especially for older people, versus whether higher protein intake may be harmful in the long term, as it may put a strain on the kidneys [2].

The protein paradox

The term "protein paradox" is indeed a very apt description of our current situation. On the one hand, it has been clearly demonstrated that increasing protein intake has an anabolic effect (i.e. it increases muscle mass), and that diets with a high proportion of protein are very effective in the prevention and treatment of obesity and the metabolic disorders that it causes [3]. On the other hand, the idea that a reduced energy and reduced protein diet prolongs life is gaining ground. Studies have shown that proteins and amino acids can trigger insulin resistance, and very recently, animal studies have shown that restriction of dietary protein and amino acids increases the production of FGF21 (fibroblast growth factor 21), a hormone that has positive metabolic effects, in the liver and that such restriction even prolongs life in mice [4].

Shedding light on the paradox

This paradox may be partially explained by the fact that each of the various studies that were conducted had different endpoints, which were then classified as either good or bad for health. There have been some interesting studies conducted in insects that aimed to find the optimal protein intake with regard to either reproductive success or life expectancy. In these studies, it was found that a proportionally higher protein intake led to increased reproductive success, whereas a proportionally lower protein intake led to fewer offspring, but a longer life.
Obviously, humans are not insects, but even in mice it was found that a lower protein intake in proportion to carbohydrates increased life expectancy [5]. However, these studies also showed that this was only the case if fat intake was low. This effect decreased with increased fat intake, and increasing protein intake when fat intake was high even prevented a reduction in life expectancy due to the diet being high in fat, as our own studies in mice have confirmed [6].

This clearly shows that protein intake cannot be viewed in isolation. The ratios of each of the macronutrients (carbohydrates, fats, and proteins) compared to each other are of vital importance.

It is of course impossible to directly investigate the effect of protein intake on human life expectancy, but targeted interventional studies can be conducted within a limited time frame. A meta-analysis, i.e. a summary analysis of a series of such studies, came to the conclusion that high protein diets (as compared to low protein diets) are likely beneficial with regard to overweight, blood pressure, and blood lipid levels, but these effects are minor [7]. One interesting aspect of this is that high protein diets are more satiating, and therefore decrease energy intake. This likely explains some of the positive effects.
With regard to mortality, an interesting epidemiological study appeared in 2014, showing that a low protein intake was associated with lower mortality and lower cancer incidence in adults aged 65 and under, which means that protein restriction certainly can have positive effects on health and life expectancy. However, in people aged 65 and over, the findings were reversed. The older the subject, the more beneficial a higher protein intake was [8]. These results support current efforts to increase the minimum protein intake recommendations for older people to 1–1.2 g per kg of

The protein paradox: Increasing protein intake was found to have positive anabolic effects in most interventional studies. For instance, it was found to increase muscle mass. However, most epidemiological studies found an association between low protein intake and improved health.

body weight. Accordingly, in 2017, the German Nutrition Society revised the reference values for dietary protein and increased the reference values/estimated values for older people (aged 65 and above) to 1.0 g of protein per kg of body weight [9].

Protein quality: the vital importance of amino acid composition

One aspect of the discussion around the protein paradox that must not be forgotten is protein quality. Since protein cannot be stored in the body, we must consume sufficient protein each day to meet our requirement for indispensable amino acids that we are unable to produce ourselves. Dietary proteins vary in their composition. Their quality is therefore calculated based on the limiting indispensable amino acid(s) they contain.

One commonly-used method of doing this is the PDCAAS (protein digestibility-corrected amino acid score), in which protein quality is calculated based on the needs of an infant, with high-quality egg protein as the reference protein. Generally, plant-derived proteins are poorer in quality than animal proteins, and the composition of animal proteins is more similar to our own amino acid profile, which has been known for some time now. Therefore, if protein intake comes exclusively from vegetable proteins, i.e. in the case of a vegan diet, complete protein nutrition can only be achieved by carefully combining different protein sources. An exclusively vegan diet may lead to deficiencies in individual indispensable amino acids. To date, optimal intake of indispensable amino acids has been calculated empirically using feeding experiments in animals, especially rats. A recently published study has highlighted an entirely new approach, in which the optimal amino acid composition of dietary protein was calculated in silico (= on a PC) – i.e. it was calculated as the composition that you get when you translate the entirety of the genetic information coded in the DNA into protein, which is to say into amino acid sequences. In fruit flies, feeding with an amino acid mixture with such a composition reduced overall food intake and also increased reproductive success without reducing life expectancy. Similar results were also observed in mice. Through the use of optimized amino acid composition, it was possible to reduce protein intake in the diet without impairing growth [10]. However, it remains to be seen whether such research approaches can be applied to humans, and therefore we can only speculate on whether the concept can be applied to the human diet.

