When Is Low Potential Renal Acid Load (PRAL) Beneficial for Bone?

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Abstract

Potential metabolic influences of dietary acid load on bone health have been discussed controversially. Here, we review the available findings in adults and healthy children regarding certain methodological aspects including (i) appropriate use of urinary biomarkers – potential renal acid load (PRAL) and net acid excretion (NAE), (ii) problems in the interpretation of results on calcium balance and bone turnover markers, and (iii) possible influences of selection bias regarding baseline diets of the population groups of randomized controlled trials. Based on the available evidence, it is concluded that calcium balance measurements and bone turnover markers are no adequate and sensitive tools to evaluate the modest but long-term prevailing influence of nutrition on bone status. Findings in children and adults exclusively conducted on the most reliable outcomes, that is, bone densitometric structure analyses, suggest that a low-PRAL diet may be especially relevant in certain population groups, for example, in children with higher dietary protein intakes, in postmenopausal women with impaired bone status, and probably in adults on a habitually acidifying nutrition. The mechanisms mediating detrimental bone effects of higher dietary acid loads under discussion include changes in endocrine–metabolic milieu, for example, impairment of GH/IGF-1 axis and higher glucocorticoid secretion as well as direct bone–cell-related changes by higher acid load. In conclusion, to identify moderate alterations in bone status exerted through nutritional influences, not only appropriate assessments of dietary proton load but also outcome measurements that are closely related to long-term bone structure are required.

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Abbreviations

BMD	Bone mineral density
DEXA	Dual-energy X-ray absorptiometry
NAE	Net acid excretion
NEAP	Net endogenous acid production
OA	Organic acids
pQCT	Peripheral quantitative computed tomography (pQCT)
PRAL	Potential renal acid load
RCT	Randomized controlled trial

Introduction

Among the modifiable influences that act on the skeleton, nutrition is – along with physical activity – one of the most relevant factors. Vitamins, especially vitamin D and K; antioxidative polyphenols; calcium; and protein intake as well as acid load with the daily nutrition are under discussion. Particularly, the latter potential metabolic influence of a higher or a lower dietary proton [H^+] delivery to the body has triggered controversies concerning its bone health relevance. Clinical studies in patients with hypercalciuria or with chronic kidney disease have proven the beneficial impact of oral or dietary alkalization for the maintenance of skeletal integrity. However, similar results in healthy subjects or humans with rather moderate medical conditions are rare. Of several available methodological approaches to assess dietary acid loads, one is the potential renal acid load (PRAL) model. PRAL is calculated from the difference of nonbicarbonate anions and mineral cations [1]. This has the advantage that it can be used directly with recorded dietary intake data and in the same way also noninvasively as a clinical–chemical biomarker if appropriate urine collections are available. Although several meaningful diet-related observational and intervention studies on bone health did not directly present PRAL values, it is possible to calculate PRAL data (from the measurement values provided) at least for some of the trials and to assess their implications for bone outcomes. We complemented these assessments of the findings in adults with own study results in healthy children and provided possible metabolic mechanisms that may explain the bone catabolic influence of long-term high-PRAL diets.

Potential Renal Acid Load (PRAL): A Biomarker for the Diet-Related Acid Load

Protein is one of the most anabolic nutrients increasing not only the body's protein synthesis and muscularity [2] but also bone strength, at least moderately [3]. Despite these positive effects, dietary protein additionally represents the major nutritional source of protons metabolized from the sulfur-containing amino acids as well as from phosphorus bound to various protein structures in the form of phosphoproteins.

