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Acid-Base Homeostasis: Latent Acidosis as a Cause of Chronic Diseases

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Background: A prerequisite for the proper functioning of the enzyme-controlled metabolic processes of the human organism is the regulation of pH both inside and outside of the cells. The ratio of acids to bases is not only important for a healthy metabolism, it also determines the structure and function of proteins, the permeability of cell membranes, the distribution of electrolytes, and the function of connective tissue. Currently, long-term disturbances of the natural acid-base homeostasis are receiving increasing attention as a risk factor for chronic diseases. **Objective:** To determine whether there is causal evidence for the pathobiochemical effects of a low-grade chronic metabolic (latent) acidosis and for the beneficial disease-modifying aspects of a well-balanced acid-base homeostasis. **Methods:** The MEDLINE data base is systematically reviewed for scientific literature since 1990 on latent acidosis and its impact on human health. **Results:** A latent acidosis resulting from a gradual reduction of the buffer reserves, mainly due to nutritional influences, does not produce major changes of blood pH because of compensatory mechanisms through urinary acid excretion. However, there is causal evidence that this compensation, in the long term, inevitably leads to loss of bone substance and impairs the structure and function of the connective tissue. **Conclusion:** In the past, pH regulation was taken for granted in persons not being severely ill and the required buffering capacity of the organism was accepted as being virtually inexhaustible. But today latent acidosis resulting from a gradual reduction of the buffer reserves is increasingly the focus of interest for the development and progression of chronic diseases such as osteoporosis and rheumatoid disorders.

Key Words: Acid-base homeostasis, latent acidosis, osteoporosis, rheumatoid disorders, nutrition, evolution

In the healthy human being, the blood has a pH value of 7.4. Even slight deviations from this value may lead to severe disturbances in metabolism which may even be life-threatening. It is for this reason that the body`s extensive buffer systems ensure that the blood pH is maintained between the very narrow limits of 7.37 and 7.43. These buffer systems bind and neutralize the additional protons (H^+ ions) or hydroxide ions (OH^- ions) respectively associated with excessive acidity or alkalinity and thereby prevent them from immediate and marked influences on metabolism. In order to maintain the optimal metabolic functioning and therefore the buffering capacity on a long-term basis, the organism is also dependent on the constant regeneration of the buffer systems.

Physiological regulation of acid-base homeostasis

What has been said above presupposes precise regulation of the acid-base homeostasis which involves many factors **(Fig. 1)**. Apart from the buffering characteristics of the blood and the extracellular and intracellular compartments, the gas exchange in the lungs and the excretion mechanisms of the kidneys are essential components of this regulatory system all of which are in functional equilibrium with each other. The bicarbonate system is of primary importance for maintaining a constant blood pH, but plasma proteins as well as the hemoglobin and the phosphate buffer also play a role

Säure-Basen-Haushalt: Latente Azidose als Ursache chronischer Erkrankungen

Hintergrund: Die Regulation des pH-Wertes innerhalb und außerhalb der Zellen ist eine wesentliche Vorraussetzung für die Funktionsfähigkeit der enzymatisch gesteuerten Stoffwechselvorgänge unseres Organismus. Das Verhältnis von Säuren zu Basen ist nicht nur für einen gesunden Stoffwechsel von Bedeutung, sondern entscheidet auch über die Struktur und Funktion von Proteinen, die Permeabilität von Zellmembranen, die Verteilung von Elektrolyten sowie die Funktion des Bindegewebes. Langfristige Störungen des natürlichen Säure-Basen-Gleichgewichtes finden aufgrund des gegenwärtigen wissenschaftlichen Erkenntnisstandes als Risikofaktor für chronische Erkrankungen zunehmend Beachtung. **Fragestellung:** Lassen sich die pathobiochemischen Auswirkungen einer geringgradigen chronischen metabolischen (latenten) Azidose und die positiven gesundheitlichen Aspekte eines ausgeglichenen Säure-Basen-Haushalts kausal belegen? **Methoden:** Systematische Auswertung der wissenschaftlichen Literatur in der MEDLINE Datenbank ab dem Jahr 1990 über die latente Azidose und deren Einfluss auf die Gesundheit. **Ergebnisse:** Eine latente Azidose als Folge einer schleichenden Verminderung der Pufferreserven, überwiegend bedingt durch Ernährungseinflüsse, ruft aufgrund der Kompensation durch die Säureausscheidung über die Nieren keine wesentlichen Veränderungen des Blut-pH hervor. Allerdings führt diese Kompensation auf lange Sicht unausweichlich zu einem Verlust von Knochensubstanz und beeinträchtigt die Struktur und Funktion des Bindegewebes. **Schlussfolgerung:** In der Vergangenheit wurde die pH-Regulation bei Personen, die nicht ernsthaft erkrankt sind, als Selbstverständlichkeit aufgefasst und die hierzu erforderliche Pufferkapazität des Organismus als beinahe unerschöpflich erachtet. Heute wird zunehmend erkannt, dass die latente Azidose als Folge einer allmählichen Abnahme der Pufferreserven für die Entstehung und den Verlauf chronischer Erkrankungen wie z.B. Osteoporose und Rheuma von Bedeutung ist.

Schlüsselwörter: Säure-Basen-Haushalt, latente Azidose, Osteoporose, rheumatische Erkrankungen, Ernährung, Evolution

as H^+ or OH^- scavengers. The highly rapid responsiveness of the buffer systems produces an extremely fast and constant regulation of the blood pH.

Apart from water, transient carbon dioxide – the intermediate product from the protonation of bicarbonate (HCO_3^-) – is produced by the dissociation of carbonic acid; it is expired via the lungs and, as a result, H^+ ions are effectively eliminated. However, since HCO_3^- is also removed at the same time, net acid excretion does not take place. Even though acute acidosis can usually be avoided by carbon dioxide expiration, the buffer systems of the kidneys are primarily responsible for the net excretion of the H^+ ions released from the breakdown of various acids.

This excretion is necessary because the production of protons (e.g. via metabolizing sulphur-containing amino acids from protein) from a normal mixed diet exceeds the absorption of alkaline substances. In the modern diet, mainly the proportionately high consumption of protein compared with that of base-supplying fruit and vegetables contributes to the daily acidification of the body. A particular example of acidification is that from imbibing phosphoric acid-containing beverages. Fasting (i.e. reducing body weight by not eating) increases the acidification of the body via the increased formation of keto acids from the breakdown of fatty acids, and so does the increased production of lactic acid under anaerobic conditions as the end product of glycolysis during sports activities.

With regard to the buffering of H^+ ions, of major importance are those alkaline vegetable substances in the form of metabolizable organic anions that can neutralize the acid produced from protein metabolism. During the dissociation of these salts, organic anions are released which can then – depending on the dissociation constant of the acid group – accept H^+ ions. The organic acids produced are neutrally metabolized to water and carbon dioxide (CO_2) and ensure in this way that protons are eliminated from the organism. As is shown for the example of sodium citrate **(Fig. 2)**, the remaining cations (e.g. Na^+) are available for reabsorption from the primary urine in the kidney in exchange for H^+ ions. By this means, the charge neutrality is maintained and acid is eliminated from the body. It can thus be seen that the level of intake of organic anions represents a major factor in regulating acid-base homeostasis.

Definition of latent acidosis and its manifestations

Compared with the clinically rather rare manifestation of respiratory or metabolic acidosis, which is characterized by a decrease in the blood pH, latent acidosis is much more commonly observed. In most cases, there is a slight shift of the blood pH in the acid direction within the normal range and the total buffering capacity of the blood is reduced. The term "latent" refers to a chronic condition which is without acute symptoms and is clinically detectable only by determining the intracellular and extracellular buffer capacity and the renal net acid excretion.

