ACID-BASE METABOLISM

Scientific insights for healthcare professionals

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PRINCIPLE OF ACID-BASE METABOLISM

Every cell in the body is constantly in a state of metabolic activity. For an optimal metabolism, cells require a stable environment including constant body temperature, the composition of the extracellular fluid and the correct pH value.[1] As acidosis impairs metabolic performance, physiological pH values must always be maintained to ensure a properly functioning metabolism. Maintaining constant pH levels in the different organs and tissues is the task of the acid-base metabolism.

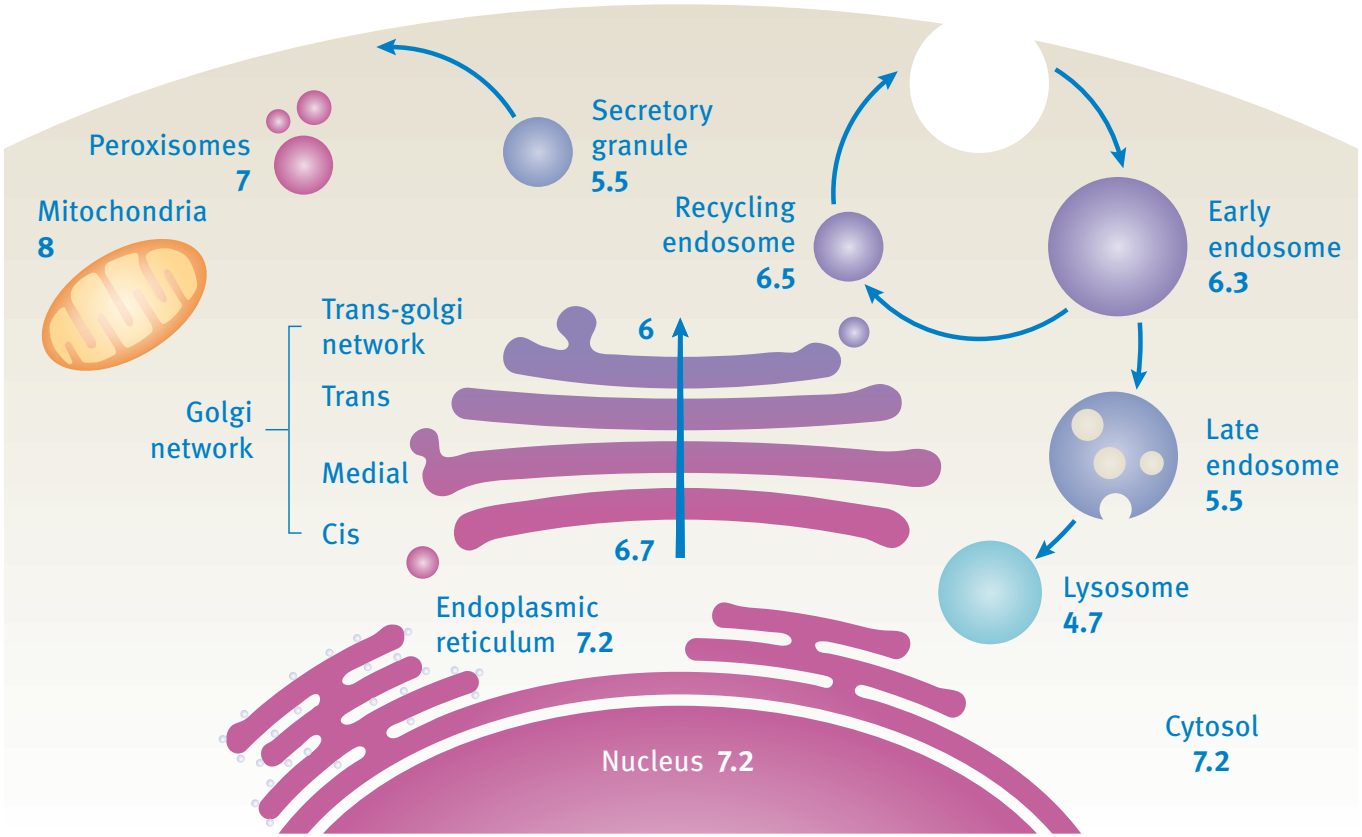

Figure 1. pH values of different subcellular compartments[3]

Over 7000 metabolic processes in the body depend on enzymatic activity.[2] Enzymes are proteins that act as biological catalysts (biocatalysts) and therefore accelerate chemical reactions. They bind to molecules and alter them in specific ways.

They are essential for respiration, digesting food, muscle and nerve function, for stimulating cellular energy production, cellular transport and almost all aspects of metabolism.

To work efficiently, enzymes require a specific pH level:

- At the enzymatic pH optimal value, enzymes work efficiently, e.g. in the destruction of macronutrients like carbohydrates, fat and protein for energy production.
- Increase or decline in pH may lead to denaturation of enzymes involved in the energy metabolism leading to structural changes and impairing their function.
- This effect in metabolic processes may lead to metabolic dysfunction.

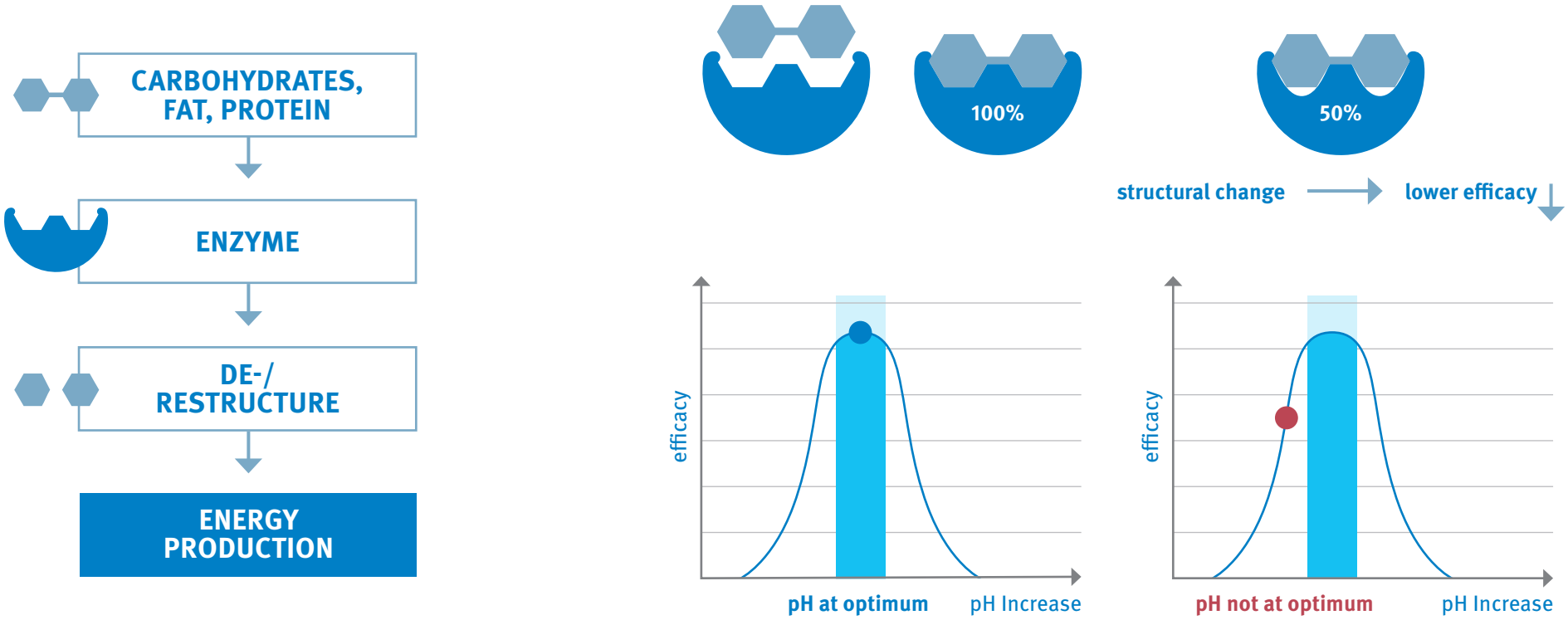

Figure 2. Enzymatic function at optimum pH level (left) and decline of pH with negative effect on efficacy (right)

REGULATION OF THE ACID-BASE METABOLISM

Several factors contribute to the regulation of the acid-base balance. These include buffer systems, internal and external cell compartments, the gaseous exchange in the lungs and the excretion through the kidneys. These systems are in a functional equilibrium with each other.[4] The key task of the acid-base metabolism is to maintain a constant pH value in the blood within the normal range of pH 7.35–7.45.

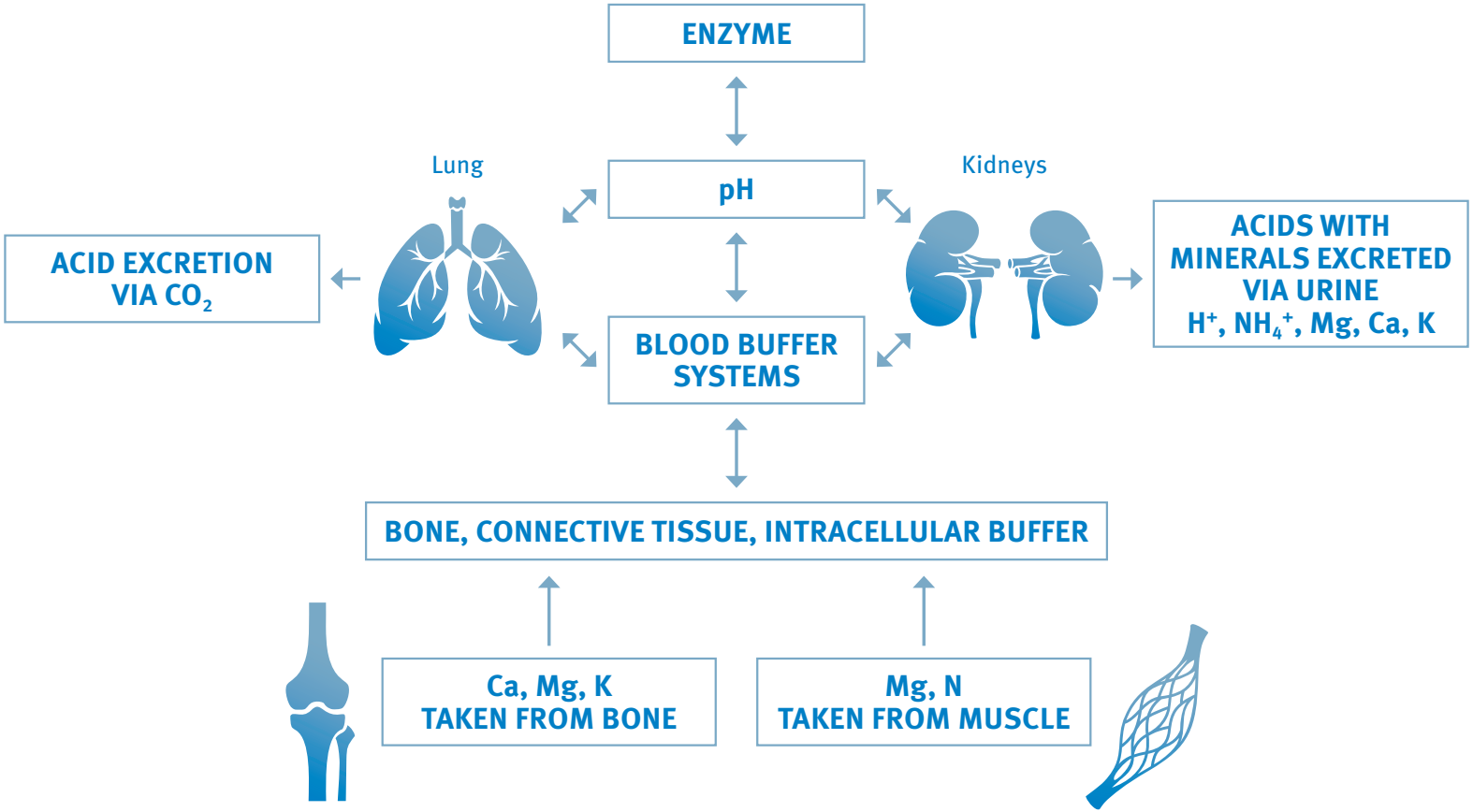

Figure 3. Parameters and organs involved in the maintenance of the physiological blood pH value

Lung and kidneys

- The most important organs in the regulation of the acid-base balance are the kidneys and the lungs.
- The kidneys are the only organ that can directly excrete acid, and therefore can effectively remove it from the body.
- The lungs contribute indirectly to the regulation of the pH value as the blood bicarbonate buffer has a tight connection to breathing.

Buffer systems

- The blood bicarbonate buffer is the most important buffer system responsible for a constant blood pH value.
- Specifically, the blood pH is balanced by the presence of both a weak acid (H_2CO_3) and a base (HCO_3^-) so that excess acid or base that appears due to any reason is neutralised.
- The exhalation of carbon dioxide (CO_2) via the lungs assists in the stabilisation of the blood pH value. Each molecule of CO_2 excreted via the lungs results from the reaction of one molecule of bicarbonate with one molecule of H^+.

