Metabolic Consequences of a High Dietary-Protein Intake in Adulthood: Assessment of the Available Evidence

Cornelia C. Metges\(^1\) and Christian A. Barth

Department Biochemistry and Physiology of Nutrition, Deutsches Institut für Ernährungsforschung (German Institute of Human Nutrition) (DIfE), 14558 Bergholz-Rehbrücke, Germany

In Western Europe and the United States, protein consumption amounts to about 1.5 to 2 times (Adolf et al. 1994) the recommended intakes (WHO 1985), which is currently considered to be harmless and, according to public opinion, may be even beneficial. Usually relatively short-term experimental studies on the effects of high-protein intakes have been performed, and so the consequences of longer-term or chronic nutrient intake are difficult to judge. Epidemiologic evidence, on the other hand, which aims to circumvent this difficulty, can be flawed by various biases, confounding effects or even limitations of the data which make it difficult to obtain clear-cut cause-effect relationships (Taubes 1995).

It was stated (WHO 1985) that “there are no functional indicators that can usefully be applied in experimental situations to detect protein inadequacy before clinically detectable changes occur.” This statement is equally pertinent for the determination of the tolerable upper intake level (TUL)\(^2\) particularly, if adequacy of protein intake in various physiological situations (i.e., maintenance, growth, pregnancy, lactation) is to be estimated. Moreover, no extensive body of data exists covering the issue.

However, there are bits and pieces of information suggesting that there is no benefit from increasing the dietary-protein intake far above the recommended intake level. Below we summarize the relevant available literature and attempt, by making prudent assumptions, to estimate a TUL which is defined as the highest level of daily intake that is likely to pose no risk of adverse health effects (Institute of Medicine, Food and Nutrition Board 1999).

### Protein intake, lean body mass and physical performance

One of the main questions is whether chronic intake of high-protein diets may be of any value in promoting increased lean body mass (Garlick et al. 1999). The answer to this question is important not only for athletes and body builders who tend to believe that a high-protein intake is crucial for their physical performance (Linseisen et al. 1993) but for all those conditions characterized by a decreasing lean body mass, as seen in the elderly (Nair 1995) and various catabolic situations.

An increase of daily protein intake from 1.35 to 2.62 g·kg\(^{-1}\)·d\(^{-1}\) for 1 mon in the habitual diet (170 kJ·kg\(^{-1}\)·d\(^{-1}\)) while performing daily weight training did not affect either strength or muscle mass (Lemon et al. 1992). Also the response of protein turnover to exercise (4 h at 40% VO\(_{2}\) max.) was independent of dietary protein intake (0.9 or 2.5 g·kg\(^{-1}\)·d\(^{-1}\)) from isenergetic diets (Carraro et al. 1990). High-protein meals did not enhance the stimulation of myofibrillar synthesis induced by resistance exercise in muscle of elderly men and women (Welle and Thornton 1998). Daily physical exercise of increasing intensity at neutral energy balance (constant protein intake 0.57 g·kg\(^{-1}\)·d\(^{-1}\)) maintained body protein by an improvement of N utilization (Butterfield and Calloway 1984). This suggests that physical activity has a positive effect on N retention even at a low level of protein intake, provided energy balance is achieved. Millward et al. (1994) stated that, “training and energy intake depress protein needs and habitual protein intake elevates protein needs.” In conclusion, the literature provides no evidence that protein nutriture and physical performance are improved by high-protein diets, the more so as Garlick et al. (1999) considered that there are currently no methods sensitive enough to detect whether high-protein intake results in a long-term increase in functional lean tissue.

### Effects of high dietary-protein intakes during adulthood

Although dietary percentage of energy from fat declined in recent years, prevalence of obesity has continued to rise in the United States (Willett 1998). In a study comparing fat intake of normal weight, moderately and severely obese subjects, there was a strong correlation of body mass index (BMI) with fat consumption but also with protein intake (g·kg\(^{-1}\)·d\(^{-1}\)) (Alfieri et al. 1997). A positive correlation between BMI and protein intake (in % total energy) is frequently reported; however, this may be caused by underreporting of nonprotein energy intake (Voss et al. 1998). On the other hand, in nonobese volunteers, intake of low-fat foods which corresponds to an increase in protein intake by 2 energy % reduced energy intake and body weight (Weststrate et al. 1998). Nevertheless, it would be worthwhile to investigate the relationship between protein intake level and the development of obesity.