It is mentioned here that latent acidosis affects a wide cross-section of the population. The cause of increased acidification is, above all, the high protein content in food which, when coupled with the declining renal function associated with increasing age, leads to latent acidosis [1]. With increasing

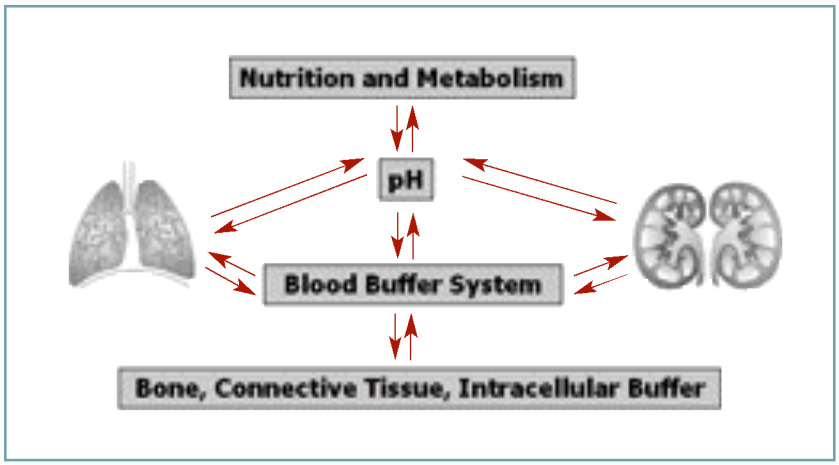

Fig. 1. Regulation of the acid-base homeostasis.

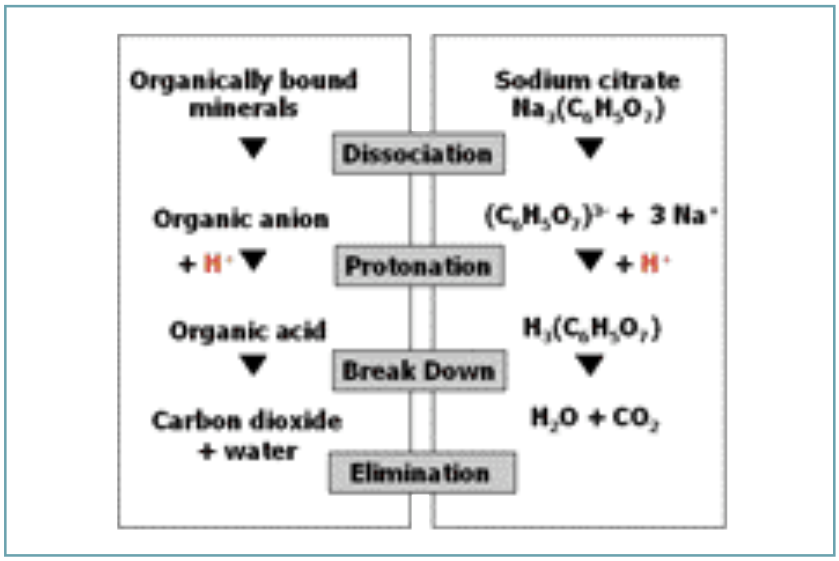

Fig. 2. Function of organically bound minerals in the elimination of acids as shown for the example of sodium citrate.

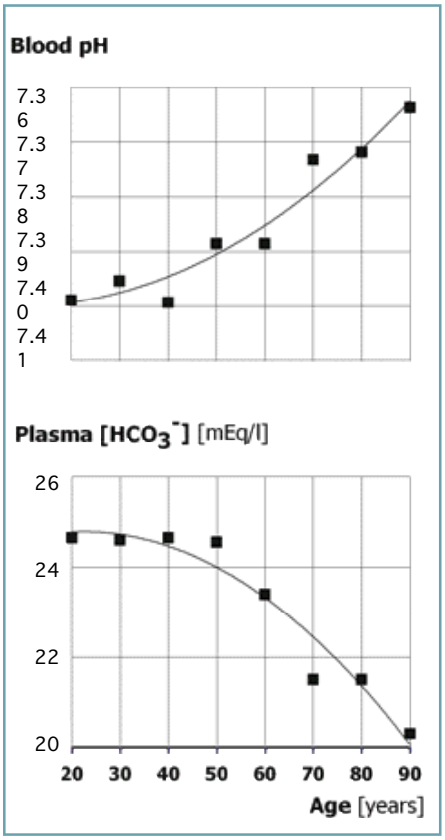

Fig. 3. Relationship between blood pH and plasma bicarbonate concentration and age (modified from [2, 3]).

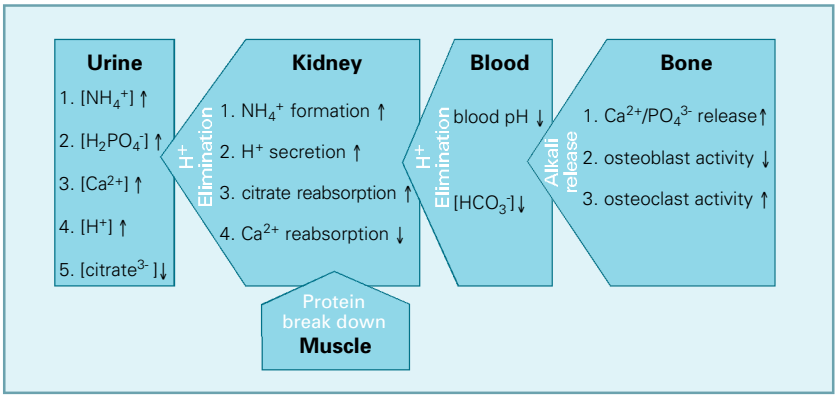

Fig. 4. Compensation mechanisms for latent acidosis (modified from [4]).

age, the ability of the kidneys to excrete acids progressively decreases [2, 3]. As is shown in **Fig. 3**, the blood pH declines within the normal range over the years, but at the same time the concentration of plasma bicarbonate buffer bases also decreases.

This in turn not only results in an increased consumption of buffering minerals from the bone reservoir, but also in detrimental effects on various metabolic functions such as the increased muscle breakdown which is frequently observed in senior citizens [3]. The age-related renal functional decline together with a constantly high protein intake exacerbates latent acidosis and its harmful influences on health.

Compensation mechanisms of latent acidosis

Nowadays, the pathobiochemical effects of latent acidosis on osteoporosis, diabetes mellitus, hyperuricemia, gout, or on restricted renal function are undisputed. These links were ultimately recognized because of the very efficient homeostatic counter-regulation of the organism in maintaining the bicarbonate and proton concentrations and therefore the pH value of the blood. The regulation mechanisms have been partially explained in recent years [4]. The adaptation mechanisms of the kidney play an essential role in compensating diet-induced latent acidosis. They are schematically depicted in **Fig. 4**. There are four basic mechanisms that compensate for latent acidosis.

Increased excretion of ammonium ions (NH_4^+)

Ammonia (NH_3) – which is produced in the renal tubular cells and freely diffuses through membranes – combines with H^+ ions in the primary urine to form ammonium (NH_4^+) ions which can hardly diffuse back and which are therefore excreted with the urine (proton trapping). Consequently most of the renal acid is excreted bound to NH_3. This latter product is formed in the tubular cells from the breakdown of the nitrogenous amino acid glutamine. With acidosis, the activity of the glutamine-degrading enzymes (glutaminase, glutamine-dehydrogenase etc.) is increased. Accordingly, there is an increased consumption of glutamine and subsequently of other nitrogen-supplying amino acids. Thus, mild latent acidosis also leads to increased activity of the protein-degrading systems via the production of ubiquitin and C2/C3 proteasoms in the muscular system with a corresponding loss of myoprotein. By increasing the intake of bases, the loss of nitrogen caused by mild latent acidosis could be prevented in postmenopausal women [5].

Increased secretion of protons (H^+) in the renal tubules

Even with mild acidosis, the quantity and activity of the Na^+/H^+ ion exchanger in the kidney is increased, resulting in increased excretion of H^+ ions with simultaneous Na^+ reabsorption.