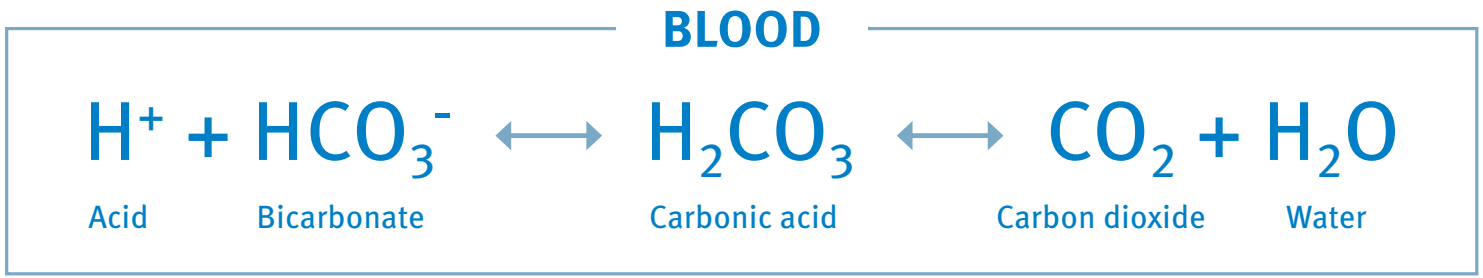

Figure 4. Bicarbonate buffer to maintain blood pH value

Food and metabolism

- The blood pH level is affected by the diet and by the formation of acids and bases due to metabolic processes. The breakdown and metabolisation of macronutrients lead to the production of diet-formed acids and bases, affecting the bicarbonate buffer and therefore the acid-base metabolism.
- Alkaline minerals such as magnesium, potassium and calcium citrate can accept acidic H^+ ions and facilitate their removal from the body.[4]
- These minerals are provided by the diet or liberated from bone, connective tissue and muscle in an effort to buffer the acid excess in blood and tissues.
- Modern Western dietary habits are linked with considerable acid excess and are a major reason for the development of chronic metabolic acidosis, a driver of chronic diseases.[5]

CHRONIC METABOLIC ACIDOSIS

Ancient diets were predominantly alkaline diets, rich in minerals and plant matter. Today, there is an evolutionary mismatch between our body's ability to regulate pH and the modern diet, which is highly acidic. The high dietary acid load from animal protein, grains, dairy products and processed foods is causing chronic metabolic acidosis with serious impact on health.[6–8]

DEVELOPMENT OF CHRONIC METABOLIC ACIDOSIS

- The human body has extensive regulatory systems to maintain a healthy blood pH value of 7.4 within the very narrow limits of 7.35 to 7.45.
- While metabolic acidosis (pH < 7.35) is a life-threatening condition, there is a low-grade and chronic form of acidosis, where the buffer system reaches its limit and renal acid excretion capacity is exhausted.
- The blood pH still remains within the normal range but is shifted to the lownormal level.[4]
- This slight decline in pH may not be immediately detectable and can remain sub-clinical for long periods of time.
- Today, from a scientific point of view, there is no doubt that the compensatory mechanisms within the body to regulate acid-base homeostasis are insufficient to deal with the long-term excess acid resulting from modern Western diets, ageing and other contributors.[6]
- This shift of blood pH within the normal range is known as chronic metabolic acidosis, latent acidosis or chronic acidosis and is associated with metabolic dysfunction and many chronic health conditions.[6]

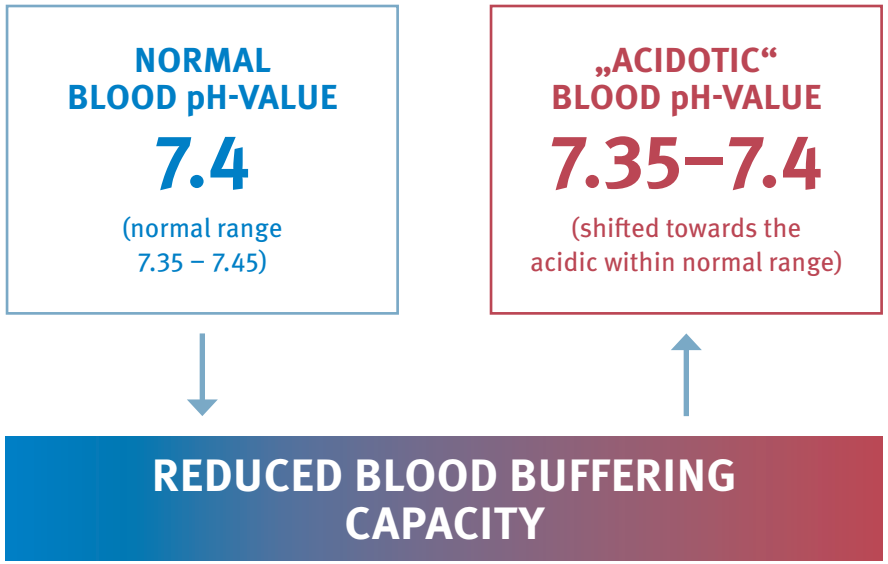

Figure 5. Normal and acidotic blood pH values

CAUSES OF CHRONIC ACIDOSIS

Diet

The most frequent cause of chronic acidosis is an unbalanced diet.[9] Western dietary habits are mostly linked with considerable excess acid essentially due to a high intake of protein-rich food, coupled with an insufficient intake of alkaline food.

PRAL values of acid and alkaline-forming food

- To understand the acidifying or alkalising nature of foods once eaten and metabolised, scientists developed a formula measuring the acidifying value of food according to their levels of alkalising or acidifying minerals, called the PRAL (potential renal acid load).
- The PRAL calculation model by Remer and Manz (1995) for classifying acid- and alkaline-forming food takes into account the content of alkaline minerals in the food as well as resorption and excretion.[10]

PRAL calculation

- PRAL calculates the protein (containing sulphurous amino acids) and subtracts the alkaline mineral (potassium, magnesium, calcium and sodium) content of food (PRAL (mEq/d) = 0.49 × protein (g/d) + 0.037 × P (mg/d) – 0.021 × K (mg/d) – 0.026 × Mg (mg/d) – 0.013 × Ca (mg/d))
- Foods are classified according to their potential acid load on the kidneys, i.e. the amount of acid or alkali that must be excreted via the kidneys after consuming 100 g of a specific food
- PRAL values with a minus sign have excess alkaline according to the definition, as they do not cause any acid load. Values with a plus sign have excess acid
- All values are given in milliequivalents (mEq), which is a unit for the acid or alkaline excess of the respective food

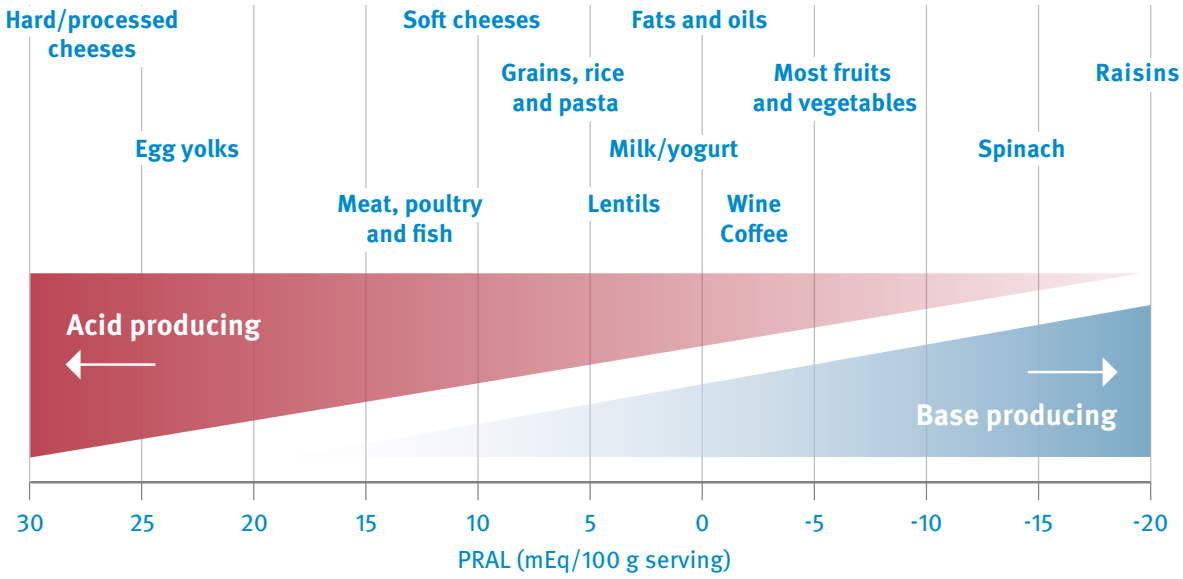

Figure 6. Estimated acid-producing potential of selected foods[11]

Acid load by diet

- Western dietary habits are mostly linked with considerable acid excess essentially due to a high intake of protein-rich food, coupled with an insufficient intake of alkaline food.
- A primary source of buffering in the body comes from the ingestion of alkaline minerals, which are bound to organic anions. Organic acids neutralise the acid produced from protein metabolism and work towards creating the acid-base balance.[10]
- Today's usual mixed diet results in an average acid load of approx. 50–100 mEq/day.[12]

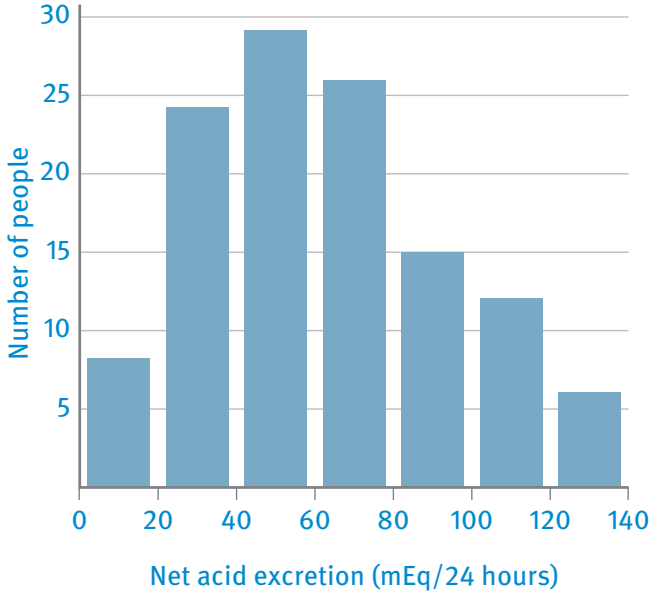

Figure 7. Daily acid load (NAE = net acid excretion) can vary between 0.8 and 134 mEq[13]

Calorie-reduced diets and fasting

The aim of a calorie-controlled diet is to break down body fat, resulting in weight loss. This leads to the production of keto acids resulting from the oxidative degradation of fatty acids, burdening the metabolism with acid. With a high-protein diet (e.g. Atkins diet, low carb/keto diet, diets with meal substitutes), an additional acid load is caused by the degradation of proteins. This acidosis results in a higher net acid excretion (NAE) in the urine accompanied by a decreased urine pH value.[14]

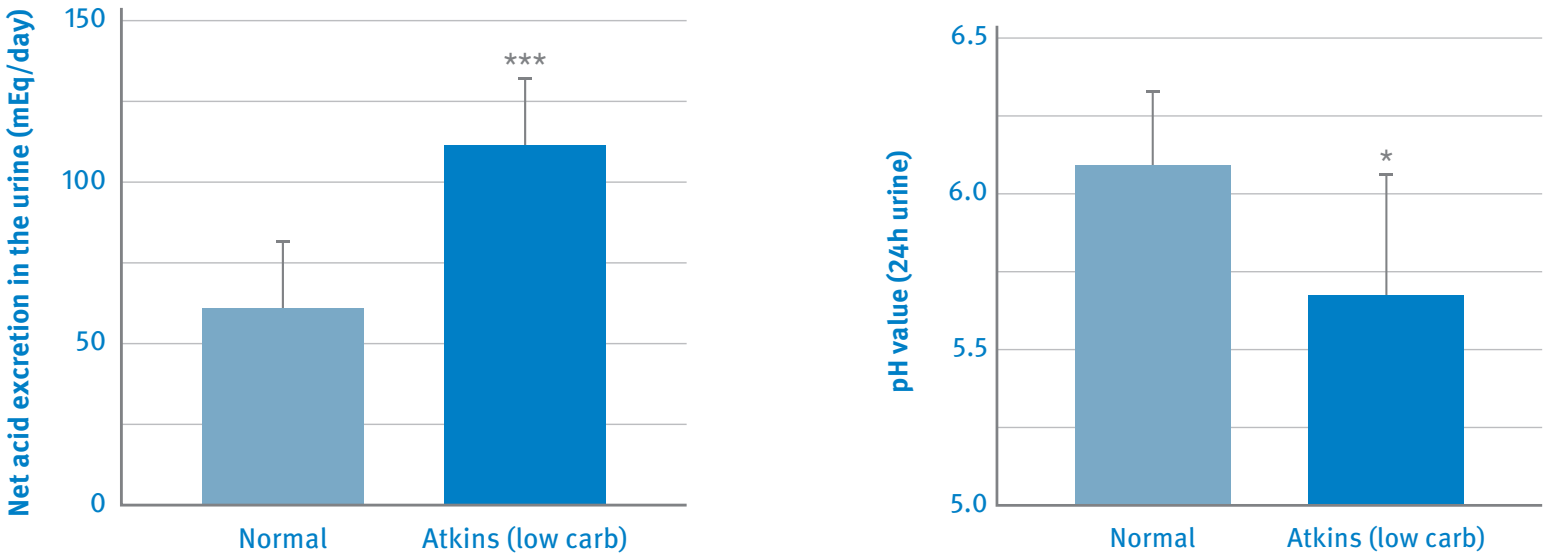

Figure 8. NAE in the urine following a normal or Atkins diet (left) and the corresponding pH values (right)[14]

Chronic diseases

Specific diseases can have a negative effect on the acid-base balance.