Accordingly, if renal acid excretion mechanisms are insufficient or immature as in preterm infants and neonates or if the systemic buffer capacity is reduced, mild forms of metabolic acidosis, not necessarily prominent in a clinically sense, can occur. Decreases in systemic pH and circulating bicarbonate levels are usually modest and still lie within the normal range. Despite this, growth retardation in low-birthweight infants [4] or impaired protein synthesis in elderly [5] can be a consequence of these mostly subclinical acidosis forms, which are positively responsive to dietary measures or manipulations [1, 6], but difficult to detect by

blood measurements [4, 6]. Appropriate noninvasive urine measurements are useful to identify states of high, medium, or low nutritionally and metabolically initiated daily proton loads. The classical way to do this is to measure net acid excretion (NAE) which formally represents the sum of urinary PRAL and the total amount of renally excreted organic acids (OA), with urinary PRAL reflecting the major renally excreted mineral anions minus the major urinary mineral cations.

$$\begin{aligned} \text{NAE} &= \text{urinary PRAL} + \text{OA} \\ &= \text{mineral anions} - \text{mineral cations} + \text{OA} \\ &= (\text{SO4}+\text{PO4}+\text{Cl}) - (\text{K}+\text{Mg}+\text{Ca}+\text{Na}) + \text{OA} \end{aligned}$$

Consumption of a rather plant-based fruit- and vegetable-rich diet results in higher intakes of mineral cations, especially of potassium and magnesium which even in absolute terms exceed the phosphorus and sulfur intake originating from dietary protein. In this situation, PRAL is negative or at least varies around zero (provided that sodium and chloride excretion rates, mostly reflecting salt intake, are nearly equimolar).

The PRAL model for the calculation of the diet-dependent daily acid load in humans assumes a theoretical metabolic steady state (for data standardization and practicability) during which the amounts of mineral cations and anions (or anion precursors) intestinally absorbed correspond to the amounts renally excreted. Urinary PRAL represents a biomarker providing the advantage that it reflects clearly defined nutritional influences on net proton loads to the body, whereas the NAE measurement which includes the large fraction of OAs has a strong body size-related component. For normal mixed diets, most of the OAs excreted stem from physiological daily degradation processes related to energy metabolism and body size [7]. Therefore, depending on the research question, quantification of urinary PRAL can be advantageous compared with NAE titration (for more details see [8]).

PRAL Inappropriately Used in Bone Health Studies

In epidemiological studies estimates of endogenous H^+ loads like PRAL or net endogenous acid production (NEAP) [9] commonly applied are diet based. Until now only a few studies have made use of the noninvasive biomarker urinary PRAL that relies on clinical–chemical measurements of mineral anions and cations in urine samples. One of these recent studies reporting urinary PRAL values suggested that neither a low urine pH nor a high acid excretion predicts bone fractures or the loss of bone mineral density. In this prospective cohort study, the authors examined 2-h urine samples that were collected in the morning under fasting conditions in a random sample of Canadian adults 25 years of age and above participating in the Canadian Multicentre Osteoporosis Study [10]. The authors (i) claimed that the use of urine to measure the diet acid load did allow them to avoid random and systematic errors inherent in food intake measurements and (ii) considered it possible that the *fasting-morning-2-h-second-void urine* samples they have analyzed are more reliable measures of dietary acidity than 24-h collections which are more prone to incomplete collection. In this study of Fenton et al. [10], no associations between the above-outlined urine measure of dietary acid load and changes in bone mineral density (BMD) over 5 years (lumbar spine, femoral neck, or total hip) or the occurrence of fragility fractures over 7 years were found. In this context, however, it has to be stated that a 2-h-fasting urine (collected after an 8-h fast) does by no means reflect nutrition: not of that day and even less of the habitual nutrition over years. Such an approach rather yields a snapshot of particular circadian characteristics of renal mineral excretions. In order to properly use urinary PRAL or other noninvasive biomarkers of dietary intake, the collection of 24-h urine samples (preferably, more than one sample for each subject) is necessary. Possible urine collection errors that cannot be fully excluded over a 24-h period bear tolerable risks of inaccuracies, which in any case are inherent in food intake measurements.