Reduction of urinary citrate excretion

With acidosis the relative reabsorption of critrate^{3-} (the trivalent negatively charged anion of citric acid) from the primary urine is increased. Compensation occurs by the following mechanism: the absorption of citrate^{3-} in the tubular cells occurs mainly in the protonated form, i.e. H-citrate^{2-}. The activity of the citrate transporter is therefore increased with reduced pH. Intracellularly, citrate^{3-} is converted by the acceptance of additional protons to uncharged citric acid, which is then pH-neutrally broken down into carbon dioxide and water. By the absorption of one molecule of citrate^{3-} from the primary urine, 3 H^+ ions can therefore be eliminated. As a result, the concentration of citrate in the primary urine decreases (see **Fig. 4**). However, citrate is essential for complexing calcium ions (Ca^{2+}). The lack of formation of soluble calcium-citrate-complexes increases the urinary concentration of free Ca^{2+} ions and therefore the availability of calcium to

form renal calculi, e.g. with oxalic acid.

Increased release of minerals from the bones

On the one hand, mild acidosis leads to the removal of minerals from the bone matrix; on the other hand, acidosis results in an increase in the activity of the bone-decomposing osteoclasts and inhibition of the activity of the bone-forming osteoblasts (see **Fig. 10**). All in all, increased renal excretion of Ca^{2+} ions takes place with the consequence of the increased risk of formation of renal calculi, as described above.

Effects of latent acidosis on calcium and bone metabolism

Epidemiology and dietary implications

With experimental acidosis, first a reduction of the blood buffering capacity occurs, then, with further increase of acid load a reduction of the intracellular buffering capacity and a strain on the buffering capacity of bone occurs. And finally, with increasing acid load buffering is achieved by the release of minerals from bone [6]. This and comparable investigations led already in the Sixties to the hypothesis, that one of the significant causes of osteoporosis is a high dietary acid load [7].

Numerous epidemiological studies are available on the obvious relationship between the type of diet and the development of osteoporosis. The influence of a vegetarian diet on bone mineral density is based on the significant effect of dietary content of acid and base: a higher base content is correlated with a higher bone mineral density [8]. A comparative study on omnivorous and vegetarian women [9] showed that a high proportion of base generating foodstuffs leads to a clearly improved calcium balance in vegetarians. In spite of equal calcium intake in both groups, the women who consumed a mixed diet showed not only a significantly higher excretion of acid but also a significantly higher excretion of calcium. For premenopausal women a correlation was shown between the intake of alkaline foods and bone mineral density [10]. Although the intake of alkaline food components (especially potassium and magnesium) and the high consumption of fruit and vegetables were correlated with an increased bone mineral density in a study on elderly subjects, this was not the case for the calcium content of the consumed food [11]. No associations with other food components, e.g. the calcium intake or the total caloric intake, were found in this study.

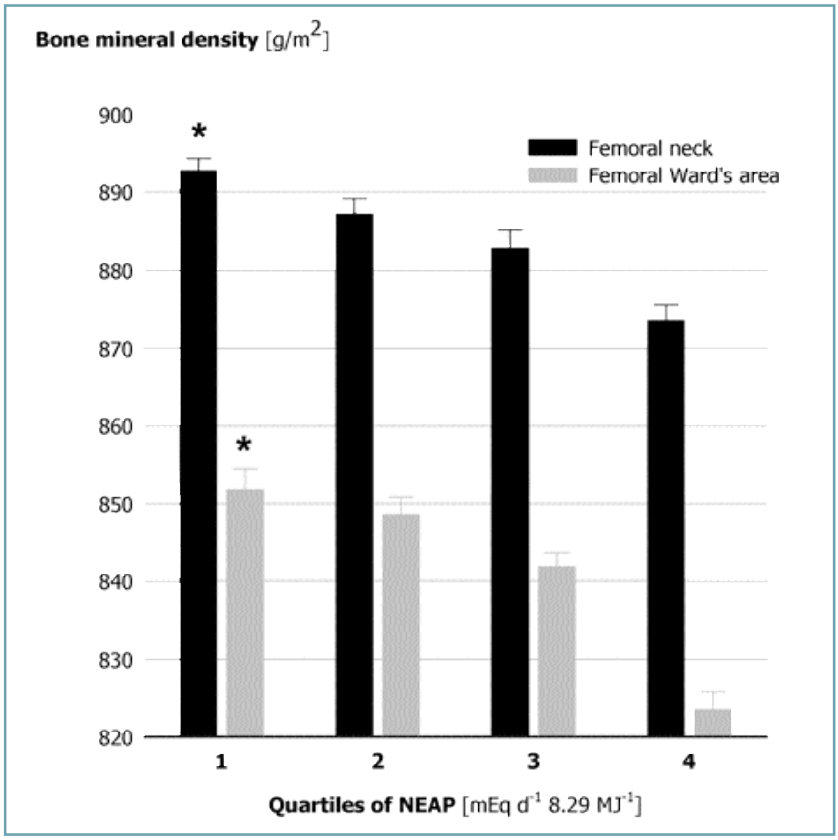

Fig. 5. Mean (± SEM) bone mineral density of pre- and perimenopausal women by quartile of net endogenous non-carbonic acid production (NEAP). *Significantly different from quartile 4, p<0.04. Modified from [12].

Recent epidemiological studies on the nutritional effects on bone loss during menopausal transition demonstrated that with decreasing endogenous acid production femoral bone mineral density of pre- and perimenopausal women significantly increased [12], see **Fig. 5**.

Another epidemiological study showed the beneficial effect of calcium, alcohol, and fruit and vegetable intake and the detrimental effect of fatty acids. The authors conclude that although menopausal status and hormone replacement therapy dominate women's bone health, diet may influence early postmenopausal bone loss with fruit and vegetable intake protecting against premenopausal bone loss [13]. These findings are confirmed by the results of a study which investigated the relationship between dietary potassium and protein intake, net endogenous acid production and potential renal acid load and markers of bone health. Low dietary potassium intakes and high dietary estimates of net endogenous acid production were found to be associated with low bone mineral density at the femoral neck and lumbar spine in premenopausal women **(Fig. 6)** and increased markers of bone resorption in post-menopausal women [14].

On the whole, the epidemiological data indicate a correlation of the intake of alkaline acting-substances from fruits and vegetables and the corresponding dietary acid load over the years and their effects on calcium and bone metabolism from the viewpoint of osteoporosis.

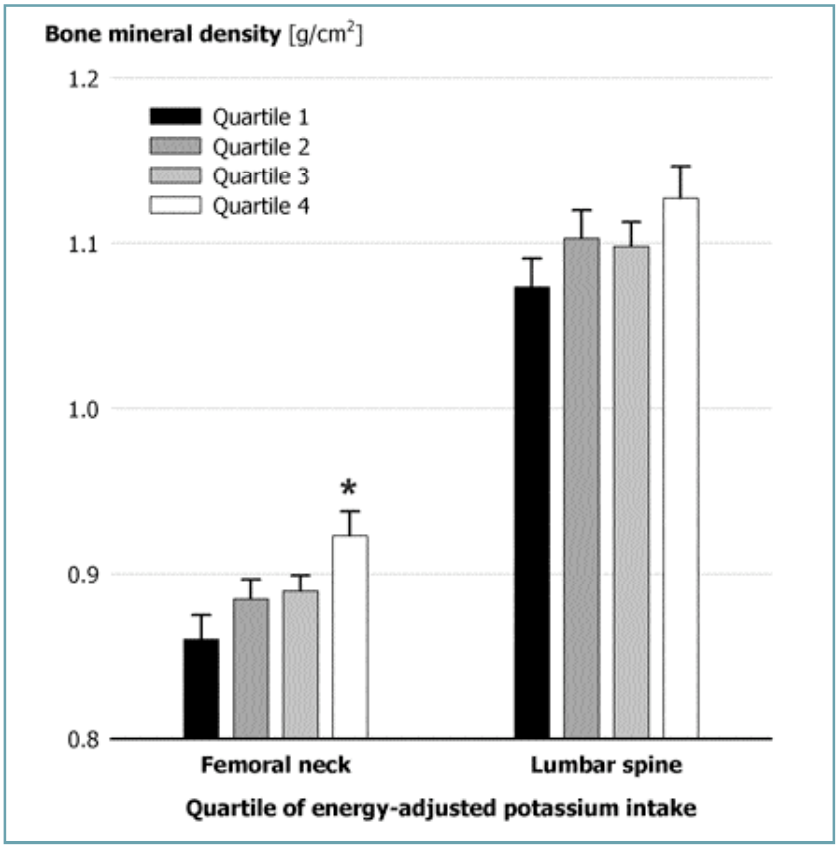

Fig. 6. Mean (± SEM) bone mineral density at the femoral neck and lumbar spine with increasing quartiles of energy-adjusted potassium intake for premenopausal women (n=336). *Significantly different from quartile 1, p<0.01. Modified from [14].

