Lysine Requirement through the Human Life Cycle¹,²

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Abstract

Lysine cannot be synthesized by mammals and, as a consequence, is an indispensable amino acid. The main role of lysine is to participate in protein synthesis. The catabolism of lysine is principally located in the liver. Lysine released from digested protein undergoes a significant first-pass metabolism of ~30 to 42% in humans and piglets. An important question regarding the biological basis of the requirement of lysine is the possible participation of microbial de novo synthesized amino acids in the whole-body fluxes. Recent intake recommendations to meet the lysine requirement range from 64 to 30 mg/(kg · d) for 0.5-y infants and adults (>18 y), respectively. Lysine intake in the Western human diet is in the range 40–180 mg/(kg · d). An upper limit of 300–400 mg/(kg · d) can be considered in humans. J. Nutr. 137: 1642S–1645S, 2007.

L-lysine is a basic amino acid characterized by the presence of an amino group at the end of a 4-carbon aliphatic side chain [(CH₂)₄-NH₃⁺]. This structure makes lysine a relatively reactive component in different chemical reactions including carbonyl-amine interactions. As a consequence, a fraction of lysine can be degraded, and another part can become unavailable in different food systems because of its involvement in different interactions with amino acid side chains or with other components including carbohydrates or lipids. Moreover lysine, together with threonine, is a strictly indispensable amino acid in humans and animals; i.e., the intact molecule has to be provided in the diet. Last, lysine is low in all cereal proteins. Taken together, these different factors make lysine a limiting amino acid in different diets. L-lysine hydrochloride is used for cereal fortification for human consumption in some developing countries and is also used in animal feed formulation. A range of 12 to 45 mg·kg⁻¹·d⁻¹ was reported for lysine requirements in the adult, as discussed subsequently.

Lysine metabolic pathways

Lysine cannot be synthesized by mammalian and as a consequence is an indispensable amino acid. Moreover lysine, as threonine, does not participate in transamination reactions and is consequently a strictly indispensable amino acid.

The main role of lysine is to participate in protein synthesis. In mammals, catabolism of lysine through the saccharopine pathway also results in the irreversible formation of glutamate and α-amino adipate, which are then subjected to deamination and oxidation. The catabolism of lysine is principally located in the liver (1). Some data in piglets (2), but not in infants (3), suggest that lysine could also be oxidized in enterocytes under conditions of generous protein intake, although there is no evidence that enterocytes express the enzymes necessary for lysine catabolism (4). In addition to its importance as a precursor for protein synthesis, lysine is also a precursor for the biosynthesis of carnitine, which plays an important role in β-oxidation (5).

Tracer studies aimed at characterizing the metabolic fate of ingested lysine have shown that like all indispensable amino acids, lysine released from digested protein undergoes a significant first-pass metabolism of ~30 to 42% in humans and piglets (2,6–8). Lysine first-pass metabolism seems to occur mainly in intestine in piglets (2,7,8). Intestinal extraction of dietary lysine represents an obligatory component of the lysine requirement in piglets as it remains unchanged in situations where protein intake is low (2). In this experimental model, dietary lysine represents almost all the lysine consumed by the portal-drained viscera (8). In liver, dietary lysine is extracted only to a limited extent, and this low amount serves principally in protein synthesis, as shown in piglets (7).

An important question regarding the biological basis of the requirement for lysine and those for other indispensable amino acids is the possible contribution of microbial de novo synthesized amino acids to the whole-body fluxes. Different well-designed studies have attempted to provide evidence of this contribution in humans, rats, or pigs (9–15). It is clear that microbially derived amino acid enters the systemic circulation and that the site of synthesis and absorption is the terminal ileum rather than...
Determination of lysine requirement in adults

The requirement for lysine has received attention because of its nutritional importance as the first limiting amino acid in cereals. According to various studies and experimental approaches, a range of 12–45 mg kg\(^{-1}\) d\(^{-1}\) has been reported for lysine requirements in adults (Table 1).