Calcium Balance and Bone Turnover Marker: Less Appropriate Outcomes for Examining Long-Term Acid–Base Effects of Habitual Nutrition on Bone

Both dietary acid loads and higher protein intakes result in elevated urinary excretion rates of calcium. These renal calcium losses have long been thought to remain unbalanced by compensatory increases in intestinal calcium absorption so that calcium release from bone had to fill the gap, not only increasing circulating calcium levels but concurrently titrating the noncarbonic acids endogenously produced by higher nutritional acid loads [11]. Frassetto et al. stated the view that this might result in a kind of vicious circle in that – although the kidney daily excretes the bulk of the diet net acid load – the body retains a small fraction of acidity sufficient to induce a persisting low-grade metabolic acidosis. This may ensure continued titration of the alkaline salts of bone, with attendant loss of calcium and phosphorus in urine, since impairment of renal calcium reabsorptive efficiency is a characteristic of metabolic acidosis [12]. The corresponding bone catabolic effects should become discernible in negative calcium balances, that is, in lower daily intestinal net calcium absorption than in daily renal calcium losses. In fact, impaired calcium balances have been observed in a few short-term studies, for example see [13]. However, other studies did not confirm negative calcium balances with higher nutritionally induced proton loads. In a recent meta-analysis performed by Fenton et al., no significant overall association between calcium balance and NAE was observed [14]. The authors concluded that their meta-analysis did not support the concept that the calciuria associated with higher NAE reflects a net loss of whole body calcium.

All together this paper of Fenton et al. [14] contributes to our understanding that calcium balance measurements are not an adequate and sensitive tool to evaluate the modest but long-term prevailing influence on bone quality or bone mineral status exerted through nutrition. In line herewith, Rafferty et al. [15] reported that healthy postmenopausal women on potassium-rich diets over many years did not demonstrate notable improvements in (*short-term-tested*) *calcium balances* since the clearly enhanced renal reabsorption of calcium (i.e., the reduced calciuria) in these females was offset by a parallel reduction in intestinal calcium absorption. Similar findings were obtained in a randomized feeding study by Hunt et al. [16] who observed that higher renal excretion rates of calcium with high protein (and concomitant low calcium) intake were almost balanced by a parallel elevation in intestinal calcium absorption (determined by ^{47}Ca isotope retention methodology). From these data it appears that a dynamically adapted response in intestinal calcium absorption does balance the ups and downs in calcium handling of the healthy kidney, provided that enough vitamin D and its activated metabolites are available and calcium intake is low to moderate (not deficient). At high calcium intakes the corresponding calcium flood (passive influx) suppresses much of the regulatory calcitriol activity, but calcium absorption is elevated per se. In any case, even at not-so-high calcium intakes occurring along with higher renal calcium losses, for example, through a higher dietary acid load, most or almost all of the calcium losses via the kidney can be compensated by intestinal upregulation of active absorption. A finally resulting net negative balance developing over the years cannot be easily identified by conventional short-term balance measurement techniques.

Sustained mildly unfavorable effects with reductions in bone quality and bone mineral content in the long run, that is, over years or even decades, require other more bone structure-specific analysis methods. In this respect, measurements of bone turnover markers – reflecting to a large degree the momentary bone resorption activity at the time of blood and/or urine collection – are not helpful as well. For example, bone accretion is highest during puberty when adolescents' growth velocity shows the typical peak height velocity pattern. At that time with the strongest increments in mineral mass, also the bone resorption marker levels reach their maximum (Fig. 9.1). For an appropriate bone gain and bone modeling, an initial bone resorption, that is, some removal of older bone, is required. Only if such remodeling takes place, formation of new