- → Diabetics have a higher risk of acidosis because of their frequently impaired kidney function.
- → Chronic kidney disease and hyperuricemia/gout reduce the excretion of acid and therefore facilitate a higher acid load.
- → Acidosis or a high-acid diet in turn impairs kidney function [11] and the capacity to excrete the uric acid that causes gout.

Age and impaired kidney function

- → The kidneys are the only organs that can actively excrete acid. With increasing age, kidney function declines and in turn reduces the capacity to excrete acid. [15]
- → This has the effect of reducing the blood pH value within the normal range as well as the blood bicarbonate concentration.
- → Elderly people are consequently at higher risk of suffering from chronic acidosis, as acid can no longer be sufficiently excreted and neutralised.

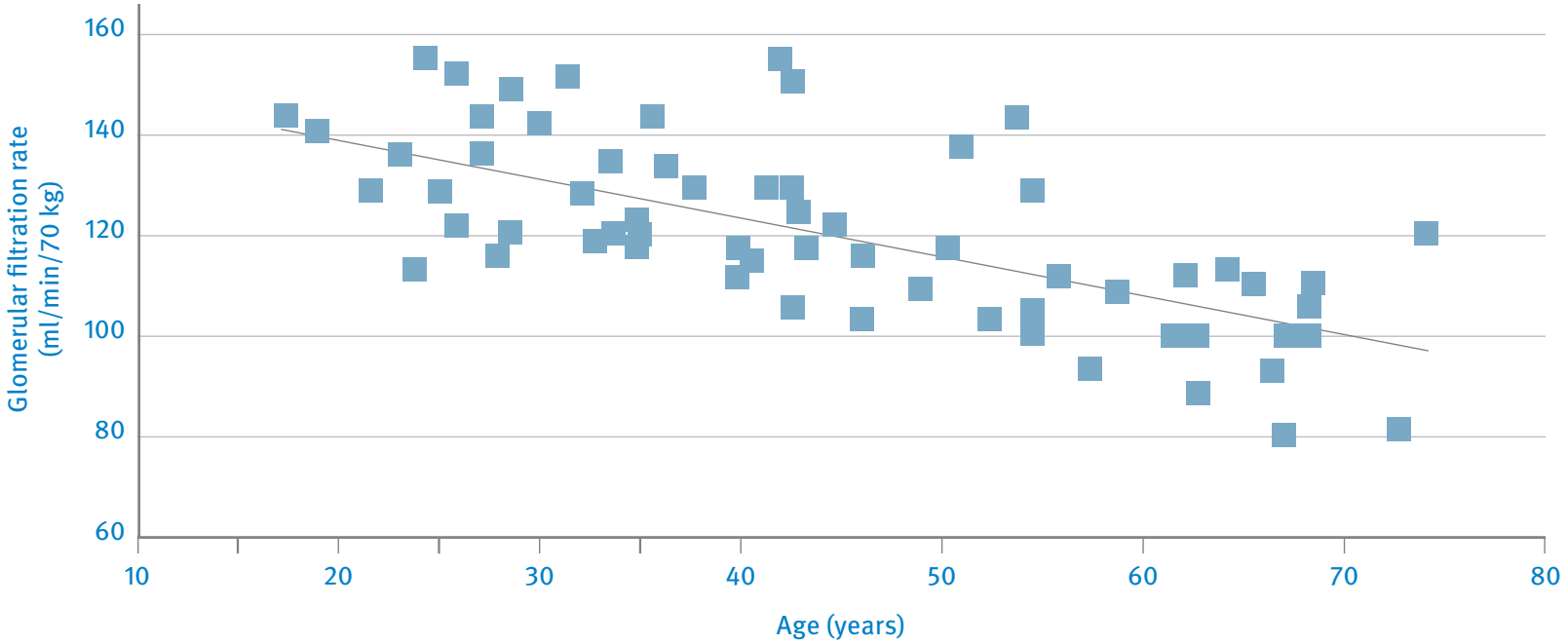

Figure 9. Decline of kidney function (estimated as glomerular filtration rate) with age [15]

SYMPTOMS OF CHRONIC ACIDOSIS

General well-being problems

Even a slight shift in the pH value in the acidic range and limited buffer capacities restrict metabolic activity, which has a negative effect on the energy metabolism.

Therefore, the following symptoms can be caused by chronic acidosis:

- Tiredness and exhaustion
- Reduced performance
- Increased sensitivity to stress
- Lack of concentration
- Nervousness and mood changes
- Weakened immune system

CONSEQUENCES OF CHRONIC ACIDOSIS

Multiple evidence confirms that a chronic state of low-grade metabolic acidosis is associated with the development of metabolic alterations such as insulin resistance, diabetes, hypertension, chronic kidney disease, bone disorders and loss of muscle mass and many other chronic health conditions.[6]

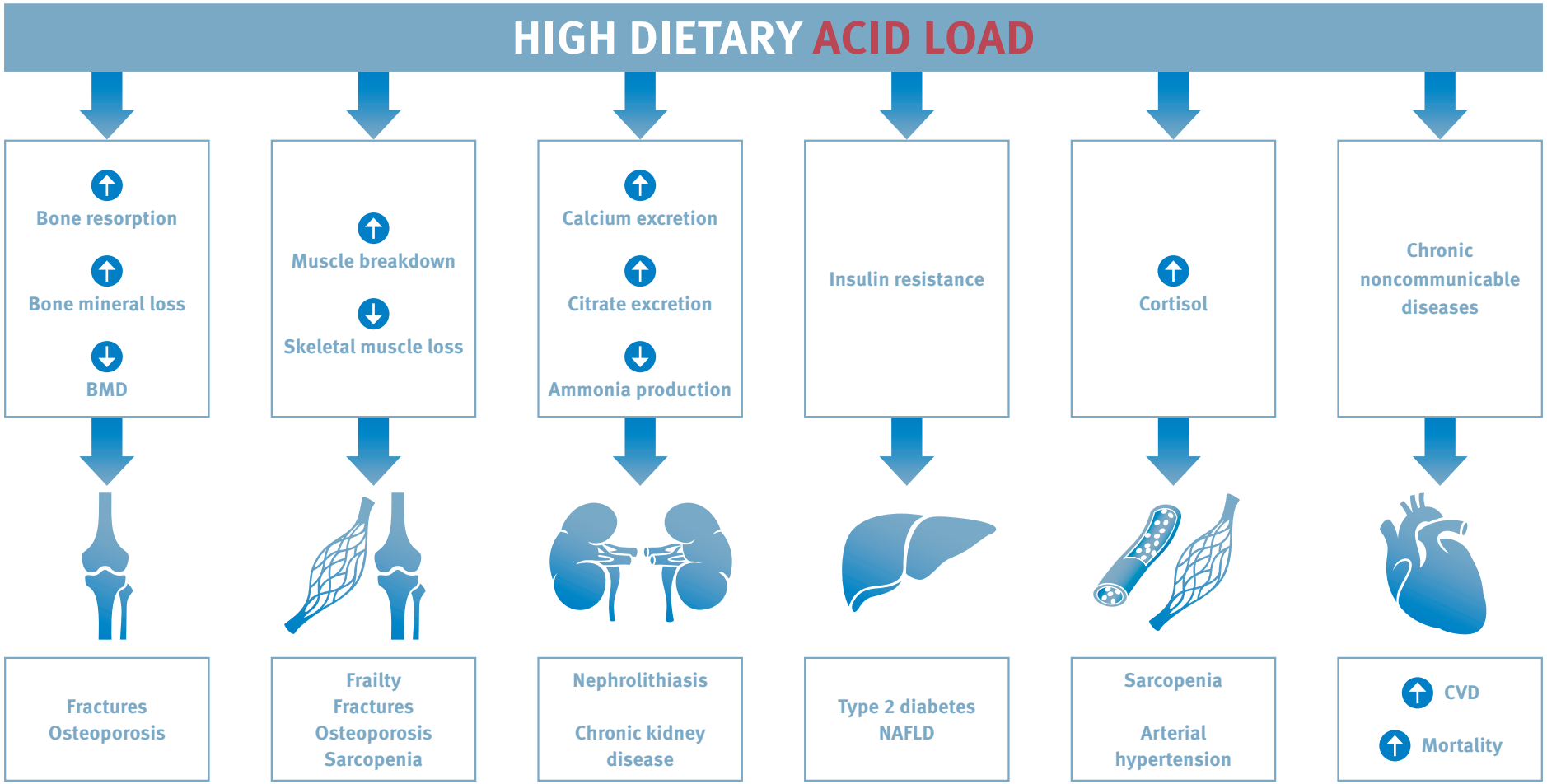

Figure 10. Health consequences by high dietary acid load[6] BMD, bone mineral density; CVD, cardiovascular diseases; NAFLD, non-alcoholic fatty liver disease

Chronic kidney disease (CKD)

There are multiple mechanisms by which chronic acidosis affects kidney function and therefore causes CKD.

- A high dietary acid load leads to an increase in factors like aldosterone and pro-fibrotic factors associated with a poor glomerular filtration rate (GFR) and renal fibrosis.
- To cope with the acid burden, increases in ammonia occur in the proximal tubule, which cause tubular toxicity and renal damage.
- These mechanisms, when persisting over a longer time period, are associated with an increased risk and progression of CKD.
- There is also a higher risk of kidney stones, as chronic metabolic acidosis causes increased urinary excretion of calcium and oxalate, in combination with reduced citrate excretion.[16–18]

Insulin resistance and type 2 diabetes

There is evidence that low-grade metabolic acidosis predisposes people to insulin resistance, type 2 diabetes and metabolic syndrome.[19]

- The acidification of the interstitial fluid can reduce insulin binding to the insulin receptor and reduce glucose uptake into the cell.
- Low urinary pH is also associated with worse insulin resistance.
- Importantly, in patients with metabolic syndrome, the 24-hour urine pH is significantly lower than in normal people and negatively correlates with the number of metabolic syndrome abnormalities.[20]

Osteoporosis

Bones are the body's own alkali stores. If the capacity of the buffer systems is exhausted, alkaline minerals are released from the bone to neutralise acid, i.e. calcium and magnesium are dissolved out of the bone.

- The release of alkaline calcium and magnesium from the bone surface (demineralisation) markedly decreases bone strength.[21]
- In addition, chronic acidosis also has negative effects on the function of the bone cells and therefore on bone growth as the activity of bone-forming osteoblasts is inhibited, while bone-resorbing osteoclasts are activated more as the pH value decreases.[22]
- In the long term these two processes result in bone resorption, which in turn increases the risk of osteoporosis.

Hypertension

- Chronic acidosis increases glucocorticoids and aldosterone influencing vasoconstriction.[23]
- In addition, there is a higher urinary loss of cardioprotective minerals like magnesium when excreting excess acids.[13]

Muscle catabolism (sarcopenia)

- To increase the availability of amino acid substrates for ammoniagenesis, metabolic acidosis stimulates muscle catabolism and inhibits albumin production through activation of the ATP-dependent ubiquitin-proteolytic pathway.
- Additionally, overt metabolic acidosis induces calciuria due to a combination of physiochemical effects on bone mineral and activation of osteoclastic bone resorption.
- As a result of these processes, chronic metabolic acidosis is associated with bone and muscle loss and growth restriction in children, each of which can be corrected by alkaline administration.[11]

Liver disease

- Epidemiological studies show that a higher dietary acid load is associated with liver diseases including non-alcoholic hepatic steatosis (fatty liver).[24, 25]
- Possible underlying mechanisms are that low-grade metabolic acidosis leads to insulin resistance and cardiovascular diseases. In addition, PRAL was associated with alanine aminotransferase (ALT) and steatosis.[26]

Cardiovascular diseases (CVD) and mortality

- Chronic metabolic acidosis-associated diseases including type 2 diabetes, hypertension and CKD among others are considered risk factors for CVD.[27]
- Independently of this, high dietary acid load itself increases cardiovascular risk and all-cause mortality.[7, 28]
- When analyses for cancer and cardiovascular mortality were performed, higher rates were found in populations who consume diets with high acid load.[29–31]

Effects on the connective tissue

Except of the collagen, connective tissue contains also so-called proteoglycans that are decorated with glycosaminoglycans. Due to the presence of sulphate and uronic acid groups they carry a vast number of negative charges. The negative charges of the proteoglycans enable the accumulation of the water molecules necessary for the elasticity and flexibility of the connective tissue.

→ In chronic acidosis, acid (H^+) consequently accumulates in the connective tissue and binds to proteoglycans.