Confirmation by intervention studies

Intervention studies largely confirm the physiological effects of latent acidosis. In animal experiments it was shown that due solely to a high-protein diet, the bone formation in young rats was impaired [15]. Another study (see **Fig. 7)** shows that an excess acid load was artificially caused by an increase of the protein intake [16]. As expected, increased renal net acid excretion (as the sum of ammonium and titratable acids) and calcium excretion were first observed. However, because of the concomitant intake of sodium bicarbonate as a base supplier, a negative calcium balance could be prevented and the protein-induced over-acidification of the organism was neutralized. The positive effects of a high intake of base-forming substances could also be proved in intervention studies with postmenopausal women: increased alkaline intake brought about both a reduction in the breakdown of bone and an increase in bone formation [17]. Thanks to a reduction of the protein intake, the calcium excretion and therefore the risk of renal calculi could be reduced in hypercalciuric patients [18]. In a placebo-controlled study comparing treatment with alkaline minerals to a placebo group for almost all syndromes involving the gastrointestinal tract, musculoskeletal system, cardiovascular system, skin, and a tendency to become easily exhausted, a considerable improvement of the symptoms was shown [19]. Moreover, laboratory parameters (e.g. acid excretion, serum cholesterol) were significantly improved by means of the alkaline therapy.

Treatment with alkaline salts such as potassium citrate is even able to reduce bone resorption. This effect of potassium citrate supplementation on bone metabolism was investigated in 46 postmenopausal women with low bone density. One group received a 3-month course of potassium citrate supplementation (0.08 – 0.1 g/kg body weight daily), another group served as control. Evaluation of electrolyte and acid-base homeostasis-related parameters, and markers of bone turnover and of renal function showed a significant decrease in net acid excretion only upon citrate supplementation. Moreover, urinary excretion of bone resorption markers decreased thus indicating that citrate ingestion positively affects bone health [20]. The equimolar replacement of dietary sodium chloride and potassium chloride with alkaline sodium and potassium bicarbonate under metabolic homeostasis conditions, thus neutralising dietary acid load, not only resulted in significant calcium retention and reduced renal excretion of bone markers but also decreased mean daily plasma cortisol and urinary excretion of tetrahydrocortisol [21]. Other endocrine factors relevant to bone such as parathyroid hormone or vitamin D were not affected. Therefore, mild metabolic acidosis may be associated with a state of cortisol excess. These acidosis-induced increases in cortisol secretion and plasma concentration may play a role in mild acidosis-induced alterations in bone metabolism as well.

Dieting and Fasting

Dieting and fasting are critical to changes of acid-base homeostasis. For example, solely because of the intake of sodium bicarbonate, the calcium release from bone in young women who had developed ketoacidosis as a result of fasting could be prevented [22]. Generally speaking, modern diets contribute to an increase in metabolic acidosis and to greater bone loss as demonstrated for low-carbohydrate, high-protein diets (Atkins). Consumption of such a diet for six weeks may in fact help an individual to lose weight, but it considerably increases acid load and results in latent acidosis with increased risk of kidney stone formation, negative calcium balance, and increased risk of bone loss, as demonstrated in **Fig. 8** [23]. **Table 1** illustrates the dietary scheme applied for three different phases.

Is animal or vegetable protein detrimental to bone health?

Judging from the most recent studies,

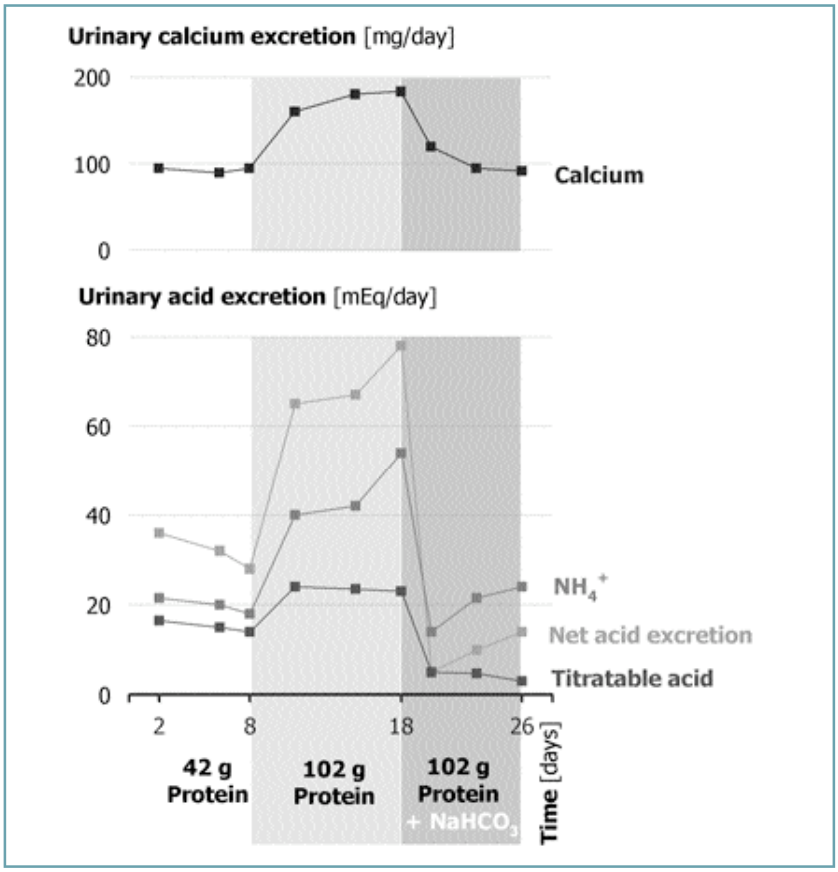

Fig. 7. Renal acid and calcium excretion with different protein intakes [g/day] with and without sodium bicarbonate substitution [70 mEq/day] (modified from [16]).

Tab. 1. Composition of normal diet, severely carbohydrate-restricted induction diet and moderately carbohydrate-restricted maintenance diet. Modified from [23].

(g/day)	Duration (weeks)	Carbo-hydrates	Protein	Fat	Body weight (kg, n=10)
Normal	2	285	81	90	81.3
Induction	2	19	164	133	78.4
Maintenance	4	33	170	136	77.2

food protein from different sources seems to have different effects on bone metabolism. Elderly women who have a high proportion of animal protein in their diet showed a more rapid loss of bone density and a higher risk of hip fractures than women with a low proportion [24]. In the latter group (low proportion of animal protein), it was found that fewer women sustained a hip fracture during the observation period of 7 years. Animal foods contain predominantly acid-forming substances whereas protein in vegetable foods is accompanied by base-forming substances.

The protective function that an increased consumption of vegetables as opposed to animal protein may have has also been confirmed in international studies. The incidence of hip fractures differs in the populations of different countries, and it is directly correlated with the level of consumption of animal protein of the different cultures. Analysis of the data on the incidence of hip factures in 33 countries in relation to the respective country-specific characteristics of the per capita consumption of animal and vegetable foods **(Fig. 9)** showed that the incidence of hip fractures is the lowest in countries with a low intake of animal protein [25].

