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Influence of nutrition on acid-base balance – metabolic aspects

■ **Summary** *Background* Nutrition has long been known to strongly influence acid-base balance. Recently, we have shown that it is possible to appropriately estimate the renal net acid excretion (NAE) of healthy subjects from the composition of their diets. *Aim of the study* 1) To briefly present a physiologically based calculation model that allows a reasonable estimation of the analytically determined urinary NAE, 2) to summarize the underlying metabolic mechanisms and 3) to study the specific effect of protein on ammoniogenesis which may counteract, to a small degree, the primary acid load-increasing potential of protein. *Methods* The calculation

model and the algorithm for predicting the dietary acid load are summarized, major metabolic (and intestinal) pathways of acid and base equivalents are explained, and urinary excretion rates of ammonium and NAE were specifically examined with special regard to the respective protein intake levels. For the latter examinations, data from diet experiments in adults and epidemiological data from children (protein intake; NAE, pH, and ammonium excretion in 24-h urine samples) were analyzed. *Results* The paper shows that the diet-induced generation of acidity and alkalinity is not only determined by the metabolism (oxidation) of sulfur-containing amino acids and organic acid anions of alkali salts, respectively. The intestine is also directly involved in the generation of food-derived acid or alkali loads which is due to the considerably different intestinal absorption rates of relevant food components, i. e., protein and minerals. Further analyses of the interrelation between diet and acid-base status re-

vealed that increasing protein intake (despite its potential to increase NAE) also significantly improves the capacity for renal net acid excretion by stimulating urinary ammonium excretion. *Conclusion* An adequate concept to estimate renal NAE and potential renal acid loads from dietary intakes must consider the specific bioavailability of the individual nutrients. Furthermore, an increased protein intake does not necessarily result in an accordingly increased use of endogenous acid excretion capacity for two reasons: 1) additional alkali loads in an appropriately composed diet can compensate for the protein-related raised acid production and 2) protein itself moderately improves the renal capacity to excrete net acid by increasing the endogenous supply of ammonia which is the major urinary hydrogen ion acceptor.

■ **Key words** Net acid excretion (NAE) – NAE prediction – NAE capacity – Nutrient bioavailability – Protein intake – DONALD study

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Introduction

There is increasing evidence that acid-base status has a significant impact on high intensity exercise performance, urolithiasis, and calcium metabolism. As diet has been known long to strongly influence acid-base bal-

ance, considerable efforts have been made to predict the net acid load from dietary intake. Earlier calculation models for the estimation of renal net acid excretion (NAE), which did not take into account the different intestinal absorption rates of those individual nutrients that are involved in the formation of acid or alkali loads, failed to provide an appropriate prediction [1, 2]. Re-

cently, a physiologically based calculation model that corrects for intestinal absorption of minerals and sulfur-containing protein and assumes a rate of urinary excretion of organic acids (OA) proportional to body surface area was successfully tested in controlled diet experiments yielding reasonable estimates of analytically determined urinary NAE [3–6]. In the present paper this calculation model is briefly presented, the underlying intestinal and metabolic mechanisms are summarized and the specific effect of protein on ammoniogenesis is studied.

Subjects and methods

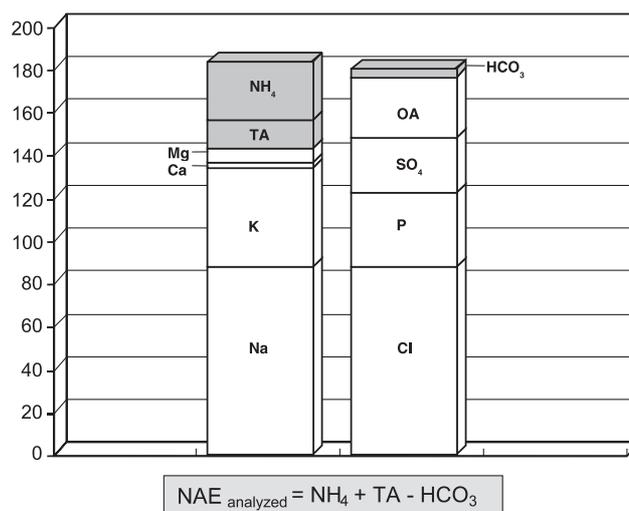
The calculation model [5, 7] and the algorithm for predicting dietary acid loads are presented as well as the underlying physiological rationale, i. e., the major metabolic and intestinal pathways of acid and base equivalents. With regard to the examination of the impact of protein on ammoniogenesis, data on 24-h urinary excretion of total NAE and ammonium (NH_4) from recent diet experiments in healthy male adults [8] were combined with the respective urinary output data obtained in healthy 8 year old boys. Eight year old children were chosen because at around this age boys commonly have their lowest growth rates [9]. A high growth rate may interfere with urinary electrolyte excretion and may thus confound relationships between biochemical urine markers. All children were participants in the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) study, an ongoing observational study, investigating the interrelations between nutrition, growth, metabolic and endocrine changes during childhood and adolescence. The study was approved by the institutional review board of the Research Institute of Child Nutrition Dortmund, and parental consent and children's assent were obtained before entry into the study. All children collected a 24-h urine sample along with a 3-day weighed diet record of the amounts of all foods and beverages consumed. To ensure compliance in the 24-h urine collection the children and their parents were carefully instructed in the collection procedure and also received written guidance. Urine specimens were stored below -20°C . Acid-base status was determined in the freshly thawed and thoroughly pooled 24-h samples. Urine pH, titratable acid (TA), NH_4 , and bicarbonate were measured according to Lüthy et al. [10].