A short-term moderate increase of protein intake (from 50 to 82 g/d) in healthy male volunteers resulted in an increase of insulin secretion as estimated by 24-h C-peptide excretion (Remer et al. 1996) (Table 1). Also an adequate (0.74 g·kg\(^{-1}\)·d\(^{-1}\))...
It has been reported that a chronic high-protein intake is associated with a range of functional and morphological changes such as increased urinary nitrogen excretion, vaso-pressin plasma levels, creatinine clearance, glomerular filtration rate, kidney hypertrophy, renal hemodynamics and eicosanoid production in renal tubules (Bankir and Kriz 1995, Brändle et al. 1996, Yanagisawa and Wadi 1998). In addition, the risk of renal and cardiovascular disease (Hoogeveen et al. 1998). A 1 SD-increase of protein intake increased the risk of diabetes by 38% in an aboriginal community in Canada (Wolever et al. 1997). That amino acids may contribute to insulin resistance was concluded from results of a recent study in myotube cells (Patti et al. 1998).

A further indication that the high intake of protein may have adverse effects can be taken from studies investigating lifestyle changes (i.e., adopting Westernized dietary habits) in Japanese men and schoolchildren. A higher incidence of non-insulin-dependent diabetes (NIDDM) correlated with increased animal protein and animal fat intakes while total energy intake was not different from controls (Kitagawa et al. 1996, Maroni and Mitch 1997). In addition, epidemiological evidence suggests a relationship between high-protein intake and prostate cancer (Vlajinac et al. 1997) (Table 1).

Further, the risk of calcium oxalate stone formation has been associated with the intake of protein, although this relationship has not been found consistently (Curhan et al. 1993, Hiatt et al. 1996, Trinchieri et al. 1991). Oxalate is generated from glycine (Elder and Wyngaarden 1960), but it appears that variations in dietary oxalate as well as absorption and excretion rates and generation of oxalate from breakdown of ascorbic acid may disguise a relationship between protein intake and calculus oxalate nephrolithiasis in epidemiological studies. However, it was shown in a controlled nutritional study that a high-protein diet (1.8 g · kg\(^{-1} · d^{-1}\)) did lead to higher oxalate excretion by female subjects and higher glycolate (precursor of oxalate) excretion in both sexes compared to a low-protein diet (0.6 g · kg\(^{-1} · d^{-1}\)) (Holmes et al. 1993). An association between high-protein intake, renal acid and calcium excretion has been reported (Ball and Maughan 1997, Remer and Manz 1994, Trilok and Draper 1989). This may be due to the oxidation of sulfur amino acids (methionine, cysteine), resulting in a decreased fractional renal tubular reabsorption of calcium (Houillier et al. 1996, Trilok and Draper 1989, Zemel 1988). Diets based mainly on plant proteins apparently do not augment calcium loss, presumably because of a higher phosphate intake and a lower intake of sulfur amino acids (Ball and Maughan 1997, Zemel 1988). However, in respect to protein quality, animal protein is superior to plant protein, maintaining nitrogen balance and thus reducing protein intake. Dietary phosphate modifies the calciuretic effect of proteins, because it increases renal tubular reabsorption of calcium. The protein-induced calciuria has potential negative effects on bone health (Barzel and Massey 1998, Feskanich et al. 1996, Kerstetter et al. 1999) although this is controversial (Heaney 1998, Munger et al. 1999).

A high-protein intake was found to result in a mild metabolic acidosis (Frassetto et al. 1998). Again, it appears that sulfur (amino acid) content correlated with renal net acid.

### Table 1

**Undesirable metabolic effects of high dietary-protein intakes in adult humans: experimental and epidemiological evidence**

<table>
<thead>
<tr>
<th>Subjects(^1)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>na</td>
<td>1.6</td>
<td></td>
<td></td>
<td>Remer et al. 1996</td>
</tr>
<tr>
<td>na</td>
<td>1.7</td>
<td></td>
<td></td>
<td>Remer and Manz 1994</td>
</tr>
<tr>
<td>na</td>
<td>2.4</td>
<td></td>
<td></td>
<td>Trilok and Draper 1989</td>
</tr>
<tr>
<td>na</td>
<td>2.4</td>
<td></td>
<td></td>
<td>Linn et al. 1996</td>
</tr>
<tr>
<td>na</td>
<td>2.5</td>
<td></td>
<td></td>
<td>Kerstetter et al. 1999</td>
</tr>
<tr>
<td>na</td>
<td>2.8</td>
<td></td>
<td></td>
<td>Kerstetter et al. 1999</td>
</tr>
<tr>
<td>na</td>
<td>2.8</td>
<td></td>
<td></td>
<td>Matthews and Campbell 1992</td>
</tr>
<tr>
<td>na</td>
<td>2.9</td>
<td></td>
<td></td>
<td>Frassetto et al. 1998</td>
</tr>
<tr>
<td>Epidemiological</td>
<td>0.65</td>
<td></td>
<td>glomerular filtration rate ↑</td>
<td>Brändle et al. 1996</td>
</tr>
<tr>
<td>na</td>
<td>0.84</td>
<td></td>
<td>noncarbonic acid production ↑</td>
<td>Hoogeveen et al. 1998</td>
</tr>
<tr>
<td>50–75 y</td>
<td>0.1</td>
<td></td>
<td>microalbuminuria</td>
<td>Wolever et al. 1997</td>
</tr>
<tr>
<td>&gt;9 y</td>
<td>0.5</td>
<td></td>
<td>diabetes</td>
<td>Chow et al. 1994</td>
</tr>
<tr>
<td>20–79 y</td>
<td>4th quartile</td>
<td></td>
<td>renal cell cancer (RR(^2) 1.9)</td>
<td>Vlajinac et al. 1997</td>
</tr>
<tr>
<td>70 y–89 y</td>
<td>3rd tertile</td>
<td></td>
<td>prostate cancer (OR 13.5)</td>
<td>Feskanich et al. 1996</td>
</tr>
<tr>
<td>35–69 y</td>
<td>&gt;1.8</td>
<td></td>
<td>forearm fracture (RR 1.22)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) na, normal adults <40 y, if not stated otherwise.