Amino acids and the cellular stress response

Amino acids are more than just a component of proteins. Some also perform specific cellular signaling functions. For example, the indispensable branched-chain amino acid leucine activates a cellular signaling pathway called mTOR (mechanistic Target of Rapamycin), which generally has anabolic effects, i.e. it stimulates cell growth and protein synthesis. On the other hand, amino acid restriction, which is to say a cellular deficiency of individual amino acids, stimulates a kinase called GCN2 (general control nonderepressible 2), which leads to global suppression of amino acid synthesis and the mTOR pathway, and interestingly, activates the cellular stress response. One of the effects of this is that it induces the formation of the aforementioned fibroblast growth factor 21 (FGF21), which is secreted into the blood and has hormonal effects on metabolism. As mentioned previously, these effects are generally considered to be good for health.

The positive metabolic effects of protein restriction do indeed appear to be mediated primarily by the increase in levels of FGF21, and they appear to occur with or without weight loss. Protein restriction could therefore represent a viable alternative to a calorie-restrictive diet intended for weight loss. However, in the case of many metabolic diseases such as diabetes or fatty liver disease, FGF21 levels are elevated, which is likely a kind of "warning signal" from the body. Conversely, high-protein diets reduce production of FGF21. A study published recently by the German Institute of Human Nutrition (DIfE) showed that increasing protein intake leads to a dramatic reduction of fatty liver disease and insulin resistance in overweight diabetes patients after just six weeks. This was associated with markedly reduced levels of FGF21 in the blood. Interestingly, both animal protein and plant protein had the same effect in this regard [3].

Therefore, the significance of FGF21 is not entirely clear. On the one hand, FGF21 levels are elevated in patients with fatty liver disease, and these levels reduce in parallel to reduction of the fatty liver disease, but on the other hand, FGF21 has been shown to have positive metabolic effects. One possible interpretation would be that a healthy body "does not need" FGF21, but in the case of metabolic disorders, FGF21 provides a buffer against the negative health effects of such disorders. In healthy people, in the case of overnutrition, FGF21 production is quickly and strongly stimulated in the case of excessive intake of carbohydrates (but not in the case of excessive intake of fats) and it then increases insulin sensitivity in the muscle, meaning that carbohydrates are eliminated from the bloodstream more effectively. At the same time, blood lipids also increase as an expression of hepatic lipogenesis and VLDL synthesis [11]. Interestingly, FGF21 inhibits the preference for carbohydrates in mice via centralized dopaminergic mechanisms [12]. Polymorphisms in the FGF21 gene were associated with a preference for carbohydrates [13]. FGF21 could therefore control the balance of an individual's appetite with regard to carbohydrates and proteins.

Interventional studies versus epidemiological studies

Interventional studies in humans, such as those mentioned above, generally showed that in overweight patients with metabolic disorders, increasing protein intake has positive effects. However, most epidemiological studies found an association between low protein intake and improved health [14]. How can this discrepancy be explained? It is important to remember here that interventional studies and epidemiological studies are very different in their designs.

Interventional studies are conducted over a defined period (usually several weeks or months). In these studies, one diet is compared with another – for example a high protein diet compared with a low-protein diet – and a predefined source of protein, such as whey protein, is used. In such a study, the number of subjects/patients to be enrolled is limited, and clear inclusion and exclusion criteria are defined at the beginning of the study.

In prospective epidemiological studies, data is recorded on the food intake of the largest and most representative group of people possible, and associations with the occurrence of certain diseases are calculated several years later. In order to calculate the disease risk associated with an individual macronutrient (such as protein), the amount of that macronutrient (in this case, protein) contained within various foods is used as the basis for calculations. This means that ultimately, it is not protein intake that is recorded, but rather the intake of individual foods. After all, what we eat is not protein, fat, or other macronutrients, but rather foods of either plant or animal origin, which have complex compositions of essential and non-essential, digestible and indigestible, and utilizable and non-utilizable components.

For example, it has been proven that consumption of red meat is associated with an elevated risk of colorectal cancer. However, this does not prove a causal association and it does not indicate which component of red meat may be responsible – whether it is the protein content, individual amino acids, or some other component of the meat, such as heme.

Another example is plant protein, which often exhibits positive effects, or fewer negative effects, compared to animal protein in epidemiological studies [15]. However, this could be due to the fact that plants always contain many other components in addition to protein, such as secondary plant compounds, carbohydrates of varying complexity, and dietary fiber, all of which may have various physiological effects on the body. Furthermore, we still do not know enough about the specific effects of individual amino acids or peptides, or the specific effect of nitrogen metabolites of amino acid breakdown, such as ammonium (NH_4^+). Therefore, solving the "protein paradox" is bound to occupy the nutritional sciences for some time to come.

Conclusion

There is a broad consensus that a relatively high protein intake is beneficial to older people in terms of maintaining muscle mass and health.

There is no conclusive evidence that high protein intake has negative health effects on healthy adults, and it certainly does have positive effects on patients who are overweight or who have fatty liver disease.

The specific mechanisms, such as proteins or individual amino acids, that influence cellular metabolism and body metabolism are still not entirely understood, so it is too early to make concrete nutritional recommendations in this regard.

Furthermore, it is of course also important to consider how recommendations can be carried out globally and what protein sources can be used to do so, as there are increasingly pressing economic, ecological, and ethical factors at play here.

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Conflict of Interest
The authors declare no conflict of interest.

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