Background, results and discussion

■ The estimation model for renal net acid excretion and potential renal acid load

There is a necessity to excrete acid (hydrogen ions, H^+) when the sum of major nonmetabolizable anions eliminated in urine exceeds the sum of the mineral cations sodium (Na), potassium (K), calcium (Ca), and magnesium (Mg) (Fig. 1). Major urinary anions encompass chloride (Cl), phosphate (P), sulfate (SO_4) and a mixture of different organic acids (OA) of which the majority cannot be metabolized (e.g., aliphatic or aromatic acids). The difference between these nonbicarbonate anions (Σ acid-forming inorganic anions + OA) and the mineral cations (Σ base-forming cations) is net acid excretion ($\text{NAE}_{\text{indirect}}$). NAE is analytically quantified as the sum of $\text{NH}_4 + \text{TA} - \text{bicarbonate}$ (Fig. 1). The urine ionogram shows that NAE may also be estimated from the dietary intakes of Cl, P, SO_4 (originating mainly from metabolism of sulfur-containing amino acids), on the one hand, and Na, K, Ca, Mg, on the other hand, provided the respective intestinal absorption rates of these nutrients are known and no quantitatively important nutrient retention or catabolic tissue degradation occurs.

In fact, we were able to show that it is possible to reliably estimate the renal NAE of healthy subjects from the composition of their diets. A physiologically based calculation model that corrects for average intestinal absorption of minerals and sulfur-containing protein and assumes a rate of urinary excretion of organic acids (OA) proportional to body surface area was successfully



$$\text{NAE}_{\text{indirect}} = \Sigma \text{ acid-forming inorganic anions} + \text{OA} - \Sigma \text{ base-forming cations}$$

Fig. 1 Urine ionogram of healthy 8 yr old children consuming common diets (NH_4 ammonium; TA titratable acid; Mg magnesium; Ca calcium; K potassium; Na sodium; HCO_3 bicarbonate; OA organic acids; SO_4 sulfate; P phosphorus; Cl chloride).

Table 1 Intestinal net absorption rates and overall calculation formulas used for estimation of NAE

Estimated electrolyte excretion	=	Intestinal net absorption	x Intake	x Ionic valence Grade of dissociation
Na (mmol)	=	0.95	... mmol	
K (mmol)	=	0.80	... mmol	
Ca (mEq)	=	0.25	... mmol	2
Mg (mEq)	=	0.32	... mmol	2
Cl (mmol)	=	0.95	... mmol	
PO ₄ (mEq)	=	0.63	... mmol	1.8
SO ₄ (mEq)	=	0.75	... g Protein x 0.325*	2
OA (mEq)		41 mEq	x Individual BS area (m ²)/1.73 (m ²)	