However, latest studies with children indicate that protein consumption is not generally detrimental to bone health because in children long-term dietary protein intake appears to act anabolically on diaphyseal bone

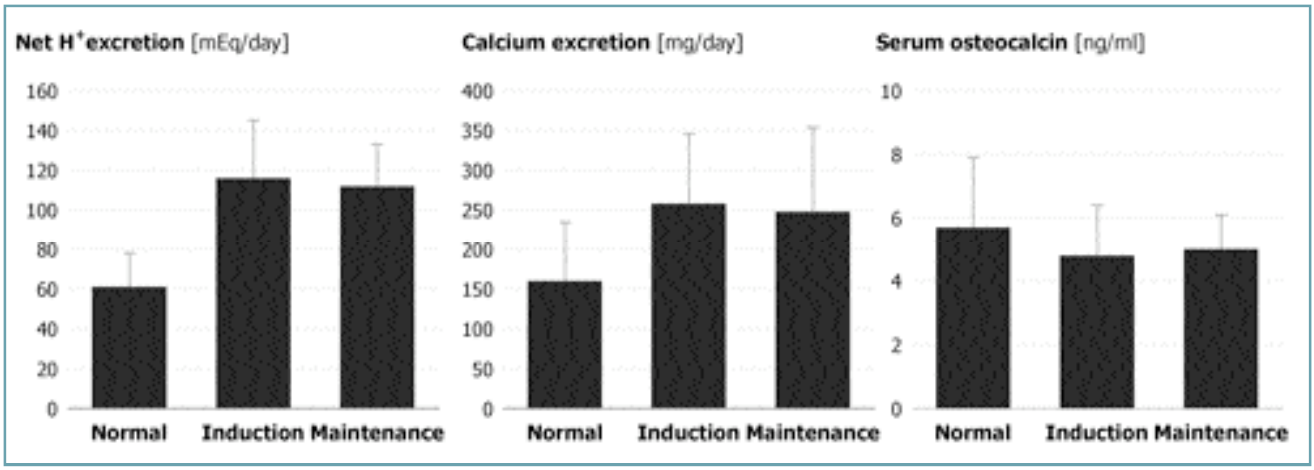

Fig. 8. Effect of low-carbohydrate, high-protein diet (Atkins diet) on renal net acid excretion, renal calcium excretion and serum osteocalcin. Patients had been on a normal non-weight-reducing diet, then a severely carbohydrate-restricted induction diet for 2 weeks, after which they followed a moderately carbohydrate-restricted maintenance diet for 4 weeks as depicted above (n=10). Modified from [23].

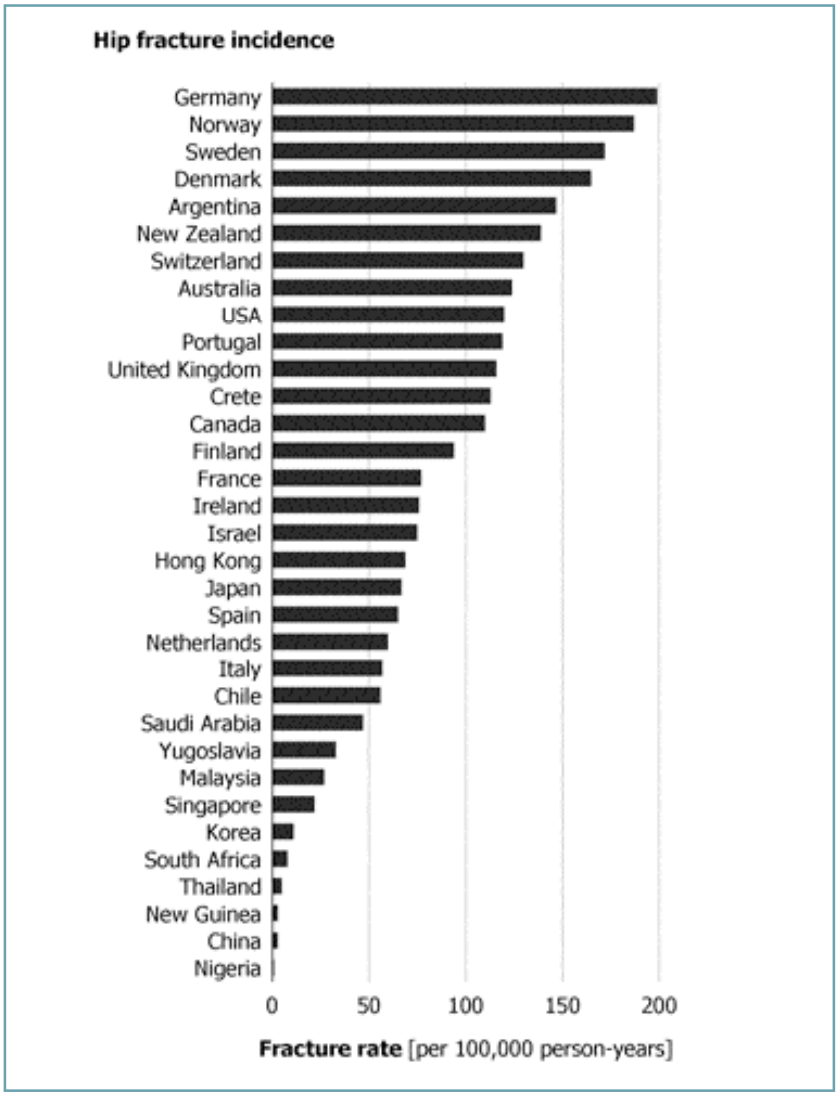

Fig. 9. Worldwide incidence of hip factures (modified from [25]).

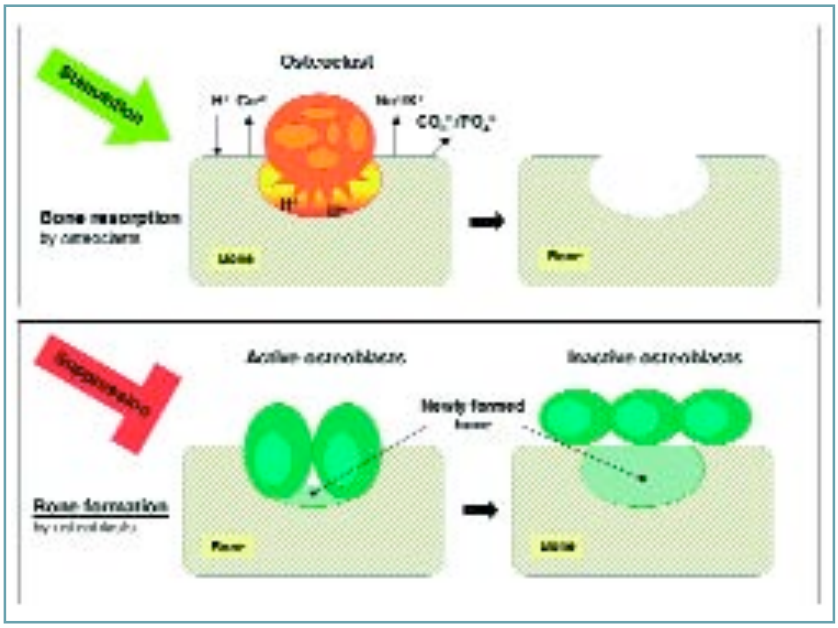

Fig. 10. Schematic diagram of the effects of latent acidosis on bone (modified from [27]).

strength during growth. This may at least partly be negated if the dietary potential renal acid load is high, i.e. if the intake of base-forming minerals, as provided by a high consumption of fruit and vegetables, is low. Children with higher dietary potential renal acid load (PRAL), however, had significantly lower bone mineral content and long-term calcium intake was not associated with any bone variable. Protein and alkalinising minerals are thus increasingly described as playing a major role in influencing bone status in children and adolescents [26].

Mechanisms of the effects of acid on bone cell function

The homeostasis for the maintenance of a stable physiological pH environment often functions only at the expense of the bone mineral content because latent acidosis causes the release of calcium from bone, thereby buffering the additional protons. Metabolic acidosis first stimulates the physicochemical release of minerals (decrease of the sodium, potassium, carbonate, and phosphate content of bones) and subsequently the cell-mediated absorption of bone, as is schematically depicted in **Fig. 10**. Acidosis results in an increase in the activity of bone-decomposing or respectively bone-resorbing cells (osteoclasts) and inhibition of the bone-forming cells (osteoblasts).