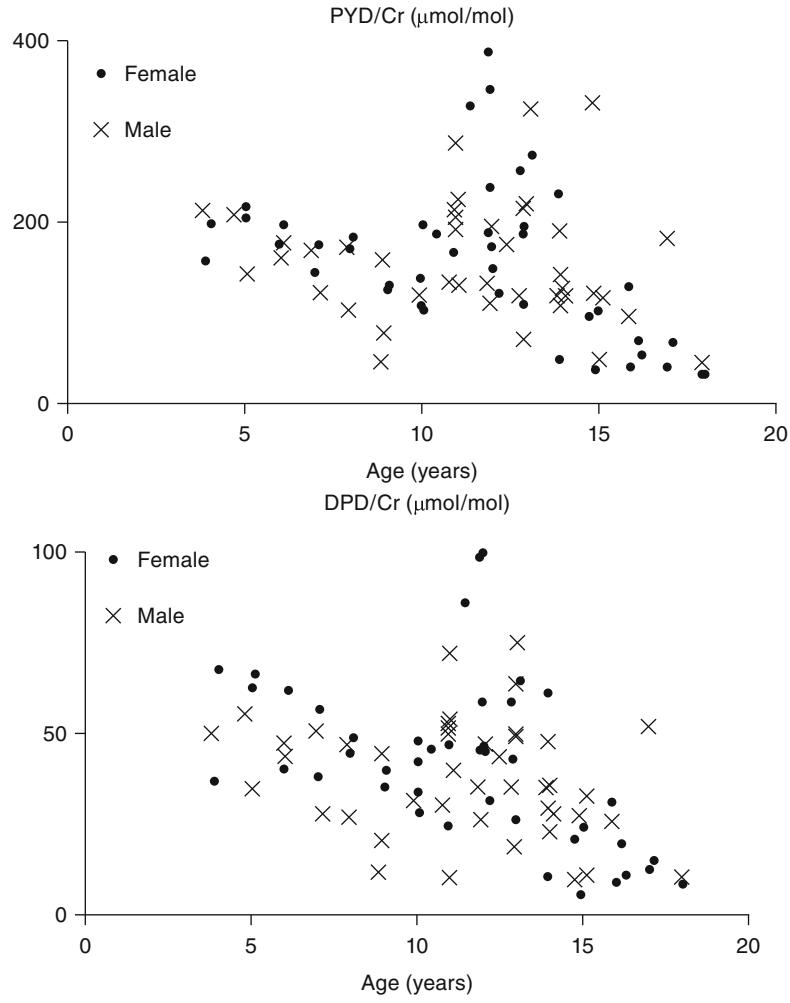

Fig. 9.1 Variation with age of 24-h excretion of pyridinoline (*PYD*) and deoxypyridinoline (*DPD*). *Cr* creatinine (Reprinted from Rauch et al. [17].With permission from Thieme Publishers)

additional mineral structures is possible, showing that bone resorption markers do by no means reflect always a bone catabolic situation. This is not only true for periods of growth, but can be found also during adulthood. For example, increases in the bone resorption marker carboxy-terminal cross-linked telopeptide of type I collagen do occur in response to exercise, that is, in a principally musculoskeletal anabolic situation as well as after growth hormone administration [18]. On the other hand, marked elevations in calcium intake have been shown to decrease specific markers of bone formation in healthy nonosteoporotic older men. These few examples show that bone resorption and bone formation markers obviously do not specifically predict subsequent bone catabolism and anabolism, respectively. For a more reliable assessment of the longer-term consequences of nutritional preventive measures like a habitual mineral-rich alkalizing diet for bone health, computer tomographic analyses of bone structures as well as other sophisticated densitometric bone measurements including high-quality dual-energy X-ray absorptiometry (DEXA) scans are obviously more expedient.

Densitometric Bone Outcomes and Dietary Acid Load in Adults

Until recently, only two randomized controlled (intervention) trials (RCTs) have been published that examined the impact of alkali supplementation for at least 1 year on acknowledged densitometric bone outcomes. A third study based on an initial examination of the influence of definite

base equivalent ingestion on renal calcium excretion [11] has recently been submitted for publication. In that study additional BMD measurements at the hip and spine had been performed, but results were not reported up to now. All three trials used DEXA to evaluate bone status and all three examined postmenopausal women. Alkali exposures were administered for 1 [19], 2 [20], or 3 [21] years. In the 2- and 3-year studies, no positive effects of alkali supplementation or additional fruit and vegetable intake [20, 21] on BMD outcomes (spine, hip) were observed. Placebo administration and potassium citrate or potassium bicarbonate ingestion at varying doses between 18 and 90 mmol/day did not yield significantly different BMD changes. Only in the 1-year study using a daily dose of 30 mmol potassium citrate, a significant improvement of spine and hip BMD was observed compared to blinded control subjects. A characteristic of all three study populations was a low baseline PRAL of around 0 mEq/day [19, 20] or −10 mEq/day [11, 21], showing a certain degree of selection bias for each participant groups. In all three trials, participating subjects did already ingest a quite low-net-acid-producing diet before the study began, strongly suggesting a considerable degree of health and nutrition consciousness. What differed between the three examined cohorts was the bone status: bone health was normal in both studies that showed no skeletal improvement with the oral alkali supplement, whereas osteopenia was present in those postmenopausal women who responded with a clear improvement in BMD.