\(^{2}\) A = calculated as protein intake divided by the recommended dietary-protein intake of 0.75 g · kg\(^{-1} · d^{-1}\) (WHO 1985). B = correlation between protein intake and outcome. C = increase in protein intake (g · kg\(^{-1} · d^{-1}\)) above mean of study population.

\(^{3}\) RR, relative risk; OR, odds ratio.
excretion (Frassetto et al. 1998). Chronic metabolic acidosis decreases protein synthesis, increases protein breakdown and may induce a negative nitrogen balance (Ballmer et al. 1995). Recently a decrease in thyroid function in metabolic acidosis was observed which might partly explain the effects on protein turnover (Brungger et al. 1997). High-protein intake (≥2 g·kg⁻¹·d⁻¹) is also accompanied by a decrease of plasma levels of glutamine, alanine and glycine (Maier et al. 1984, Matthews and Campbell 1992). The decline in glutamine can also be a function of metabolic acidosis (Wolbroun 1980), which increases renal glutamine extraction (Wolbroun et al. 1986) and decreases glutamine utilization by lymphocytes (Wu and Flynn 1995). Glutamine homeostasis at a high dietary-protein intake is maintained by a decreased de novo production of glutamine (Matthews and Campbell 1992) and an increase of hepatic glutaminase expression (Curthoys and Watford 1993).

In catabolic patients, plasma glutamine concentration decreases (Jackson et al. 1999, Newsholme and Calder 1997). Glutamine is an important fuel for the intestine and rapidly dividing cells, such as lymphocytes (Newsholme and Calder 1997), and reduction in plasma glutamine was shown to be linked to loss of CD4 + T cells in response to anaerobic training (Hack et al. 1997). Decreased glutamine concentration impaired the ability of cultured lymphocytes to produce interleukin (IL)-2 and to proliferate (Yaqob and Calder 1997). Further, glutamine plays a role in the regulation of gluconeogenesis (Perriello et al. 1997), in protein homeostasis (Hankard et al. 1996) and in an experimental human model of glutamine depletion, whole body protein synthesis decreased (Darmaun et al. 1998). Low plasma glutamine levels due to a high-protein intake may reduce immunologic competence and impair body protein synthesis, particularly when subjects are metabolically stressed.

Based on the foregoing, it is not evident that high-protein intakes confer any advantage in terms of strength or health. Moreover, high-protein intakes must be considered in relation to the possible untoward consequences mentioned. Due to the lack of systematic data, a specific TUL cannot yet be set for a healthy adult population. However, it would be prudent not to increase protein intakes above those consumed habitually by well-nourished populations in the technically prudent not to increase protein intakes above those consumed habitually by well-nourished populations in the technically 

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**LITERATURE CITED**


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**FULL TEXT**

**Gluconeogenesis**

Glutamine is an important fuel for the intestine and rapidly dividing cells, such as lymphocytes (Newsholme and Calder 1997), and reduction in plasma glutamine was shown to be linked to loss of CD4 + T cells in response to anaerobic training (Hack et al. 1997). Decreased glutamine concentration impaired the ability of cultured lymphocytes to produce interleukin (IL)-2 and to proliferate (Yaqob and Calder 1997). Further, glutamine plays a role in the regulation of gluconeogenesis (Perriello et al. 1997), in protein homeostasis (Hankard et al. 1996) and in an experimental human model of glutamine depletion, whole body protein synthesis decreased (Darmaun et al. 1998). Low plasma glutamine levels due to a high-protein intake may reduce immunologic competence and impair body protein synthesis, particularly when subjects are metabolically stressed.

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