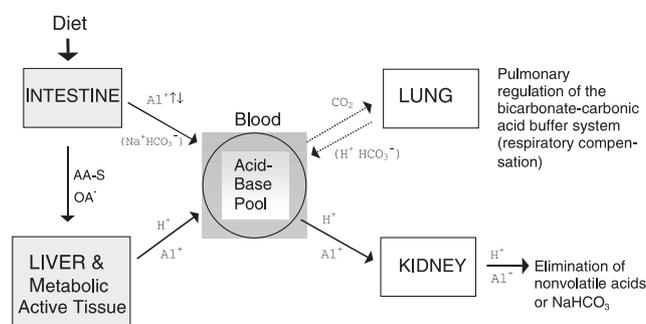
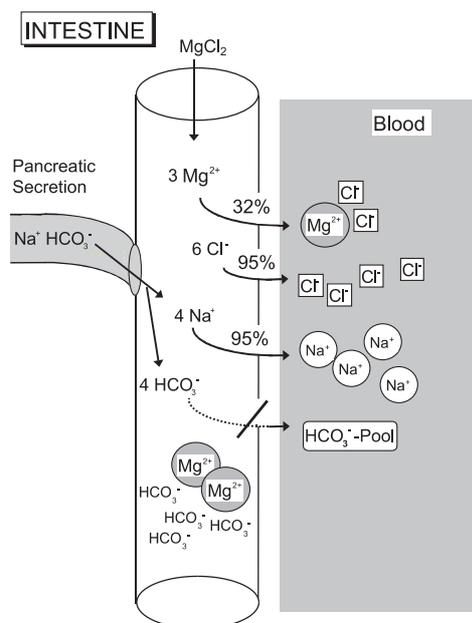
* Estimated average content of methionine and cysteine (2.4% and 2% of total protein, respectively) expressed as mmol/g protein
 $NAE_{est} = (Cl + P + SO_4 + OA)_{est} - (Na + K + Ca + Mg)_{est}$

tested in controlled diet experiments yielding reasonable estimates of analytically determined urinary NAE [4]. The calculation model used for prediction (i.e., a slightly simplified algorithm) is shown in Table 1. According to literature findings (cited elsewhere [4, 5]), average intestinal net absorption rates between 25% (Ca) and 95% (Na) were assumed. The constant values for average net absorption rates for P, Mg, and Ca, shown in Table 1, were calculated from more specific regression equations. These equations describe the relationship between daily mineral intake and corresponding daily electrolyte excretion [5]. With regard to OA, a relatively constant daily excretion has been observed in healthy children and adults after analyzed OA data were corrected for individual body surface (BS) area [11].

Because this calculation model to appropriately predict renal NAE from nutrient intake and individual anthropometric data has also been proven in a second diet study [8], we were then encouraged to calculate the potential renal acid load (PRAL) of selected, frequently consumed foods. The PRAL calculation (related to 100 g edible portion) was based on the same calculation formulas as shown in Table 1 with the only exception that for foods and beverages in general no OA could be estimated, as this parameter is not consistently food-dependent but primarily anthropometry-dependent. When nutrient data from current food composition tables were used, the calculation model yielded negative PRAL values for fruits and vegetables, meaning they reduce acid excretion; milk and yogurt yielded about 1 mEq, whereas meats, fish, poultry, cheeses and even some grain products potentially had 7 mEq or more per 100 g serving. In the meantime, our model for NAE estimation and the tabulated PRAL values of foods are internationally used in clinical nutrition and nutrition research [12].

Physiological background: major metabolic pathways of acid and base equivalents

A schematic representation of how the different organs interact in managing acid-base balance is given in Fig. 2. The initial organ with an important impact on acid-base metabolism after the ingestion of food is the intestine. The intestine itself does not specifically generate acid or base equivalents, but depending on diet composition it modulates the blood bicarbonate level by increasing or decreasing the amount of alkali (from pancreatic secretion) that is continuously reabsorbed (for more details see below, Fig. 3). In addition, the gut determines the absorbed amounts of sulfur-containing amino acids (AA-S) and alkali salts of metabolizable OA, which then are

**Fig. 2** Interaction of organs in acid base metabolism (AA-S sulfur-containing amino acids, OA⁻ alkali salts of organic acids, Al⁺ alkali loads).**Fig. 3** Involvement of the intestine in the generation of acid load. Here, an example of an increase in net acid as a result of a physiologically low cation (Mg) absorption (along with a high inorganic anion absorption) leading to a reduction in circulating bicarbonate buffer.

available in the liver or other metabolically active tissues as substrates for the generation of either acids or alkalis. After oxidation of AA-S and OA the released protons or alkali ions add to the total acid-base pool in blood and are finally excreted by the kidney (Fig. 2). On the other hand, the lung regulates the carbonic acid-bicarbonate buffer system and herewith the blood pH is maintained within a narrow range (respiratory compensation). However, this process cannot cause any sustained loss or gain in hydrogen ions.