→ This causes the connective tissue to lose its water-binding capacity resulting in a loss of elasticity which is detrimental to the function of cartilage, ligaments and tendons.[32]

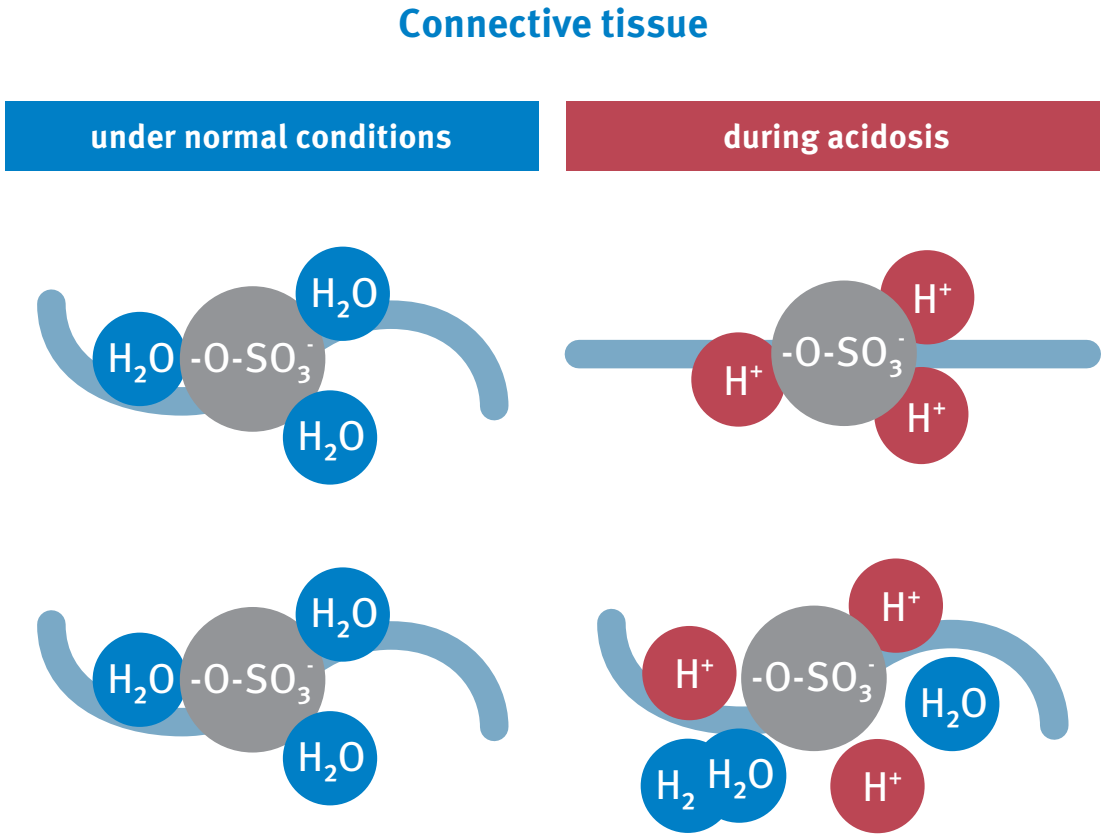

Figure 11. Structure of connective tissue under normal conditions (left) and in the case of chronic acidosis (right)

DIAGNOSIS OF CHRONIC ACIDOSIS: MEASUREMENT METHODS

pH test strips

This method is easy and can be useful for other purposes. However, for determination of chronic acidosis, usage of pH test strips makes little to no sense due to the following reasons:

- A single urine measurement can determine neither the "acid status" of body cells, tissues, blood or organs nor the buffer capacity.
- The urine composition is influenced by the time of day, diet, medication and illness/disease, and its pH value naturally varies between 5 and 8
- The majority of excreted acid in the urine occurs as ammonium compounds, which cannot be detected by test strips.
- Just approx. 1% of acid is excreted as free acid (H^+ ions), only this form can be detected by pH test strips.

Lab diagnostic methods

NAE in 24-hour urine

- Measurement of the NAE allows accurate conclusions to be drawn regarding the acid-base balance.
- The urine collected over 24 hours is analysed in terms of all excreted compounds that are relevant for evaluating the acid-base status.
- The higher the NAE via the kidneys, the higher the acid load of the body.

Sander method

- The Sander method is used to determine the urine pH and the buffer capacity of the urine via five measurements spread over the day.
- In each measurement, urine is titrated (alkali and acid are separately added to the urine until neutralisation occurs) – this determines urine buffer capacity, or in other words, the acidity quotient.
- The daily profile of the acidity quotient provides information on the status of the acid-base balance.

Bicarbonate concentration in blood serum

- This method determinates the concentration of bicarbonate in the blood serum by photometry
- The higher the bicarbonate concentration in the blood, the higher the buffer capacity and the more acid can be neutralised (note – excessively high blood bicarbonate is a sign of alkalosis).

Dietary anamnesis

The medical anamnesis of dietary habits and lifestyle is practical and beneficial in identifying chronic acidosis. Keeping a dietary record helps clarify whether predominantly acid-forming or alkaline-forming foods are consumed. Such analysis of the dietary record should always be based on the PRAL model.

Meat and Meat Products Average	9.5
Lean Beef	7.8
Chicken	8.7
Canned, Corned Beef	13.2
Liver Sausage	10.6
Lunch Meat	10.2
Lean Pork	7.9
Rump Steak	8.8
Salami	11.6
Turkey Meat	9.9
Veal Filet	9.0
Fish Average	7.9
Cod Fillet	7.1
Haddock	6.8
Herring	7.0
Trout	10.8

Vegetables Average	-2.8
Asparagus	-0.4
Broccoli	-1.2
Carrots	-4.9
Cauliflower	-4.0
Celery	-5.2
Chicory	-2.0
Cucumber	-0.8
Eggplant	-3.4
Leeks	-1.8
Lettuce	-2.5
Mushrooms	-1.4
Onions	-1.5
Peppers	-1.4
Potatoes	-4.0
Radishes	-3.7
Spinach	-14.0
Tomato Juice	-2.8
Tomatoes	-3.1
Zucchini	-2.6

Milk, Dairy, and Eggs	
Milk and non-cheese average	1.0
Low protein cheese average	8.0
High protein cheese average	23.6
Buttermilk	0.5
Low Fat Cheddar	26.4
Gouda Cheese	18.6
Cottage Cheese	8.7
Sour Cream	1.2
Whole Egg	8.2
Egg White	1.1
Egg Yolk	23.4
Hard Cheese	19.2
Ice Cream	0.6
Whole Milk	1.1
Whole Milk, Pasteurized	0.7
Parmesan Cheese	34.2
Processed Cheese	28.7
Whole Milk Yogurt Fruit	1.2
Whole Milk Yogurt Plain	1.5

Grain Products	
Flour Average	7.0
Rye Flour	5.9
Wheat Flour	8.2
Oats	10.7
Bread Average	3.5
Mixed Grain Rye Bread	4.0
Rye Bread	4.1
Mixed Grain Wheat Bread	3.8
Wheat Bread	1.8
White Bread	3.7
Noodles Average	6.7
Egg Noodles	6.4
White Spaghetti	6.5
Whole Grain Spaghetti	7.3
Brown Rice	12.5
White Rice	1.7
Cornflakes	5.0
Rye Crackers	3.3

Figure 12. Food categorised according to their PRAL value

TREATMENT OPTIONS

ALKALINE SUPPLEMENTATION

Dietary behaviour and lifestyle influence the acid-base balance.

- In general, Western diets are considered acidogenic due to the high amount of animal protein and an insufficient intake of fruits and vegetables.
- This is associated with a high dietary acid load and a low intake of alkaline minerals.[33]
- For prevention and treatment of chronic metabolic acidosis, sometimes dietary changes alone are not enough to correct acid-base imbalances.
- Here, alkalising treatment by alkaline mineral supplementation may help restore optimal physiological pH levels. From a scientific point of view, alkalising therapy is indicated in the following medical situations and diseases.

ALKALISING EFFECT OF DIFFERENT ALKALINE SALTS

- 2 weeks of alkaline supplementation in the form of potassium citrate or potassium bicarbonate (but not potassium chloride) resulted in a significant reduction of urinary NAE and a significant increase in urinary pH (Fig. 9)[34]
- Alkaline supplementation reduces acid load. Potassium citrate, an organic citric acid salt, has a stronger alkaline effect than inorganic potassium bicarbonate[34]

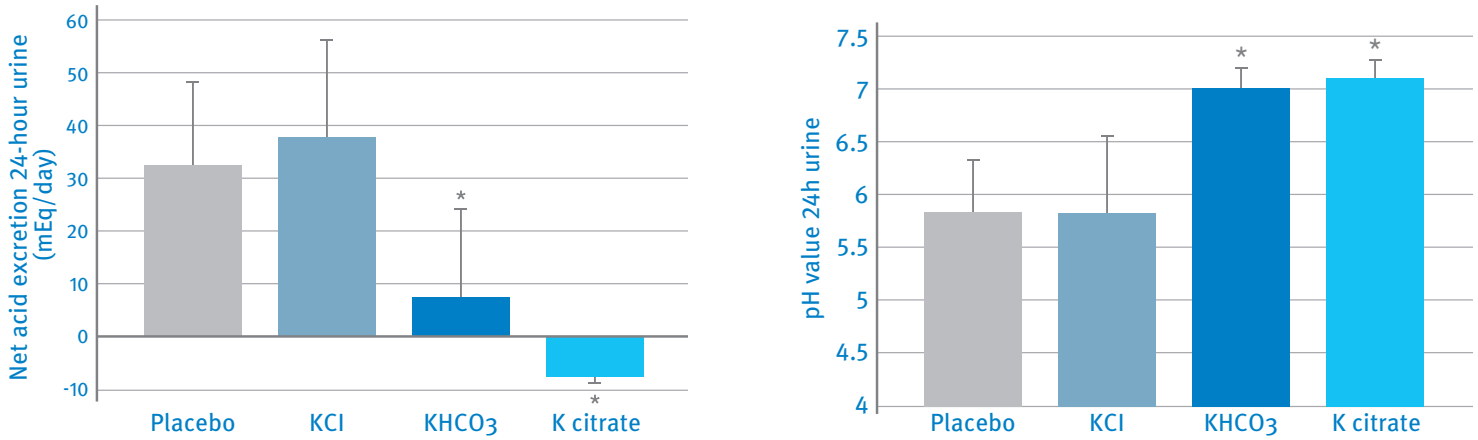

Figure 13. NAE (left) and 24-hr urinary pH (right) after supplementation with placebo, potassium chloride, potassium bicarbonate and potassium citrate.[34] * p ‹0.05

CHRONIC KIDNEY DISEASE (CKD)

High acid loads and decreased acid excretory capacity result in the development of metabolic acidosis, which is common in CKD patients and leads to an accelerated reduction in kidney function (glomerular filtration rate, or GFR). Kidney adaptive responses to metabolic acidosis over the long term can cause decline of renal function:

- → Increased production of angiotensin II, aldosterone, and endothelin-1 mitigates the immediate benefit of increased kidney acid excretion, but their chronic upregulation promotes inflammation and fibrosis.
- → Stimulation of ammoniagenesis increases acid excretion but also leads to ammonia-induced complement activation and nephron damage.

These effects together with acid accumulation in kidney tissue accelerate the progression of CKD.[35]

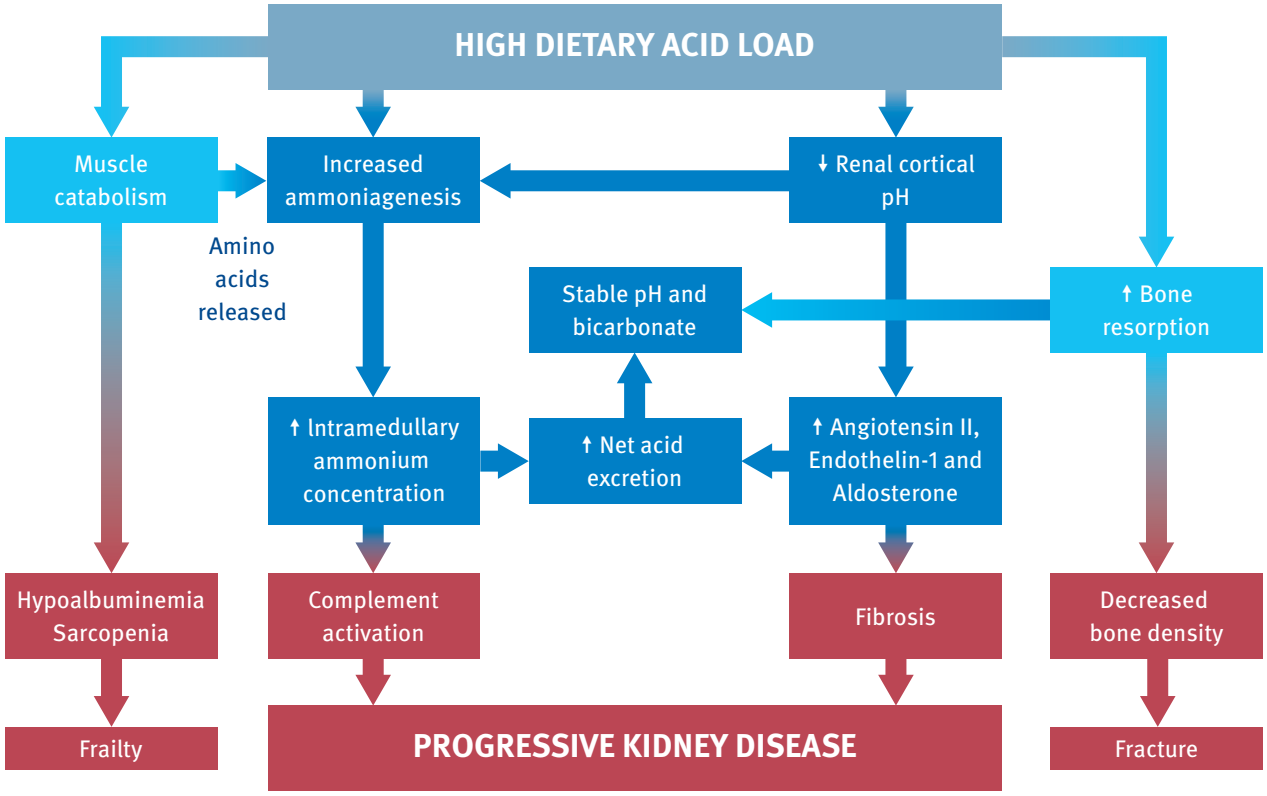

Figure 14.
High dietary acid load affects progression of CKD by different mechanisms[11]