Genes that regulate the early "immediate reaction" of the osteoblasts are inhibited as are genes that control the formation of bone matrix; gene inhibition leads to an overall reduction of bone remodelling and formation. Several in vitro studies with artificially cultured bone cells confirmed their characteristics as potent acid buffers [27].

Figure 11 shows the dependence of the net calcium flux of cultured bone cells on the pH value of the surrounding medium. With a physiologically acidic pH value below 7.4, calcium flows out of the bone cells into the medium, whereas a net absorption of calcium was only detectable with a pH value above 7.4.

Growth and maturation of the osteoclasts is dependent on the interplay of

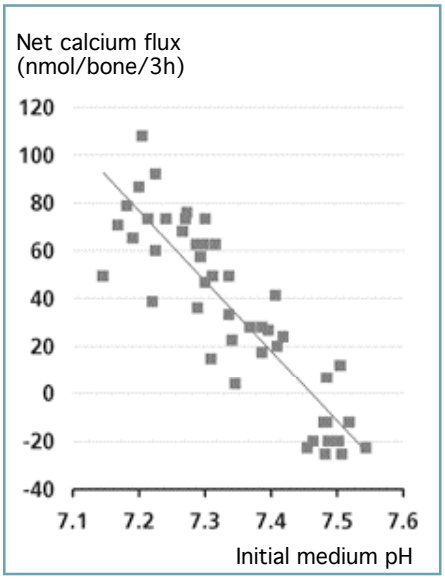

Fig. 11. Effect of medium pH on the net calcium flux in cultured bone cells. A positive value shows a net calcium flow out of the bone cells into the surrounding medium, negative values indicate net calcium influx (modified from [27]).

a number of factors. One of the explanations of the mechanisms of latent acidosis on bone cell function is the induction of osteoblastic prostaglandin synthesis, which is activated by metabolic acidosis and is followed by the induction of a "receptor activated NFκB ligand" (RANKL). This increase in RANKL is expected to augment osteoclastic bone resorption by interaction with the osteoclastic cell-surface receptor RANK as shown in **Fig. 12**. The RANKL/RANK interaction not only initiates a differentiation cascade of pre-osteoclasts to osteoclasts, that culminates in mature bone-resorbing osteoclasts, but also increases the resorptive capacity and survival of osteoclasts [28]. This acidosis-induced increase in RANKL is expected to augment osteoclastic bone resorption and offers an appropriate explanation for the increase in cell-mediated net calcium efflux as described above.

Finally, thanks to the mechanisms of compensation dietary-induced latent acidosis does not provoke any significant changes of blood pH but the compensation inevitably consumes the body's reservoir of buffering substances. When excess intake of animal protein and deficient dietary base supply persists for a longer time this will have a negative impact on bone mass. The undoubted positive influence of a diet rich in fruit and vegetables can be explained not only by a high intake of micronutrients and secondary herbal ingredients but also by the positive effects of an adequate base supply.

Effects of latent acidosis on connective tissue function

Connective tissue is an important transit pathway for metabolic products such as oxygen, carbon dioxide, nutrients, electrolytes, water, acids and bases. Even slight changes of the blood pH lead to a change in the physicochemical characteristics of the proteoglycans, the branched protein-saccharide constituents of connective tissue. These proteoglycans directly exchange with the extracellular fluid.

Proteoglycans are composed of a protein component and a glucosaminoglycan component, which contains a multitude of negatively charged functional groups (e.g. sulphate residues $R\sim O\text{-}SO_3^-$). This negative charge enables the binding of water molecules which contribute to the elasticity and flexibility of the connective tissue. In latent acidosis the negative charge of the sulphate residues is diminished and the water binding capacity is decreasing thereby reducing the elasticity and flexibility of the connective tissue.

In cartilage as well, proteoglycans with the hyaluronic acid molecules that are bound to them represent a high-molecular-weight polyanionic complex that forms the important compressible component of cartilage because of the high water-binding capacity [29]. The water-binding capacity of the extracellular matrix proteins is very much determined by the degree of dissociation of the functional acid residues whose dissociation is again highly pH-dependent. Acidosis of the synovial fluid therefore decreases cartilage elasticity due to reduced water binding. Effects of latent acidosis on the function of cartilage can be explained in this way. At present, however, the complex structure of the extracellular matrix does not allow direct measurement of the function of cartilaginous tissue with different degrees of dissociation. In patients with rheumatoid arthritis the pH of the knee joint's synovial fluid is significantly more acidic compared to the normal range (pH 7.4 – 7.8), as shown in **Fig. 13** [30]. Consequently, acidosis encourages joint cartilage abrasion by mechanical stress that promotes the vicious circle of deformation and

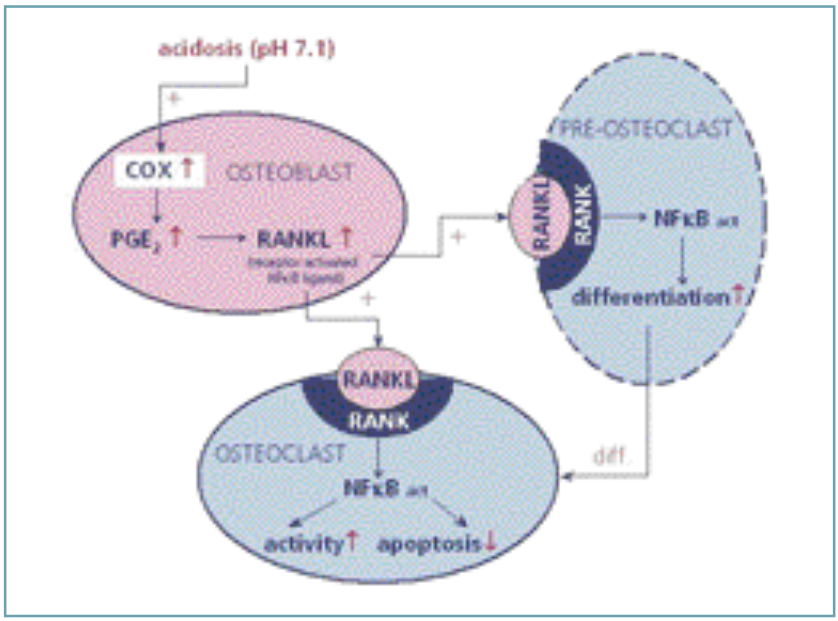

Fig. 12. Scheme of acidosis induced activation of RANKL/RANK interaction initiating the differentiation cascade of pre-osteoclasts and increasing bone resorptive capacity and survival of osteoclasts (modified from [28]).

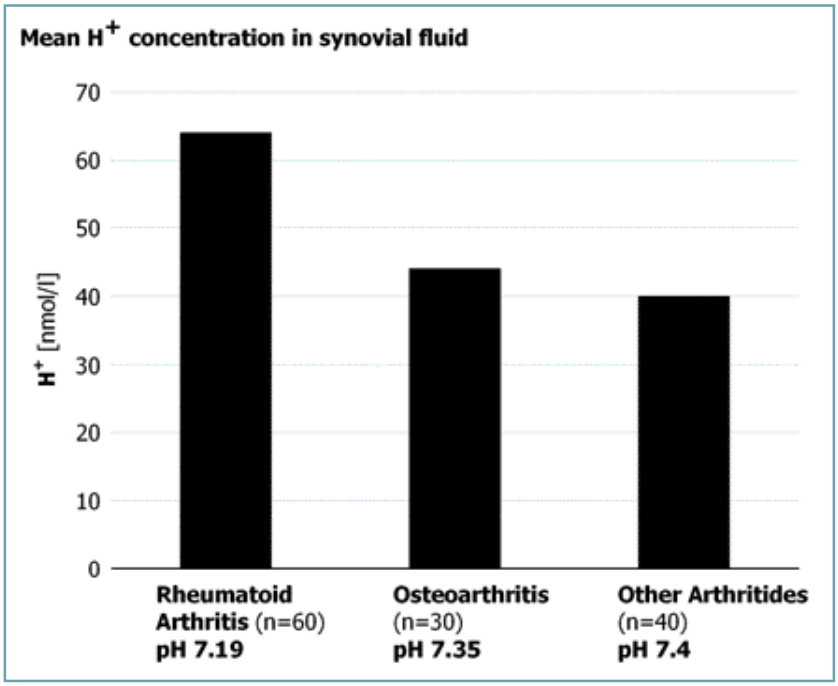

Fig. 13. Mean H^+ concentration in the synovial fluid from the knee joints of patients with different forms of arthritis (modified from [30]).