The intestine does indeed not directly generate acids or alkalis, but it generates “so-called” acid or alkali loads. The reason for this is the specific absorption rate of each electrolyte. For example, from a given amount of Mg only about one third is absorbed (Fig. 3), whereas the average bioavailability of Cl is 95%. If $MgCl_2$ is ingested a clear excess of Cl over Mg enters the blood (Fig. 3). Due to the principle of electroneutrality it is clear that other cations need to compensate. The primary cation that is abundantly available to be absorbed along with an excess of anions (such as Cl) is Na stemming from pancreatic secretion of large amounts of sodium bicarbonate. The bicarbonate anion forms carbonate salts with the unabsorbed portion of Mg. As a result the circulating bicarbonate pool is not appropriately replenished (Fig. 3). This lack of sodium bicarbonate in blood, which means a loss of buffer capacity, can be called *acid load*. Comparable consequences for the intestinal bicarbonate reabsorption are seen when Ca salts of unmetabolizable acids are ingested. Thus, in metabolism $CaCl_2$ also has acidic properties [13].

A similar mechanism operates when high amounts of phosphorus are ingested in the form of phosphoproteins (Fig. 4). These proteins are hydrolyzed into the respective amino acids and phosphoric acid. Both components are absorbed to a comparable degree. The phosphate anion enters the cells of the gut along with sodium, again reducing the systemic bicarbonate pool. In this case, the intestine has not generated an acid load due to different absorption rates for anions and cations, but due to the release of an acid after digestion.

In contrast, a real production of “true” acid or alkali occurs in the liver or other metabolic active tissues (Fig. 5). For example, the oxidation of sulfur-containing amino acids to urea and carbon dioxide also yields sulfuric acid. On the other hand, the alkali salts of organic acids, for example sodium citrate, ingested with the diet are metabolized to carbon dioxide and water and yield the respective cation along with bicarbonate, thus, increasing the circulating alkali reserve or blood base pool (Fig. 5).

Fig. 6 gives an overview of the flux of an acid after it has been metabolically generated within the body (e. g., within the liver). In blood, the acid (sulfuric acid) is buffered by bicarbonate. Thereby neutral sodium sulfate and carbonic acid are formed. The latter is eliminated as

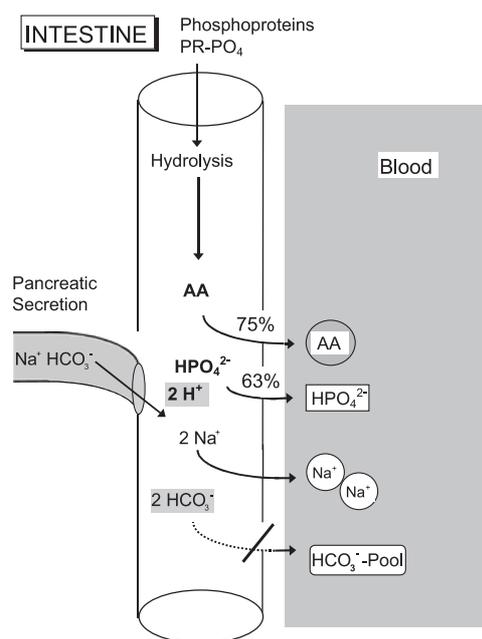


Fig. 4 Involvement of the intestine in the generation of acid load. Here, an example of an increase in net acid as a result of ingestion of phosphoproteins leading to a reduction in circulating bicarbonate buffer.

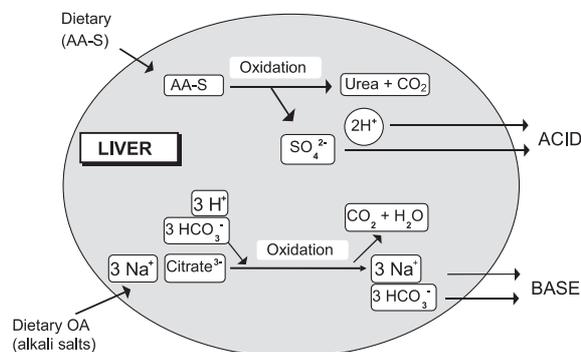


Fig. 5 Contribution of metabolically active tissues’ metabolism of sulfur-containing amino acids (AA-S) and metabolizable organic acids (OA) in the formation of acid and base.

carbon dioxide by the lung. The neutral salt, sodium sulfate, is transported to the kidney and the sodium is reabsorbed for the restoration of the circulating bicarbonate pool. An active renal hydrogen ion secretion, for example through a H⁺/Na⁺ antiporter transport protein in the distal renal tubular duct, drives this process. Since the kidney can not elaborate urine more acid than pH 4.4, only negligible quantities of strong acids, such as sulfuric acid, can be eliminated in free titratable form. Consequently, appropriate hydrogen ion acceptors must buffer most of the secreted hydrogen ions. The most important proton acceptor is NH₃.

est and those (n=26) with the lowest protein intake. A significantly higher NH_4 excretion (29.4 ± 5.0 mmol/day versus 25.2 ± 4.5 mmol/day; $P < 0.01$) was seen in the high protein group (protein intake: 66 ± 9.0 g/day) compared to the low protein group (43 ± 8.2 g/day). NAE was statistically undistinguishable between the two subgroups. These data confirm the specific stimulating effect of protein on renal ammoniogenesis, also for children.