These findings led to the following conclusions:

- Alkalization, for example, with potassium citrate or bicarbonate for at least 1 year does not show relevant bone-anabolic effects in healthy (postmenopausal) subjects with normal bone status (no osteopenia) who already at baseline consume “healthy” low-PRAL diets.
- However, if bone status is impaired, a supplemental alkali load appears to improve skeletal mineral content within a year, even if initial (habitual) dietary acid load is relatively low. It appears that in healthy adults (with normal BMDs) already on a rather alkalizing diet, a further reduction in dietary PRAL might not provide additional benefit with regard to bone status at least at hip and spine.

Apart from the RCTs also four prospective observational studies (evidence level II) have been performed in adults aged 45–97 years, showing positive associations between alkaline nutrient ingestion and BMD changes over 4–7 years in two studies [22, 23], but no association in two other studies [24, 25]. In one of these latter studies done with peripheral quantitative computer tomography (pQCT) [25], a reanalysis of the data – now focusing on the outcome parameter bone area – yielded a significant association of bone area increases with lower dietary PRAL intakes [26]. This reanalysis suggesting a possible bone-anabolic influence with reduced dietary PRALs was done by the authors in response to a letter [27] that we sent to the editor of the publication journal.

Densitometric Bone Outcomes and Dietary Acid Load in Children

For healthy children no randomized controlled trials (evidence level I for epidemiological or (medical) research studies) are available that have examined the bone health–dietary acid load relationship. However, prospective observational long-term findings have been published for healthy children and adolescents and significant negative associations between diaphyseal bone parameters by pQCT (bone mineral content or cortical area) and dietary as well as urinary PRAL determined over a 4-year observation period before bone analysis were observed [8, 28]. Importantly, in these studies not only the more bone structure-specific pQCT analysis (compared to DEXA) [6] was used but also repeated 3-day weighed dietary records, considered to belong to the most valid dietary assessment tools. Furthermore, the findings of a more bone-anabolic low-PRAL nutrition could be confirmed and substantiated by repeated urinary PRAL biomarker measurements.

Figure 9.2 and the results with respect to low- and high-urinary PRAL levels are presented