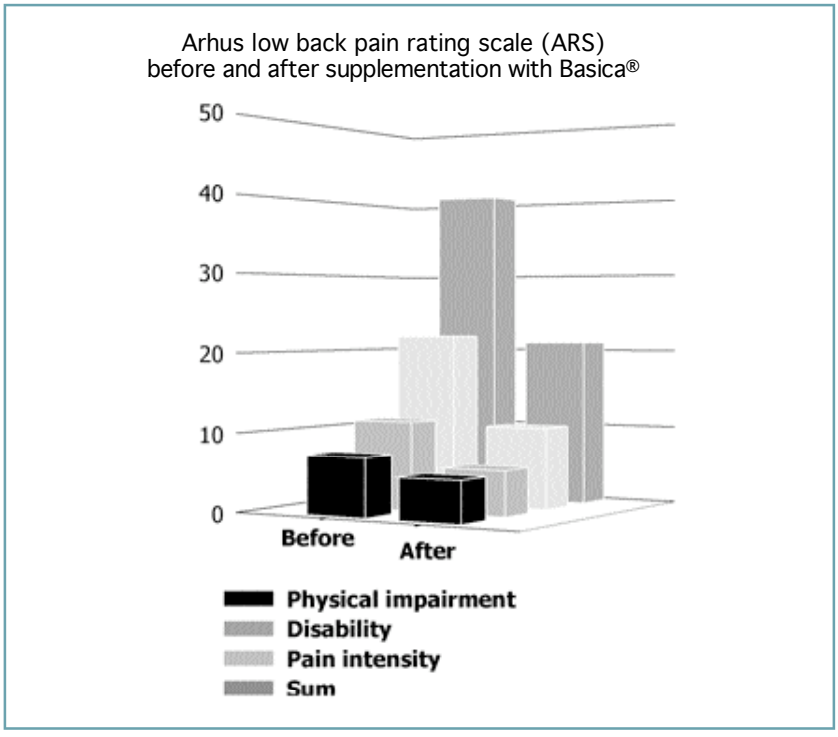

Fig. 14. Effects of alkaline mineral supplementation on patients with chronic low back pain. Arhus low back pain rating scale before and after supplementation with Basica® (n=82). Modified from [31].

inflammation. Acidosis might also impair the filtration effect of the connective tissue which may, in turn, additionally contribute to a deterioration in the nutrient supply of this poorly perfused tissue. Finally the whole locomotor system is involved because of acidosis-induced impairment of the ligaments and tendons.

Patients with chronic low back pain without radicular involvement benefited from a 4-week supplementary diet therapy by taking alkaline minerals: both the pain as well as the physical mobility improved significantly (see **Fig. 14)**, and the consumption of non-steroidal, anti-inflammatory drugs (NSAID), which may cause severe side effects when applied chronically, could be clearly reduced [31]. Indeed, long term balancing of acids and bases is required for a complete regeneration of the connective tissue and to noticeably relieve the chronic pain.

In a recent study, patients with rheumatoid arthritis of at least two years' duration were shown to have benefited from alkaline mineral supplementation (see **Fig. 15)**. At the end of a 12-weeks study there was a significant decrease in disease activity score (DAS-28) and in pain level measured on a visual analogue scale (VAS) only in the group supplemented with 30 g/day of an alkaline food supplement (Basica Vital®) compared to the control group. Moreover, the steroid or NSAID medication could be reduced with alkaline supplementation whereas no reduction of medication was considered to be possible for the control group [32].

Another important impact on acid-base homeostasis with long-term effects on the functions of the connective tissue occurs with chronic intake of proton pump inhibitors for the treatment of gastroesophageal reflux. After meals the parietal cells produce hydrochloric acid to enable the digestion of foods. At the same time bicarbonate is generated and transferred into the blood stream from where it afterwards is transported via the bile ducts into the intestine to neutralize or alkalize the gastric mash. This closed system does not exert any net effect on acid-base homeostasis, but acts as a kind of temporal effect reflected by the "alkaline floods" after each meal. These alkaline floods provide an important physiological process for removing the acids bound to sulphated residues of connective tissue proteoglycanes. Chronic intake of proton pump inhibitors such as omeprazol interfere with this system and may suppress the essential "purification process".

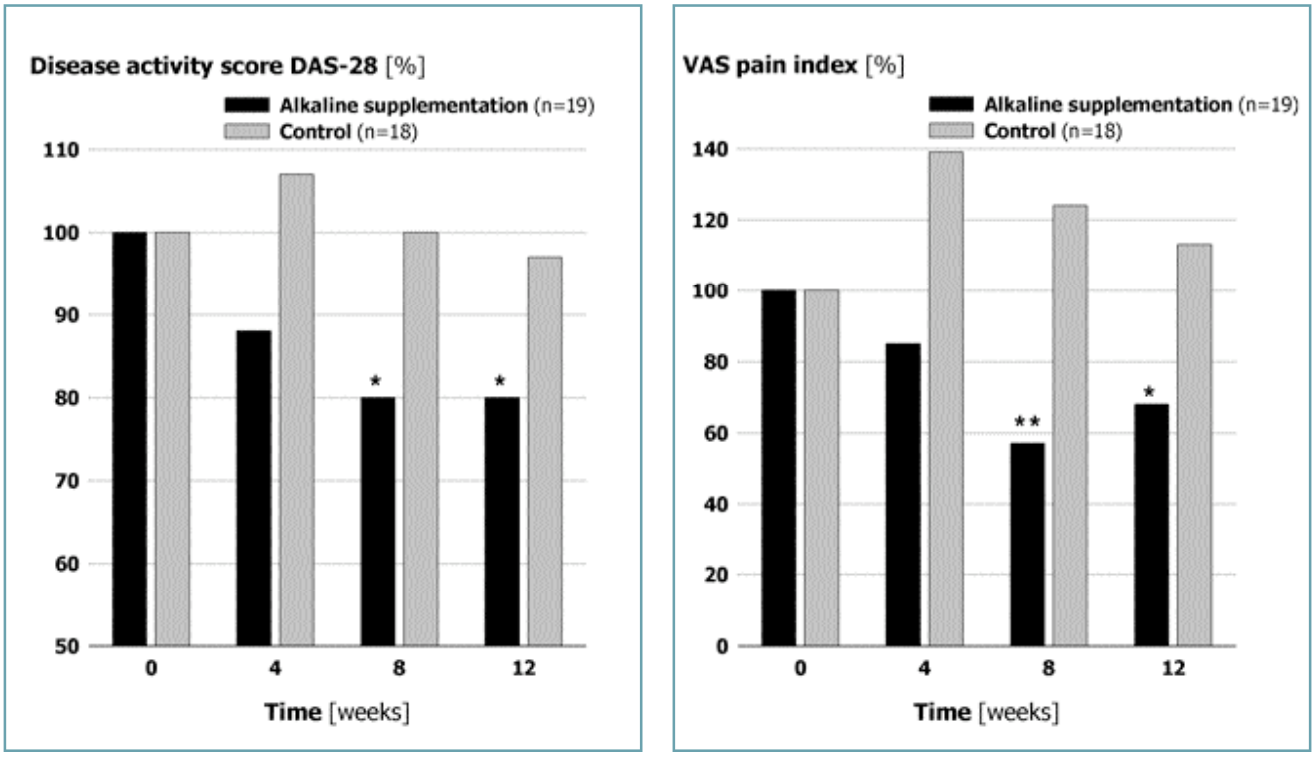

Fig. 15. Percent change of disease activity score DAS-28 (left) and percent change of VAS pain index (right) of rheumatoid arthritis patients (*p<0.05, **p<0.01). Modified from [32].