The first approach for measuring the lysine requirement was based on the determination of the quantity of dietary lysine necessary to equilibrate nitrogen balance in the adult human. Lysine requirement determined from protein and nitrogen balance studies indicates a range of 12–36 mg kg\(^{-1}\) d\(^{-1}\). The initial requirement measured by Jones et al. (18) was 8 mg kg\(^{-1}\) d\(^{-1}\) lysine for the adult, and this was confirmed by later N-balance studies (16–18). These assessments convinced the FAO/WHO expert committees in 1973 and 1985 to adopt the value of 12 mg kg\(^{-1}\) d\(^{-1}\) for the lysine requirement in adults (32,33). Reanalysis of the lysine requirement in adults (32,33). Reanalysis of the N-balance data by Rand and Young resulted in an estimation of the lysine requirement in the range of 17 to 36 mg kg\(^{-1}\) d\(^{-1}\) (19). Indeed, these authors showed that more than half of the subjects (8 of 14) in the initial study by Jones et al. did not achieve a positive N balance at a lysine intake of 10 mg kg\(^{-1}\) d\(^{-1}\).

Lysine is considered to be the first limiting AA in wheat protein, with threonine being the second limiting AA. From N-balance studies, data in children indicate a requirement for wheat protein of 280–360 mgN kg\(^{-1}\) d\(^{-1}\), as compared with a requirement of 124–163 mgN kg\(^{-1}\) d\(^{-1}\) for animal protein (34). Tracer studies on wheat protein requirements determining \(^{13}\)C-leucine balance as a proxy for protein balance after ingestion of wheat or milk-based meals indicated a postprandial protein utilization (PPU) of 0.61 and 0.93 for wheat and milk (\(P < 0.001\)), respectively (20,21). The estimated average wheat-protein requirement (0.6 g kg\(^{-1}\) d\(^{-1}\) PPU\(^{3}\)) was 0.98 g kg\(^{-1}\) d\(^{-1}\), which translated into a lysine requirement of 18.3–23.2 mg kg\(^{-1}\) d\(^{-1}\). Reanalysis of these data gave a value of the lysine requirement closer to 29.8 mg kg\(^{-1}\) d\(^{-1}\) (22), using the following assumptions: a 35% reduction in endogenous production of leucine oxidation, a change in \(^{13}\)Cbicarbonate recovery from 0.9 to 0.8 (postmeal), and an estimated average requirement (EAR) for protein of 0.66 g kg\(^{-1}\) d\(^{-1}\). Assessment of the net postprandial protein utilization (NPPU) of wheat protein following ingestion of intrinsically \(^{15}\)N-labeled wheat protein allowed one to estimate the lysine requirement, based on the observation that a wheat-containing meal providing 300 mmol N and 8.3 mg lysine/kg balanced postprandial nitrogen losses only for the 5 h after ingestion and on the assumption that lysine is the first limiting AA in wheat protein (23). This result may translate into a lysine requirement of 40 mg kg\(^{-1}\) d\(^{-1}\) in the fed state. On the basis of the total nitrogen losses of 413 mmol at 8 h, the approximate lysine requirement would then be 33.6 mg kg\(^{-1}\) d\(^{-1}\). This value reaches 31.6 mg kg\(^{-1}\) d\(^{-1}\) if corrected for a 25% recycling of ileal nitrogen.

Direct assessments of lysine requirement obtained from amino acid tracer studies range between 27 and 45 mg kg\(^{-1}\) d\(^{-1}\). The first estimate of 27 mg kg\(^{-1}\) d\(^{-1}\) was obtained using the short-term protocol of the indicator amino acid balance (25) and further reassessed at a slightly higher value ranging between 29 and 31 mg kg\(^{-1}\) d\(^{-1}\) (24,26,27) using successive improvements of the method. The indicator amino acid oxidation method with \(^{13}\)Cphenylalanine in the fed state only and without prior adaptation to the diet indicated values in the range of 37–45 mg kg\(^{-1}\) d\(^{-1}\) (29,30).