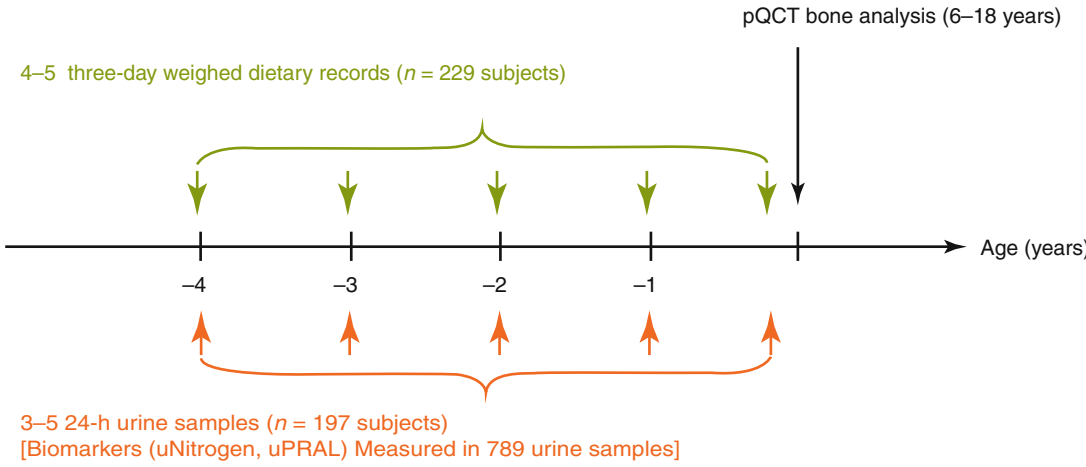

Fig. 9.2 Schematic study design of two prospective observational examinations with measured diaphyseal bone parameters by pQCT as outcomes in healthy children and adolescents using repeated 3-day weighed dietary records [28] as well as 24-h urinary biomarker measurements (PRAL) [8] determined over a 4-year observation period before bone analysis

stratified for subgroups of comparably high and comparably low protein intakes (Fig. 9.3). It is discernible that the basically known [3] bone-anabolic effect of higher protein intakes becomes particularly prominent, if children are on a habitual low-PRAL diet, that is, if they favor a fruit- and vegetable-rich diet along with higher protein intakes.

Although prospective and longitudinal observational studies are not definite proof of a causal relationship, the above findings provide a high level of plausibility because of the (i) prospective study design; (ii) computer tomographic bone analysis; (iii) repeatedly collected, highly reliable weighed dietary records; and (iv) confirmation by biomarker measurements in separate sample material (24-h urines). For ethical and practical reasons, such kind of investigation on the impact of habitual diet-related net proton loads on the skeletal system is not possible as a RCT in healthy children. Accordingly, at least for children, substantially better evidence cannot be expected soon.

Taking the findings in children and adults together, the statement put forward by a few authors – there is no evidence that an alkalizing diet is protective for bone [29] – is not supported by the specific literature focusing exclusively on the most reliable outcomes hitherto available, namely, densitometric bone measurements. The correct statement should read that there is a certain degree of evidence that an alkalizing nutrition has a preventive benefit for bone health at least in particular subject groups like children, postmenopausal women with impaired bone status, and probably adults on a clearly acidifying long-term nutrition before dietary or supplemental intervention. To date, the latter can only be deduced from prospective observational studies, as for an experimental switch from a habitual high-PRAL diet to a controlled low dietary PRAL state, no randomized trial data are available. Systematic reviews and meta-analyses done on calcium balance and bone turnover markers may or even must – for physiological reasons – yield inconsistent results with regard to an alkalizing diet, but do not yield proofs for the nonexistence of a preventive–medical relationship between a habitual base-producing nutrition and long-term development of bone quality, structure, and strength.

Potential Bone Catabolic Mechanisms of High PRAL

Several interacting mechanisms may commonly underlie the bone health strengthening effect of a long-term low dietary acid load, of which here