Metabolic acidosis develops as CKD progresses. Less than 10% of people with CKD stages 1 and 2 have metabolic acidosis, while for stages 3 and 4, its prevalence reaches ~15% and ~30% respectively, and for stage 5 even more than 50%.[36, 37] Metabolic acidosis increases the risk of rapid decline of kidney function more than twofold,[36, 38] and the risk of all-cause mortality threefold.[38]

Metabolic acidosis leads to a decrease in citrate excreted with urine, and this decrease positively correlates with CKD stage.[39] Compared with healthy people, patients with CKD have lower urine pH and citrate.[40]

- A higher dietary acid load is associated with albuminuria, low eGFR and higher risk of CKD development.[41, 42]
- Reducing the dietary acid load with fruits and vegetables or sodium bicarbonate improves metabolic acidosis and reduces kidney injury in stage 4 CKD patients[43]

Alkaline supplementation in CKD:

- increases serum bicarbonate levels (that means increased bicarbonate buffer capacity)[44]
- increases urine pH and citrate and decreases NAE[40]
- slows the rate of decline of renal function[44–47] and reduces the risk of end-stage kidney failure[46]
- ameliorates kidney injury in patients with reduced GFR[48]
- decreases all-cause and cardiovascular mortality in CKD patients[49]

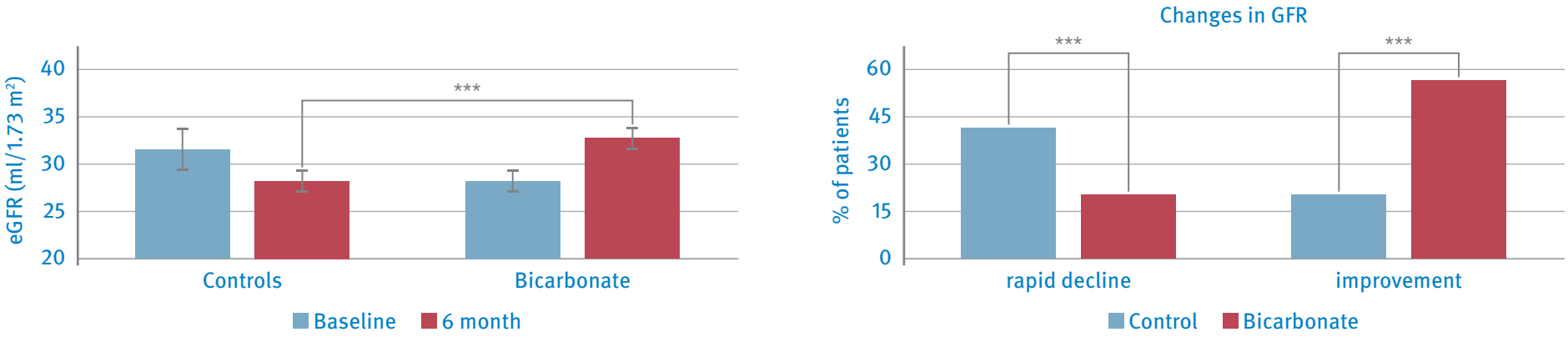

Figure 15. Effects of 6 months of sodium bicarbonate supplementation vs. standard therapy on kidney function.[47] *** $p \leq 0.001$

KIDNEY STONES

Abnormalities in urine pH and composition as well as electrolyte abnormalities, which accompany metabolic acidosis in CKD, may lead to stone formation.

→ A high dietary acid load increases the risk of renal stones 2.5- to 3-fold.[50, 51]

→ An alkaline-rich diet decreases clinical stone recurrences more than 5-fold in kidney stone formers with renal tubular acidosis.[52]

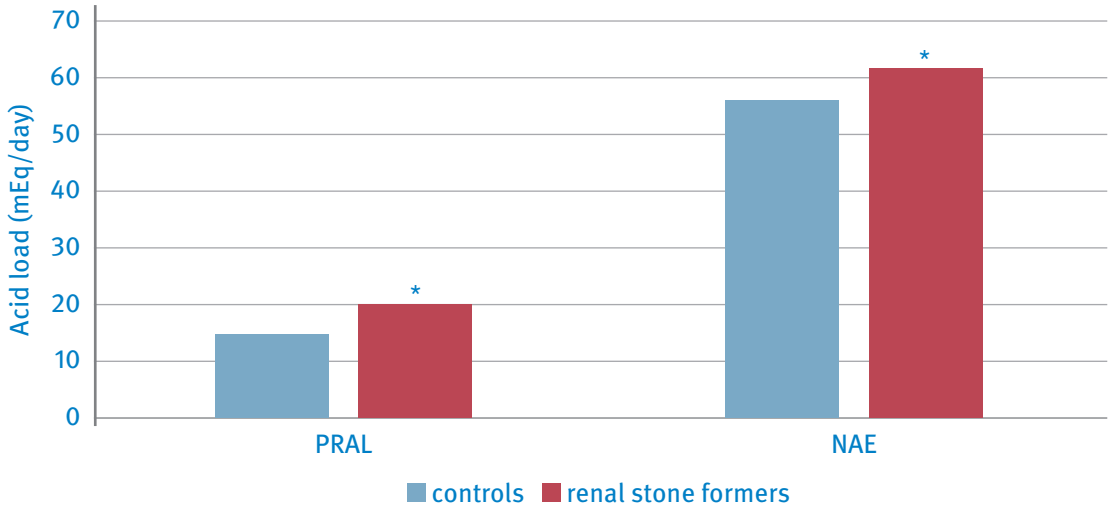

Figure 16. Higher PRAL and NAE in renal stone formers in contrast to healthy controls[50] * p ‹ 0.05

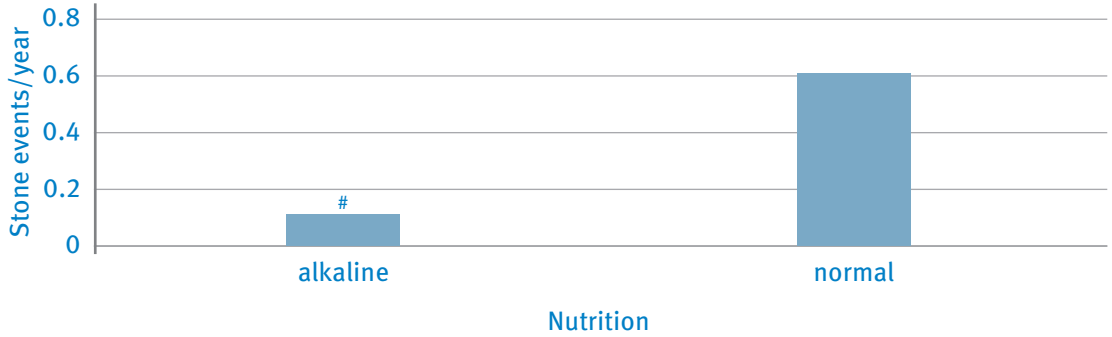

Figure 17. Stone events per year follow-up (stone passage or urologic intervention) were higher in patients non-adherent to alkali nutrition than in patients adherent to dietary treatment[52] # p = 0.006

Reducing the dietary acid load with alkali supplementation or alkali-inducing food is an effective kidney-protective adjunct to current strategies.

DIABETES

A higher dietary acid load is associated with an increased risk of insulin resistance[53] and therefore of the development of type 2 diabetes mellitus.

The acid-base balance may influence the risk of insulin resistance by:

- modulating cortisol output: metabolic acidosis increases cortisol production, and excess glucocorticoids promote insulin resistance and visceral obesity[54]
- impairing the binding affinity of insulin to its receptor through the changing pH of interstitial fluid microenvironments[55]
- affecting hormones that regulate energy levels[19]: A low pH decreases the expression of the insulin sensitiser adiponectin, which is a hormone that improves the insulin sensitivity of skeletal muscle. Leptin secretion is downregulated in adipocytes exposed to a low pH medium, whereas administering sodium bicarbonate to people with renal-induced acidosis increases serum leptin levels

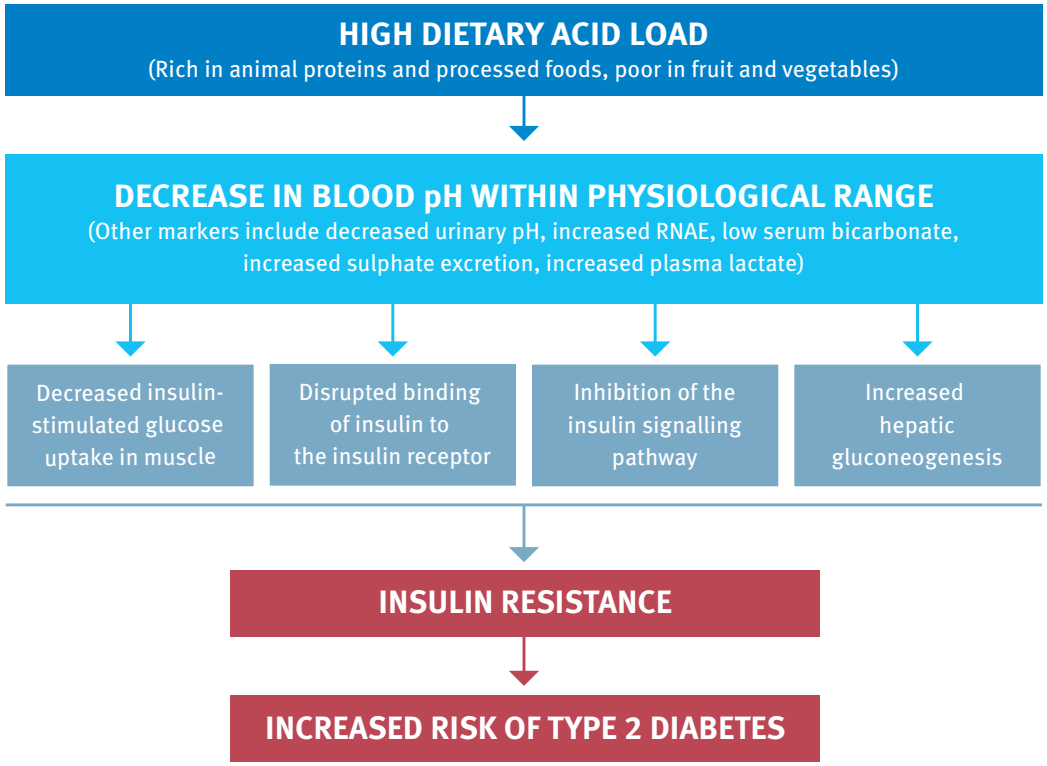

Figure 18. High dietary acid load enhances the risk of developing type 2 diabetes via different mechanisms

High dietary acid load:

- → increases insulin resistance (HOMA-IR) and fasting insulin levels[56]
- → increases the risk of type 2 diabetes independently of other known diabetes risk factors[57, 58]

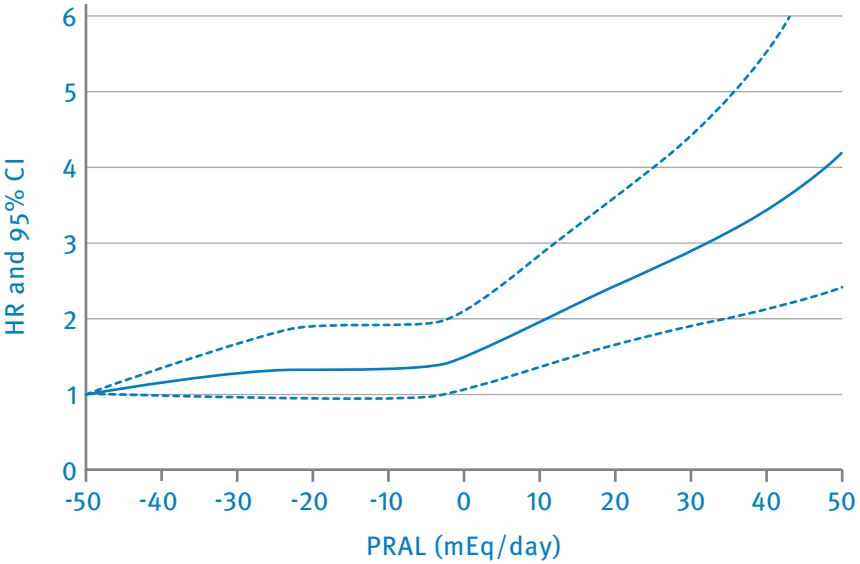

Figure 19. Cubic spline regression model between PRAL score and risk of type 2 diabetes (E3N-EPIC cohort data, n=66,485)[57]