On the basis of the tracer studies, the current lysine requirement value proposed by the Food and Nutrition Board is 31 mg kg\(^{-1}\) d\(^{-1}\) (35).

Modulation of the lysine requirement

The lysine requirement is higher in infants than in adults, and recent recommendations indicated a lysine requirement that ranges from 64 mg kg\(^{-1}\) d\(^{-1}\) to 30 mg kg\(^{-1}\) d\(^{-1}\) for 0.5 y infant and adult (\(> 18\) y), respectively (Table 2).

Most estimates of an indispensable amino acid requirement have been made in Western well-nourished young male adults, and their modulation by factors such as gender, dietary, and nutritional factors has started to receive attention only recently. One study measured the lysine requirement in women and reported an influence of the menstrual cycle phase on this number (35 and 37.7 mg kg\(^{-1}\) d\(^{-1}\) during the follicular and luteal phase, respectively), a difference that was ascribed to hormonal factors (35). This estimate of lysine requirement in healthy women is close to the results obtained in young adult men using the same method (29).

The possibility that the indispensable amino acid requirement might differ among populations living in other environments is of importance. From a series of recent studies re-evaluating the indispensable amino acid requirements in Indian subjects, it appears that the lysine requirement is not different between well-nourished young adults living in the United States and those in India (27). However, the situation is different in undernourished Indian adults whose lysine requirement is significantly higher than that of healthy subjects and reaches

<table>
<thead>
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<th>Method of determination</th>
<th>References</th>
<th>Lysine requirement in adults, mg kg(^{-1}) d(^{-1})</th>
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<td>N balance studies</td>
<td>References</td>
<td>N balance studies (16–18) 8–12</td>
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<td>Reanalysis of data</td>
<td>(19)</td>
<td>17–36</td>
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<tr>
<td>Postprandial protein utilization</td>
<td>Protein and wheat protein requirements and (^{15})N-leucine balance</td>
<td>(20, 21) 18.3–23.2</td>
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<tr>
<td>Reanalysis of data</td>
<td>(22)</td>
<td>29.8</td>
</tr>
<tr>
<td>Net postprandial protein utilization of (^{15})N-wheat protein</td>
<td>Fed state</td>
<td>(23) 40.0</td>
</tr>
<tr>
<td>Daily requirement</td>
<td>(23)</td>
<td>31.6</td>
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<td>Direct amino acid balance method</td>
<td>Healthy western males</td>
<td>(24, 25) 27–30</td>
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<td>Indicator amino acid balance method</td>
<td>Healthy Indian males</td>
<td>(26, 27) 30</td>
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<td>Chronically undernourished Indian males</td>
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<tr>
<td>Indicator amino acid oxidation method (fed state)</td>
<td>Healthy Western males</td>
<td>(29, 30) 37–45</td>
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<tr>
<td>Healthy Western females</td>
<td>(31)</td>
<td>35–37.7</td>
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\(^{3}\) Abbreviations used: EAR, estimated average requirement; NOAEL, no observed adverse effect level; NPPU, net postprandial protein utilization; PPU, postprandial protein utilization.
TABLE 2  Protein and lysine requirements of infants, children, adolescents, and adults

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Protein, g·kg⁻¹·d⁻¹</th>
<th>Lysine, mg·kg⁻¹·d⁻¹</th>
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<tr>
<td>0.5</td>
<td>0.686</td>
<td>0.46</td>
</tr>
<tr>
<td>1–4</td>
<td>0.686</td>
<td>0.19</td>
</tr>
<tr>
<td>4–10</td>
<td>0.686</td>
<td>0.06</td>
</tr>
<tr>
<td>10–14</td>
<td>0.686</td>
<td>0.07</td>
</tr>
<tr>
<td>14–18</td>
<td>0.686</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt;18</td>
<td>0.68</td>
<td>—</td>
</tr>
</tbody>
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1 Sum of the lysine requirement for maintenance (maintenance protein × the adult scoring pattern) and growth (tissue deposition adjusted for a 58% dietary efficiency of utilization × the AA tissue pattern) (36).