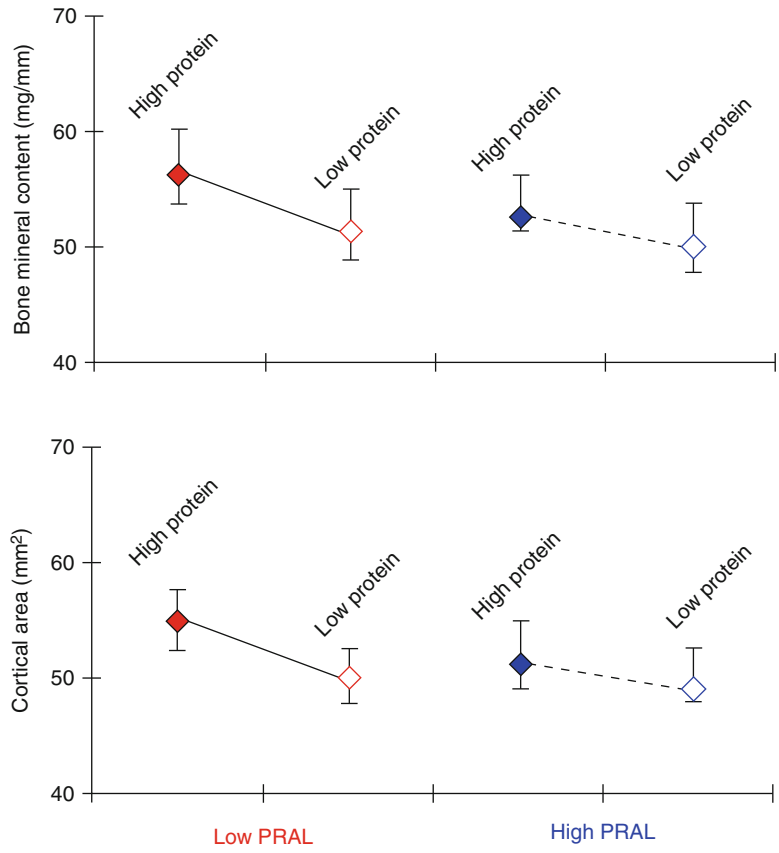

Fig. 9.3 Bone mineral content and cortical area by low (−5 mEq/d/m²) and high (14 mEq/d/m²) mean urinary PRAL levels further stratified according to high (1.5 g/kg body weight) and moderately high (1.2 g/kg body weight) protein intakes (median split)

only three will be shortly outlined: (i) GH/IGF, (ii) cortisol, and (iii) direct proton effects.

With regard to (i), impairments of the GH/IGF-1-axis with a higher proton load have been observed in vitro [30] and in animal studies [31]. In humans, induction of metabolic acidosis in healthy adults [32] as well as alkali therapy in acidotic hemodialysis patients [33] suggest a hepatocellular GH resistance and reduced IGF-1-levels under acidotic conditions. (ii) A higher glucocorticoid secretion with a higher acid load was indicated by an increased cortisol excretion in humans on experimental acidosis [34] and by reduced plasma cortisol levels and a diminished excretion of cortisol metabolites after alkali administration in healthy young adults on a rather acidifying diet [35]. Both higher IGF-1 [36] and reduced cortisol levels [37] can contribute to an improved bone health.

Apart from these indirect endocrine mechanisms that may mediate beneficial effects of a lower dietary proton load on bone health, (iii) direct effects of even moderate changes in extracellular pH or bicarbonate concentration on bone cells [38, 39] have been observed. In this context it is important to consider that small changes in systemic acid–base status, as inducible by dietary means, may result in greater changes in interstitial pH and bicarbonate because the buffer capacity of the interstitium is lower than that of plasma due to a lower interstitial albumin concentration [40].

Conclusions

In principle, a low dietary PRAL appears to be beneficial for bone in the long term. This can be deduced from several prospective observational (epidemiological evidence level II) studies in adults, although it has not been confirmed in all studies [24, 25]. Hitherto performed RCTs on healthy subjects without osteopenia could not prove the potential bone-anabolic influence of a reduction in dietary acid load as

they were all done in populations who already at baseline consumed diets yielding only minor net proton loads. For a proof of causality through a RCT, all volunteers included in that trial must have been on a high-PRAL diet for years before study onset, that is, before alkali equivalents are provided, for example, in the form of potassium citrate. However, such a study design appears not to be easily achieved, since compliance of habitual unhealthy eaters cannot be expected to be high.

In children, evidence for an influence of dietary alkalization on bone health through RCTs cannot be expected to be performed in the near future. Observational studies, however, suggest that a low-PRAL diet may be especially relevant in some subgroups, for example, in children with higher dietary protein intakes. Thus, a moderate high protein intake with a concurrent high ingestion of base-forming nutrients (i.e., a diet high in fruit and vegetables) might be most beneficial.

The mechanisms mediating bone strengthening effects of lower dietary acid loads are probable more subtle than acutely detectable positive calcium balances and may include several endocrine as well as direct bone–cell-related changes. In any case, to identify moderate alterations in bone status exerted through nutritional influences, not only accurate measurements of dietary proton load (either using carefully collected dietary data or biomarkers reflecting current nutrition) but also outcomes that are closely related to long-term bone structure may be required.

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