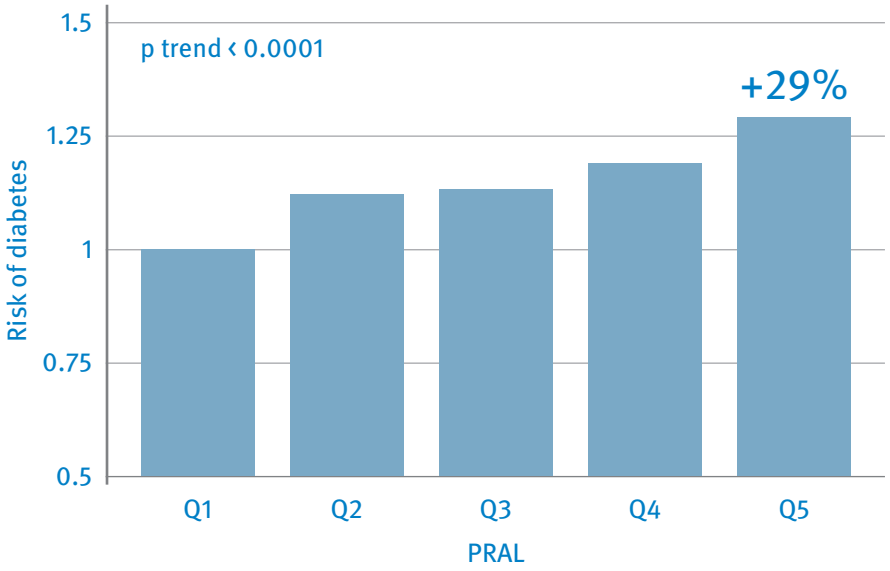

Figure 20. Higher dietary acid load increases the risk for diabetes by 29%[58]

Alkaline supplementation in patients with combined glucose intolerance[59]

- → attenuates metabolic acidosis by increasing bicarbonate concentration in the blood
- → improves insulin resistance (HOMA-IR)
- → improves insulin sensitivity (Quicki)

METABOLIC SYNDROME AND OBESITY

Insulin resistance together with obesity, hypertension and dyslipidemia are defining criteria of metabolic syndrome.

Higher dietary acid load

- → increases the risk of metabolic syndrome 17-fold[60]
- → increases the risk of hypertriglyceridemia more than 2-fold[60]
- → predicts low diet quality and increases odds of both obesity and abdominal obesity 2.4-fold.[61]

In turn, overweight and obese people (BMI > 25) have significantly lower serum bicarbonate levels, which likely indicates metabolic acidosis[62]

DIETS AND FASTING CURES

Diets and fasting may cause acidosis due to formation of keto acid resulting from fatty acids degradation. An alkaline supplementation combined with a diet or fasting is a beneficial adjunctive therapy aimed at maintaining the acid-base balance, optimising metabolic performance, and alleviating a diet or fasting crisis, and is therefore important for successful weight loss.

- → Fasting acidosis caused by a diet is minimised or prevented by taking an alkaline supplement compared to placebo (Fig. 21)[63]
- → Decrease of PRAL and net endogenous acid production (NEAP) due to alkaline (vegan) nutrition correlated significantly with decrease in body weight and fat mass[64]

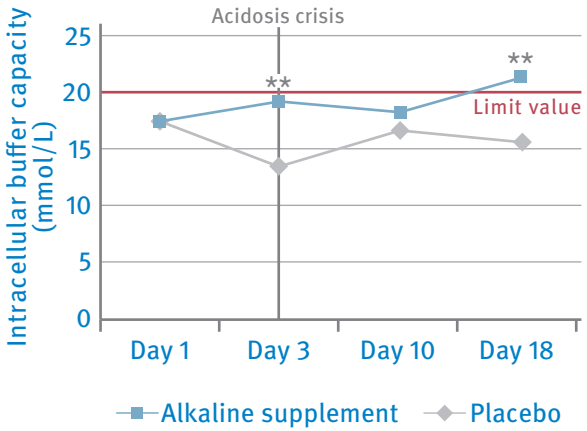

Figure 21. Intracellular buffer capacity when taking a placebo or alkaline supplementation during fasting.[63] ** $p < 0.01$

A placebo-controlled, double-blind, randomised study showed that a combination of intermittent fasting, exercise training, and alkaline supplementation (Basica® Direct) in healthy overweight subjects has several positive effects[65]:

- → The 12-week training programme led to significant weight loss and loss of body fat, and intermittent fasting (1–2 fasting days per week) enhanced these effects
- → Alkaline mineral supplementation resulted in the highest body weight loss (Fig. 22, left) and body fat loss (Fig. 22, right)
- → In both the fasting and non-fasting group, the alkaline supplement also resulted in a higher bicarbonate concentration in the blood as an indication of improved buffer capacity (Fig. 23, left) and a higher urinary pH (Fig. 23, right)

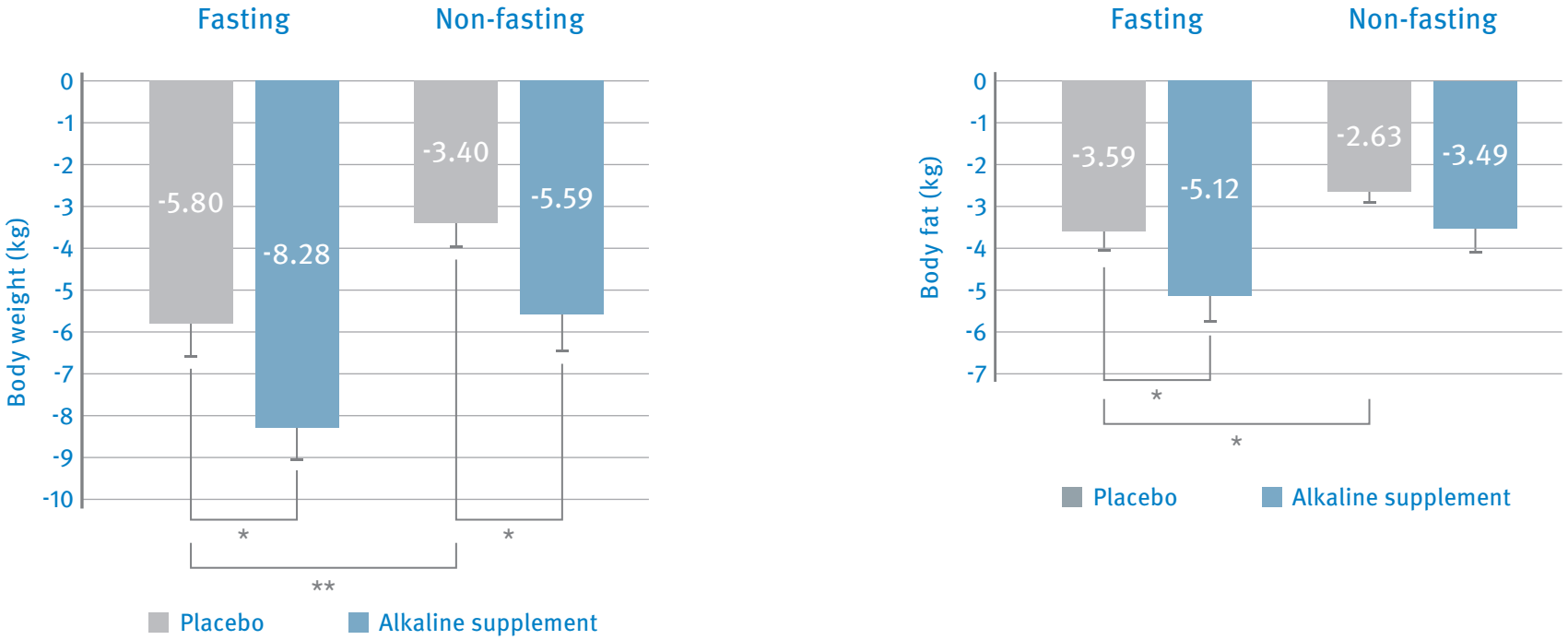

Figure 22. Significant differences in body weight loss (left) and body fat loss (right) in fasting and non-fasting groups taking placebo or alkaline supplement.
* $p < 0.05$; ** $p < 0.01$

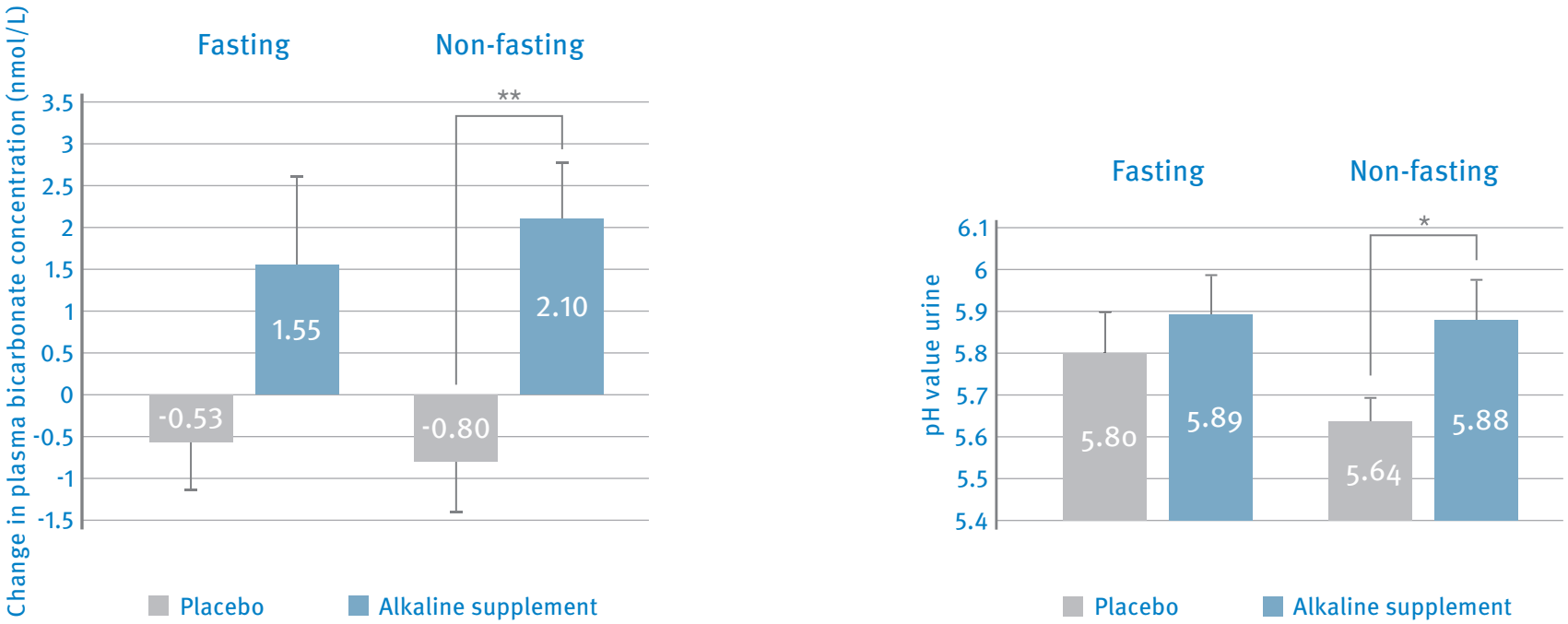

Figure 23. Change in blood bicarbonate concentration (left) and urinary pH (right) in fasting and non-fasting groups taking placebo or alkaline supplement.
* $p < 0.05$; ** $p < 0.01$

CARDIOVASCULAR DISEASES

Metabolic acidosis may mediate adverse CVD outcomes by:

- Endothelial inflammatory processes. Acidosis stimulates the expression of a wide range of inflammatory genes in endothelial cells and regulates endothelial cell adhesion
- Increasing extracellular potassium, which could influence cardiac contractility as well as heart rhythm

Patients with acidosis (serum bicarbonate < 22 mEq/l) have a 54% higher risk of unfavourable CVD outcomes (myocardial infarction, acute coronary syndrome, stroke, heart failure, and CV death).[66] Moreover, each 1 mEq/l increase in serum bicarbonate decreases the risk of such major adverse cardiovascular events by 4%.[67] Increased dietary acid load, consequently, increases the risk of CVD mortality by 6–12%.[29, 68]