44 mg·kg⁻¹·d⁻¹ (28). This 50% higher requirement was shown to result from intestinal parasite infestation (37).

Another yet unknown source of lysine requirement modulation may occur through the microbial lysine synthesis and absorption, as discussed previously. The contribution of this flux, if of nutritional significance, could be influenced by dietary factors quantitatively or qualitatively affecting the microflora, such as undigestible fibers, or by conditions altering the microflora (disease, antibiotics) and remains to be explored. Available data on the adaptation to diets low in lysine have indicated complex and paradoxical responses (14).

Upper limit of lysine intake

Lysine intake in diets of western populations is in the range of 40–180 mg·kg⁻¹·d⁻¹. The existence and level of an upper limit of lysine intake remain unclear in humans.

The lysine dose associated with no observed adverse effect level (NOAEL) was estimated at 3.3–4.0 g·kg⁻¹·d⁻¹ in rats (38). In this study, male and female Sprague-Dawley rats were fed with lysine at doses equal to 1.25, 2.5, and 5.0% (wt:wt) in a standard diet fed ad libitum for 13 wk and followed by a 5-wk recovery period with only the standard diet. A lysine-related drop in serum concentrations and an increase in urine excretion of chlorides were compensatory reactions to the ingested hydrochloride. No treatment-related changes were observed in the clinical signs, body weights, diet consumption, water intake, ophthalmology, gross pathology, organ weights, or histology. No functional, biochemical, or histological changes in renal function were found. Under those conditions, the NOAEL for lysine was estimated at 5.0% for both genders (male, 3.36 ± 0.12 g·kg⁻¹·d⁻¹; female, 3.99 ± 0.28 g·kg⁻¹·d⁻¹). As a consequence, an upper limit of 300–400 mg·kg⁻¹·d⁻¹ can be considered in humans.

It has been reported that large doses of infused amino acids induced acute renal failure. In particular, lysine-induced renal failure was observed in rats and dogs. For instance, infusion of 4.5 g·kg⁻¹·d⁻¹ lysine hydrochloride is nephrotoxic in dogs (39). In this experiment, female dogs were infused through the posterior vena cava with 4.5 g·kg⁻¹·d⁻¹ (3.75 mL·kg⁻¹·h⁻¹) lysine hydrochloride for 3 consecutive d. Blood biochemistry showed increases in ammonia, urea nitrogen, urea nitrogen/creatinine ratio, and creatinine. Urine analysis showed increases in urine volume, total protein, albumin, y-glutamyl transpeptidase, and N-acetyl-b-D-glucosaminidase. Kidneys showed pale, congested capsules, hypertrophy of proximal convoluted tubule (mainly S1 segment), and degeneration/desquamation of urinary tubule (mainly S3 segment with hyaline casts). It is concluded that 4.5 g·kg⁻¹·d⁻¹ lysine is nephrotoxic and is related to direct tubular toxicity and to tubular obstruction in dogs.

Lysine is toxic in the autosomal recessive human disease glutaric aciduria type I because of glutaryl-CoA dehydrogenase deficiency, which disrupts the mitochondrial catabolism of lysine and tryptophan (40).

The establishment of a lysine requirement in adult humans has now reached consensus. However, despite the nutritional and physiological importance of lysine, it remains to clearly identify the modulation of lysine requirement in humans. In particular, there are still numerous uncertainties regarding lysine metabolism and oxidation by individual tissues and the dietary and lifestyle factors influencing lysine metabolism. Finally, the modulation of lysine requirement by development and aging and the consequences of lysine deficiency or excess warrant further research.

Literature Cited