In order to check whether this protein effect may be different between adults and children, the data of the children were then combined with the above shown experimental data of healthy men. To control for effects of growth all variables (protein intake, NAE and NH_4 excretion) were BS area-adjusted. As is depicted in Fig. 9 urinary NH_4 excretion (adjusted for a given NAE level) was higher to a comparable degree in men and boys with higher protein intakes. This NAE-independent effect of protein on NH_4 excretion is probably one reason why epidemiological studies frequently show closer associations between protein intake and urinary NH_4 output than between protein intake and urinary NAE.

In summary, the combined findings from controlled diet experiments in adults and epidemiological data in children strongly suggest that, in healthy subjects, the final degree of the renal capacity to excrete NH_4 (and thus

to excrete net acid) is modulated by the amount of protein ingested. This mechanism would allow the kidney to meet acid-base demands more efficiently and thus leaves a renal surplus capacity for the elimination of additional acid loads.

As the urine pH is regarded to reflect the primary stimulus for renal ammoniogenesis, urinary NH_4 output was also plotted against the urine pH (Fig. 10). For this, data from another diet study with high and low protein intake [4] were also included. As can be seen, renal NH_4 output is also elevated for any given urine pH range, whether it is high, medium or low. Furthermore, this clearly increased capacity for net acid excretion is associated with a small but significantly ($P < 0.05$) elevated urine pH – even under conditions of an already alkaline urine. This has practical implications: as under our living conditions (common Western diets) the protein intake is at least moderately high [16], special care should be taken if higher amounts of alkalinizing supplements are ingested. In that case, the additional ingestion of higher amounts of calcium supplements should be avoided since the alkalinizing agent together with a relatively high protein intake would result in the highest possible urine pH levels, thus, increasing the risk of urolithiasis because calcium phosphate is poorly soluble at higher urine pH values.

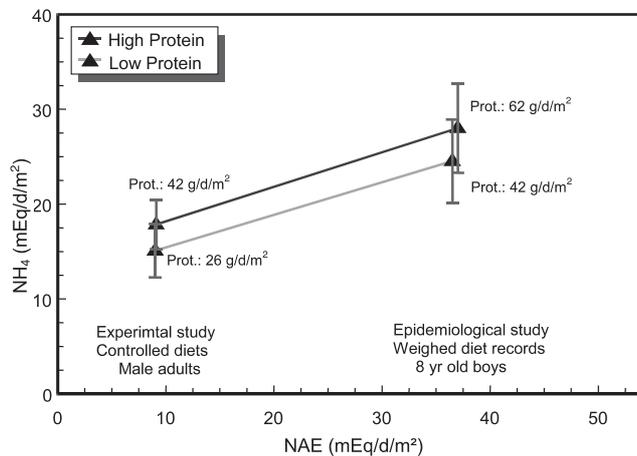


Fig. 9 Ammonium (NH_4) plotted against net acid (NAE) excretion at different protein intake levels (body surface-related) of healthy boys and men. Protein intakes (and resulting NH_4 excretions) were experimentally or epidemiologically adjusted for two definite NAE ranges.

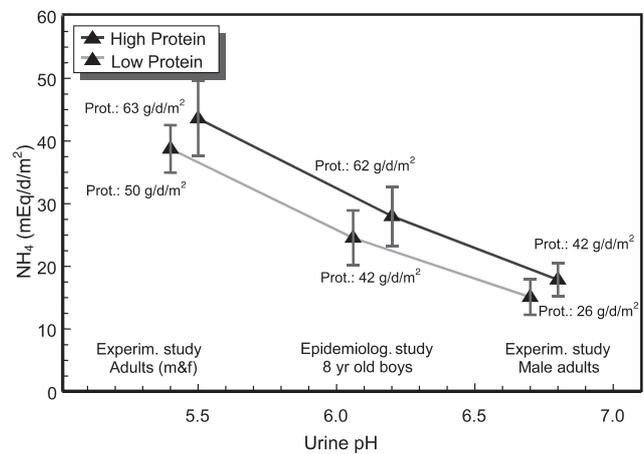


Fig. 10 Dependency of ammonium (NH_4) excretion on urine pH at different protein intake levels (body surface-related) after NAE had been adjusted.

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