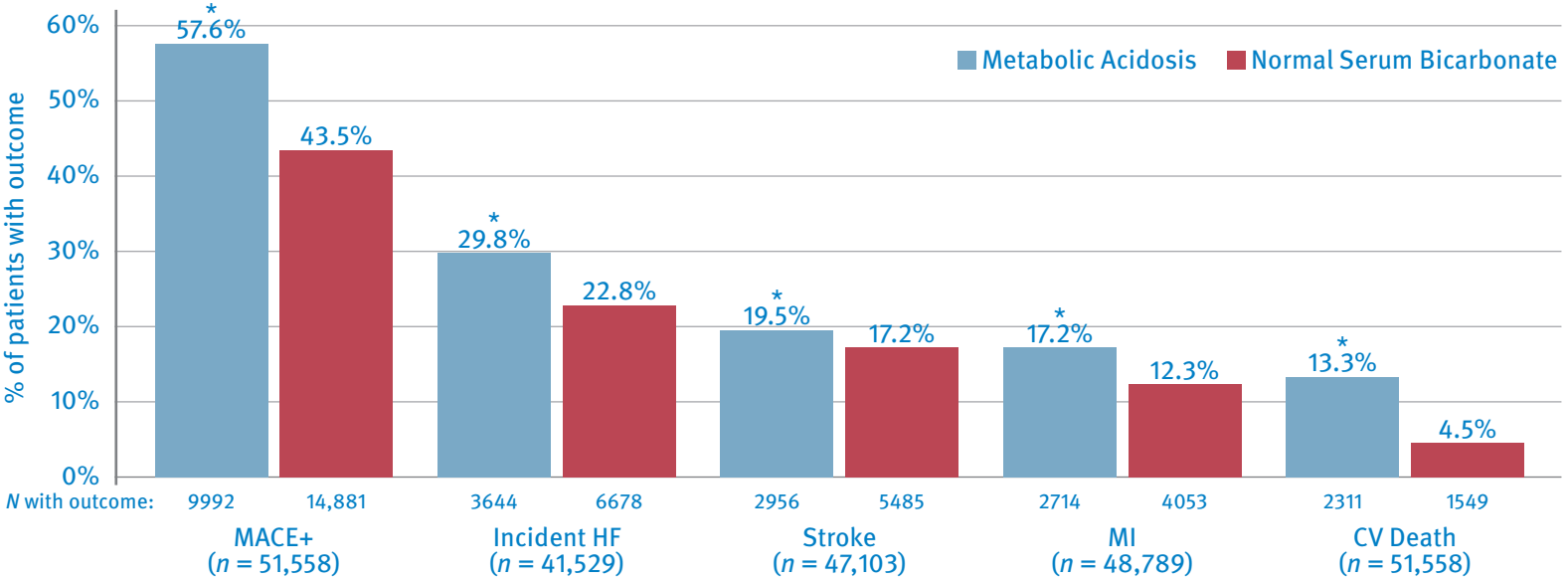

Figure 24. Unadjusted 2-year incidence rates of major adverse cardiovascular event (MACE+), incident heart failure (HF), stroke, myocardial infarction (MI), and cardiovascular (CV) death in the metabolic acidosis versus normal serum bicarbonate groups.[67] * p ‹ 0.001

HYPERTENSION

Hypertension is known as one of the most important causes of mortality in the world with increasing prevalence. The association between dietary acid load and risk of hypertension has received considerable attention.[69] A high dietary acid load affects blood pressure by:

- excessive excretion of calcium and magnesium via the kidneys, which increases blood pressure
- stimulating the production of cortisol and aldosterone, an excess of which may induce essential hypertension
- decreasing urinary citrate excretion, which can cause hypertension

High PRAL is associated with elevated systolic and diastolic blood pressure[69–71], and increased NEAP leads to 35–40% higher risk of hypertension.[70, 72] Higher dietary acid load is also associated with increased blood pressure in healthy children.[73]

Consequently, alkaline supplementation decreases systolic and diastolic blood pressure as well as vascular calcification in CKD patients.[44]

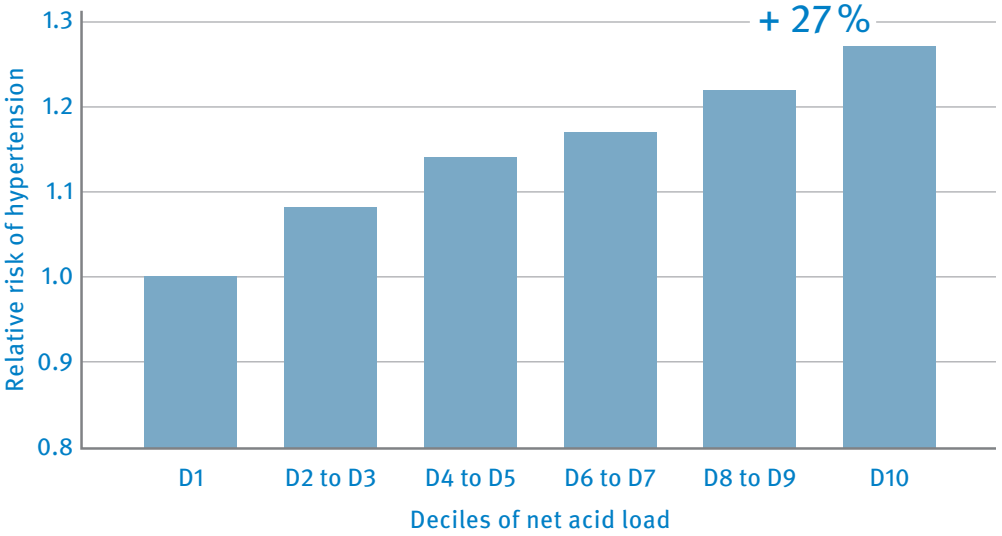

Figure 25. High diet-dependent net acid load increases the risk of hypertension in United States women by 27%[74]

MUSCLES CATABOLISM (SARCOPENIA)

Metabolic acidosis stimulates muscle catabolism through activation of the ATP-dependent ubiquitin-proteolytic pathway[75] and decreases the rate of muscle protein synthesis (Fig. 26).[76]

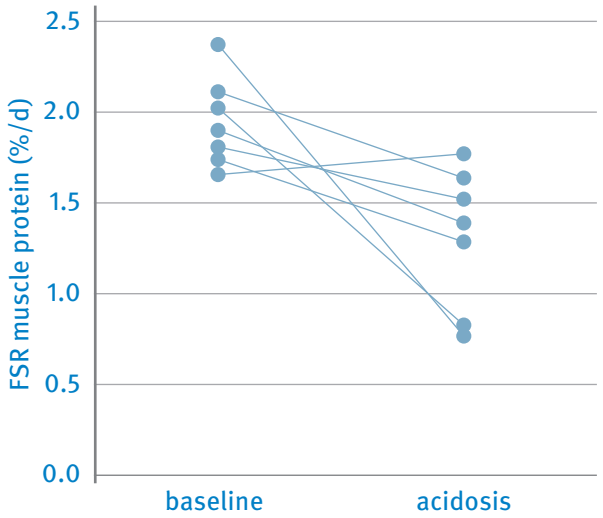

Figure 26. Significant decrease ($p < 0.05$) of fractional synthesis rates (FSRs) of muscle protein by acidosis[76]

Higher dietary acid load

- → is associated with 1.5–3% lower muscle mass (Fig. 27)[77, 78]
- → increases the risk of frailty (geriatric syndrome associated with muscle weakness) by 59% if calculated for PRAL and by 42% if calculated by NEAP[79]

Moreover, elder people with sarcopenia (muscle atrophy/loss that occurs with aging and/or immobility) had significantly more acidic urine than healthy elderly (pH = 5.5 vs 6.2, respectively).[80]

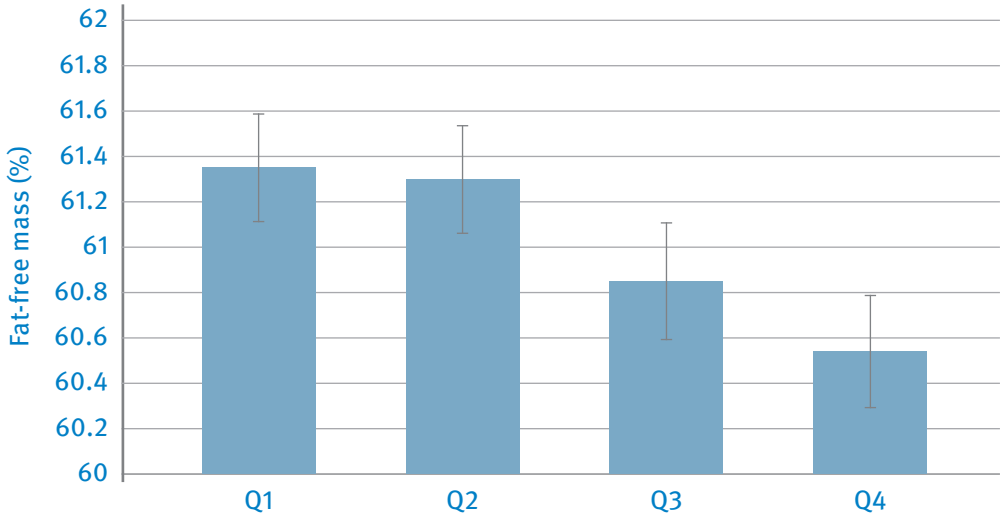

Figure 27. Percent of fat-free mass (muscle mass) according to quartiles of PRAL[78]

In CKD, chronic fatigue and muscle loss due to metabolic acidosis are a common symptom.

- → Alkaline supplementation significantly increases mid-arm muscle circumference and lean body mass in CKD patients.[47]
- → Moreover, alkaline supplementation in CKD leads to increase in serum bicarbonate, increases muscle mass and decreases myostatin, a protein that inhibits muscle cells growth (Fig. 28).[81]

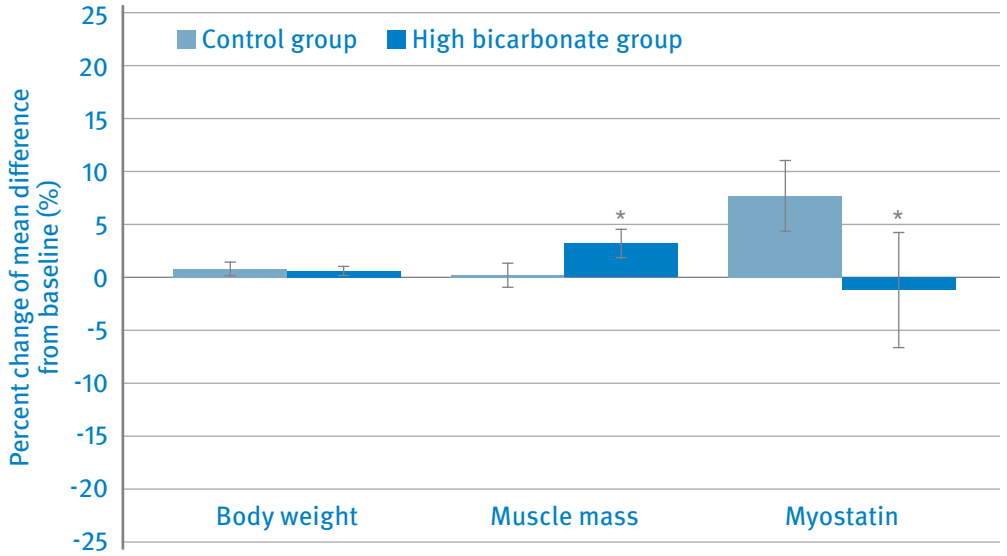

Figure 28. Alkaline supplementation leads to increased muscle mass and decreased myostatin levels[81]
* $p < 0.05$ compared to baseline

PAIN

A number of pain-causing stimuli, such as inflammation, lower extracellular pH. This observation hints at the existence of pH-sensitive receptors on nociceptive neurons and suggests that their activation causes pain. Possible candidate receptors include acid-sensing ion channels (ASICs), which produce acid-evoked cation currents and are present both in the cell body and at terminals of peripheral nociceptive neurons.[82]

Increased acidity is associated with pain sensitivity:

- While injection of a physiological solution under the skin causes only minor pain, increasing the solution acidity led to an almost 9-fold increase in pain, with the greatest sensitivity registered already at pH 5.5 (Fig. 29)[83]
- There is a positive and relative association between dietary sulphur amino acid intake (acidic) and severity of pain in musculoskeletal pains[84]
- Higher dietary acid load drastically increases the risk of migraines (4-fold for NEAP, 7-fold for PRAL)[85]
- High PRAL and NEAP significantly increase migraine frequency and migraine-related disability[86]
  - High acid load may contribute to elevated odds of migraines by increasing the inflammatory state, elevating cortisol levels, modifying the NO signalling pathway, blood flow, and gut microbiota, and affecting body weight as well as hypertension risk

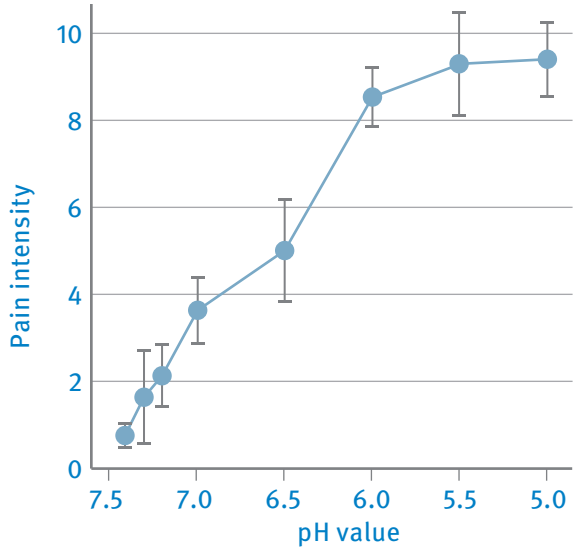

Figure 29. The lower a solution's pH value, the higher the pain intensity[83]

Alkaline supplementation has been shown to reduce pain:

- A significant reduction in symptoms was observed after alkaline supplementation (Basica® Vital) for 4 weeks in patients with chronic back pain (Fig. 30):[32]
  - Arhus back pain index and the intake painkillers were reduced substantially
  - Physical mobility improved accordingly
  - Increase in blood buffer capacity indicates a positive effect on the acid-base balance