Evolutionary aspects of acid-base homeostasis

There is a growing awareness that the profound changes in the environment including diet and other life-style conditions that began with the introduction of agriculture and animal husbandry approximately 10,000 years ago, occurred too recently on an evolutionary time scale for the human genome to adjust. In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural, and activity patterns of contemporary Western populations, many of the so-called diseases of civilization have emerged. In particular, agriculture and food-processing procedures introduced during the Neolithic Period and during the Industrial Period fundamentally altered crucial nutritional characteristics of the diets of our ancestors: in addition to changes in the glycemic load, fatty acid composition, macronutrient composition, micronutrient density, sodium-potassium ratio, and fibre content, considerable changes have taken place in the acid-base homeostasis. Comparison of the estimated net endogenous acid production (NEAP) from 159 retrospective ancestral preagricultural diets with contemporary diets clearly demonstrates that 87% were net base-producing with a mean NEAP of –88 ± 82 meq/day [33].

The average contemporary American diet provides an acid surplus of 48 meq/day and is characterized by an imbalance of nutrient precursors of hydrogen and bicarbonate ions thereby inducing a lifelong, low-grade pathogenically significant systemic metabolic acidosis. The historical shift from negative to positive NEAP was accounted for by the displacement of highly alkalising plant foods in the ancestral diet by cereal grains and energy-dense, nutrient-poor foods in the contemporary diet – neither of which are net base-producing. Therefore the evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilization [34].

Further research fields related to acid-base homeostasis

In sportsmen and sportswomen, frequent lactate acidosis increases the susceptibility to physical injury. In contrast, it is suggested that an adequate base supply may have a beneficial impact on performance by delaying the onset of lactate acidosis but also by avoiding physical impairment. Muscle activity during sports performance is in fact known to be associated with an increase in both intra- and extracellular proton concentration. It is known that alkaline sodium citrate ingestion could reduce plasma proton concentration and improve physical performance [35, 36, 37].

Extracellular pH affects mineral cation flux through cell membranes as well. It seems that there is a strong correlation between interstitial proton concentration and the potassium release from muscle cells during exercise since potassium efflux is regulated by voltage-dependent K channels and pH-dependent K_{ATP} channels. Potassium efflux and accumulation in the

interstitium is not only important for muscle function but also for the development of fatigue resulting from exercise. Microdialysis measurements have recently demonstrated that sodium citrate ingestion (300 mg/kg body weight) reduces the exercise-induced interstitial acidosis in human skeletal muscle **(Fig. 16)** [38].

It was also shown by the latter authors that this reduction of H^+ ion concentration was associated with a reduced interstitial accumulation of potassium during muscle activity. These results accordingly suggest a delayed onset of muscle fatigue and sustained muscle performance by alkaline sodium citrate ingestion prior to exercise in sports.

Of considerable interest was the finding, in a study on 42 boys [39], of a significant positive correlation between the pH in the brain and the intelligence quotient (IQ), i.e. the lower the actual acid concentration in the brain, the higher the IQ.

Conditions representing physiological acidosis in vitro induced the aggregation of human Ab amyloid proteins (Ab) [40]. Metal ions such as copper, zinc and iron are enriched in the amyloid plaques in Alzheimer's disease and unlike other biometals tested at maximal biological concentrations, marked copper-induced aggregation of Ab emerged as the pH of the surrounding solution was lowered from 7.4 to 6.8. The reaction was completely reversible with either chelation or alkalinization. Since a mildly acidic environment together with increased copper and zinc concentrations are common features of inflammation, it is suggested that Ab aggregation by these factors may be a response to local injury and that metabolic acidosis may also play a role in the development of Alzheimer's disease.

The acid-base homeostasis dependent modulation of cortisol output may influence the risk of insulin resistance syndrome. This hypothesis appears to be consistent with previous epidemiological reports correlating high potassium consumption, or a high intake of fruits and vegetables, with a reduced risk for diabetes and coronary disease. Metabolic acidosis is known to promote renal acid excretion by the induction of ammonia-generating glutaminase and other enzymes in the renal tubules (see earlier: Compensation mechanisms of latent acidosis). This process is also strongly correlated with increased cortisol and aldosterone production. Since cortisol promotes the development of visceral obesity, and has a direct negative impact on insulin function throughout the body, even a modest sustained up-regulation of cortisol production may have the potential to increase the risk of insulin resistance syndrome and type 2 diabetes [41]. Future prospective epidemiology should assess whether the estimated acid-base homeostasis of habitual diets correlates with the risk of insulin resistance syndrome and diabetes.

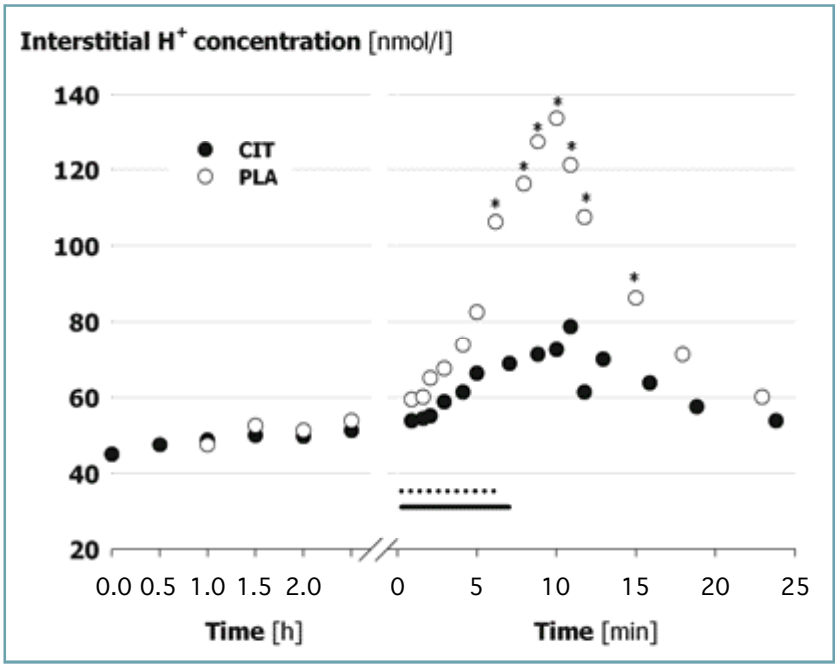

Fig. 16. Mean (± SEM) interstitial proton concentration during ingestion, exercise period (solid line: citrate ingestion; dotted line: placebo) and recovery from exercise (n=7). *Significant difference between citrate ingestion (CIT) and placebo (PLA). Modified from [38].

Conclusion

To what extent the diet can affect the acid–base homeostasis has been the subject of controversy for many years. Acute acidosis or alkalosis cannot be produced by the consumption of certain foods. However, the pathobiochemical effects of latent acidosis on impaired renal function, diabetes mellitus, hyperuricemia, or gout are undisputed. Based on new scientific findings, causal evidence has also now been furnished for the positive effects of a well-balanced acid-base equilibrium empirically established in naturopathy. Although diet-induced latent acidosis does not produce major changes in the blood pH because of the compensation mechanisms of the kidney, this compensation inevitably leads to the consumption of endogenous buffer reserves and, therefore, predominantly to a loss of bone substance if the increased acidification caused by a surplus of animal protein and a shortage of alkaline substances in the diet exists for a long period of time. A disturbance of the muscle protein metabolism as well as the structure and function of cartilage are other negative consequences of the endogenous compensation, which can also aggravate degenerative diseases such as arthrosis or rheumatism.

Our Stone Age ancestors preferred a more or less mixed diet which in spite of containing a high proportion of animal protein was also characterized by a surplus of base-forming substances. In contrast, the diet in today's Western industrial nations is charac-

terized by a large quantity of acid-forming nutrients, above all due to the surplus of animal protein. On the other hand, a high proportion of fresh fruit and vegetables in the diet contributes to the formation of the surplus of bases in the body.

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