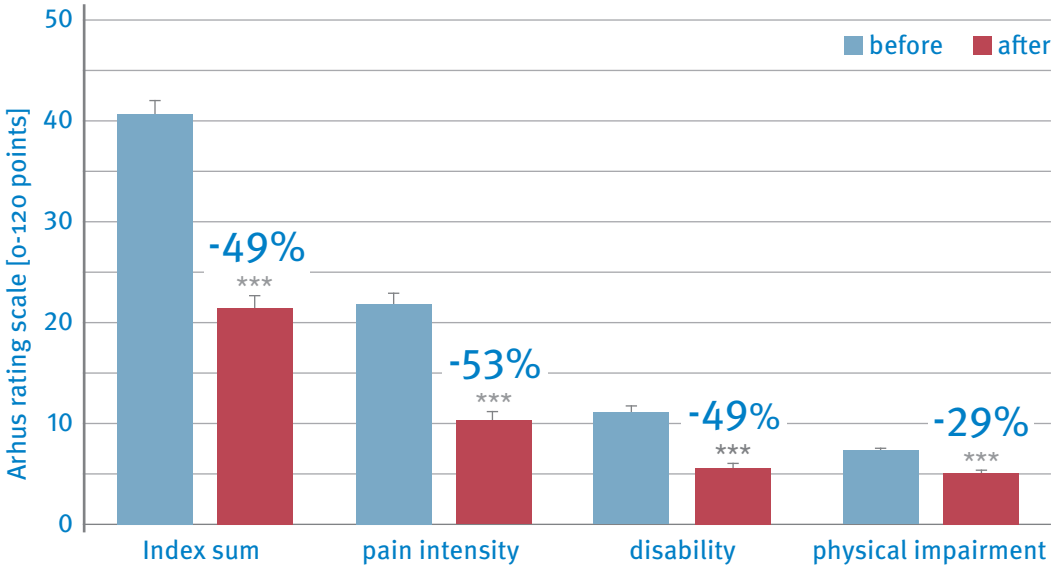

Figure 30. Arhus back pain rating scale before and after 4 weeks of alkaline supplementation[32] *** p ‹ 0.001

- Alkaline treatment (Basica® Vital) additionally to physical therapy also showed positive results in patients with chronic tendonitis and Achilles tendonitis (Fig. 31)[87]

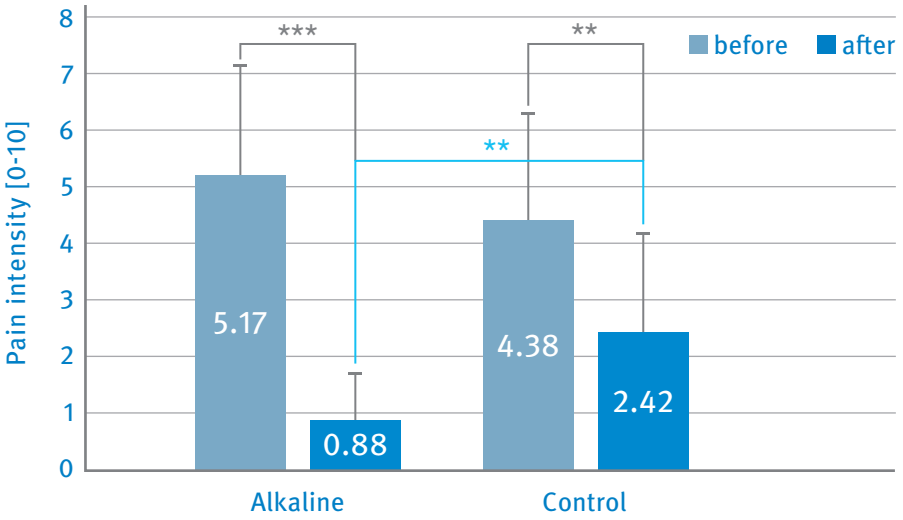

Figure 31. Significantly greater decrease in pain intensity of chronic tendonitis after 8 weeks of alkaline supplementation. ** p ‹ 0.01; *** p ‹ 0.001

RHEUMATIC DISEASES

As acid can trigger pain receptors and increase pain perception, chronic acidosis is proven to facilitate chronic diseases such as arthritis and rheumatism. Joint fluid in inflamed joints has a higher acid (H^+) concentration and a lower pH (Fig. 32): the pH value of joint fluid in patients with rheumatoid arthritis is 7.19[88], while in healthy people it is between 7.4 and 7.8. Moreover, acid concentration in joint fluid was positively associated with several inflammation markers and with a higher clinical knee score (a parameter of locally active disease).

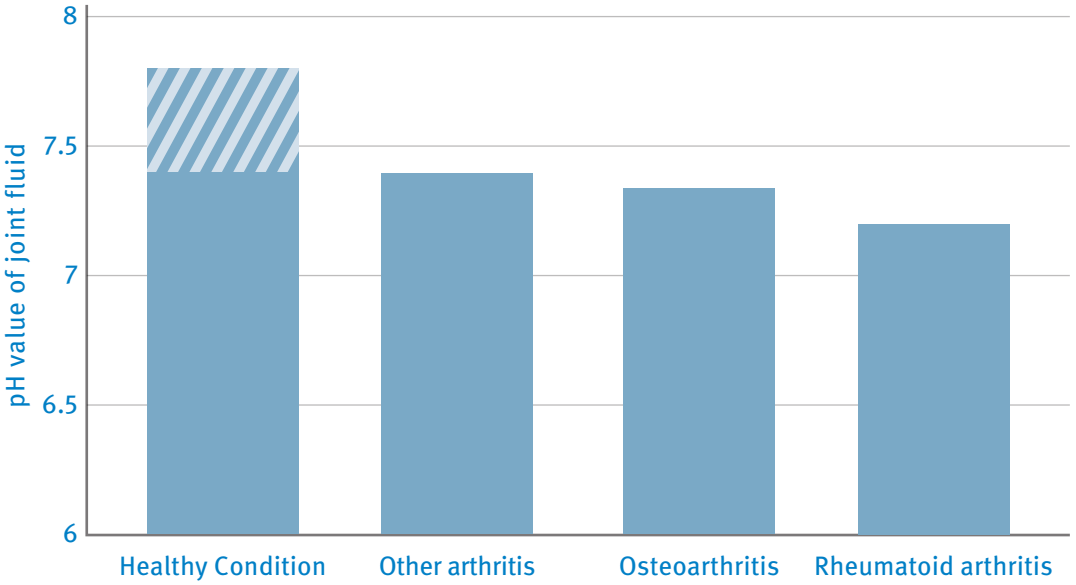

Figure 32. pH values of the synovial fluid in the knee of healthy people and of patients with different forms of arthritis[88]

Alkaline supplementation for 12 weeks (Basica® Vital) significantly improved the symptoms of patients suffering from stable active rheumatoid arthritis for at least two years and receiving long-term medical treatment with non-steroidal anti-inflammatory drugs (NSAID).[89]

- → Significant reduction of the visual analogue scale (VAS) pain index (Fig. 33)
- → Disease Activity Score decreased by 20% in the alkaline supplement group, while there was no significant change in the control group
- → At the end of the study, 16% of patients in the supplementation group reduced medication with steroids or NSAID, and 16% of patients completely abandoned NSAID medication, with no changes in the control group

Due to the potential side effects of chronical NSAID use, alkaline mineral supplementation provides a safe and simple adjuvant treatment option.

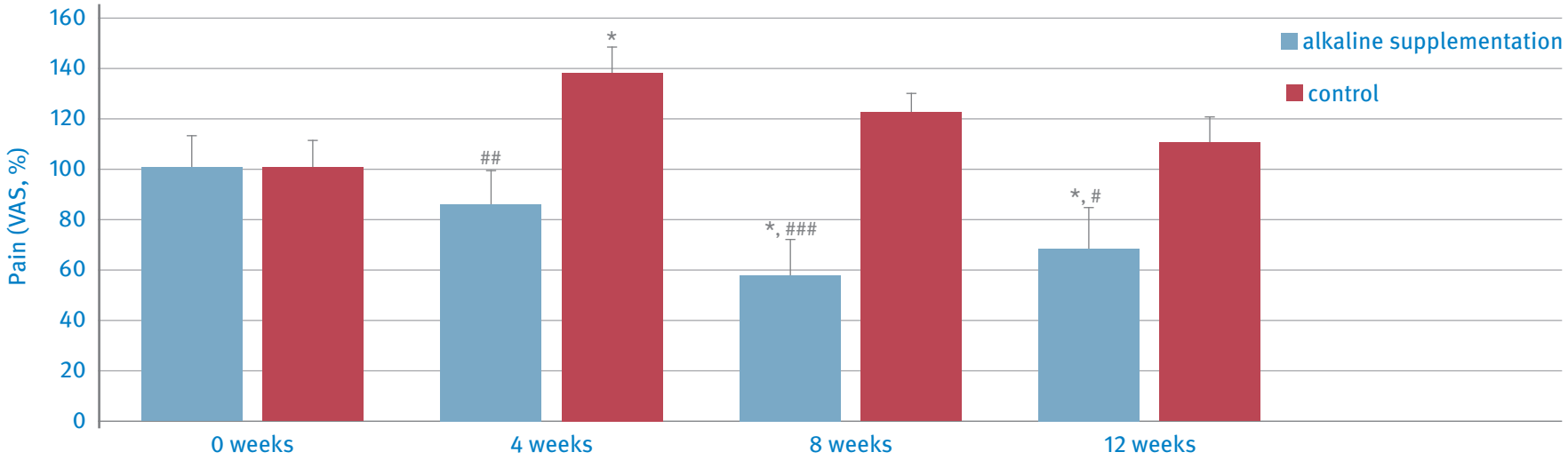

Figure 33. Pain level according to a VAS in rheumatoid arthritis patients.[89]
* p ‹ 0.05, ** p ‹ 0.01 compared to week 0; # p ‹ 0.05, ## p ‹ 0.01, ### p ≤ 0.001 compared to control group

HYPERURICEMIA AND GOUT

Hyperuricemia and gout are characterised by high level of uric acid in the blood. Below a certain limit (6.0 mg/dl), uric acid is soluble in blood. If the value exceeds this limit, uric acid can crystallise, and these urate crystals formed in joints and tissue can result in a gout attack. Gout is manifested as an acute or chronic, extremely painful inflammation of various joints caused by uric acid crystals.

Uricemia is affected by a diet:

- Compared with a highly acidic diet, an alkaline diet results in a significantly higher urine pH (Fig. 34 left), which in turn positively correlates with excretion of uric acid (Fig. 34 right).[90] The more alkaline the urinary pH, the more uric acid is excreted
- Higher renal NAE increases the risk of hyperuricemia by 51–73%[91]
- High dietary acid load increases the risk of hyperuricemia by 21% for PRAL and by 17% for NEAP[92]
- Lower dietary acid load decreases the risk of hyperuricemia by 40% (for PRAL)[93]

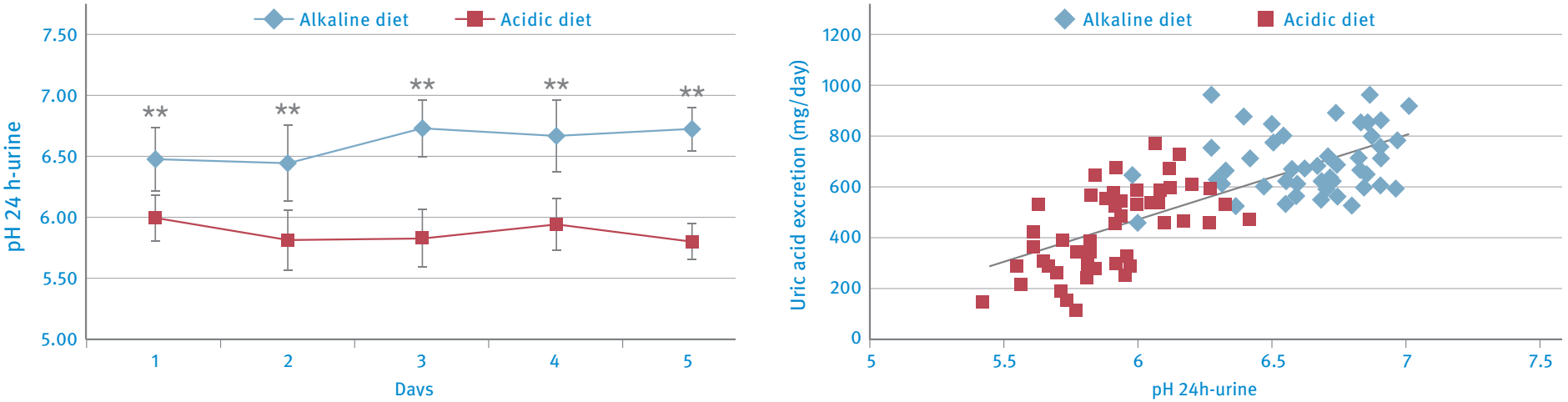

Figure 34. Significantly higher 24-hour urinary pH in probands on an alkaline diet compared to those on an acidic diet (left, ** p < 0.002). An alkaline diet results in greater excretion of uric acid than an acidic diet.[90]

The intake of an alkaline citrate-based supplement in addition to the standard gout treatment with Allopurinol was performed in 70 patients with uric acid serum levels > 7 mg/d[94]:

→ While serum uric acid levels decreased in both groups (monotherapy with Allopurinol and combined therapy with Allopurinol and citrate), only the combined therapy group achieved a significant increase in urinary pH and uric acid clearance (Fig. 35)

→ In a sub-group of patients with impaired kidney function, the additional citrate treatment improved the glomerular filtration rate, i.e. kidney function

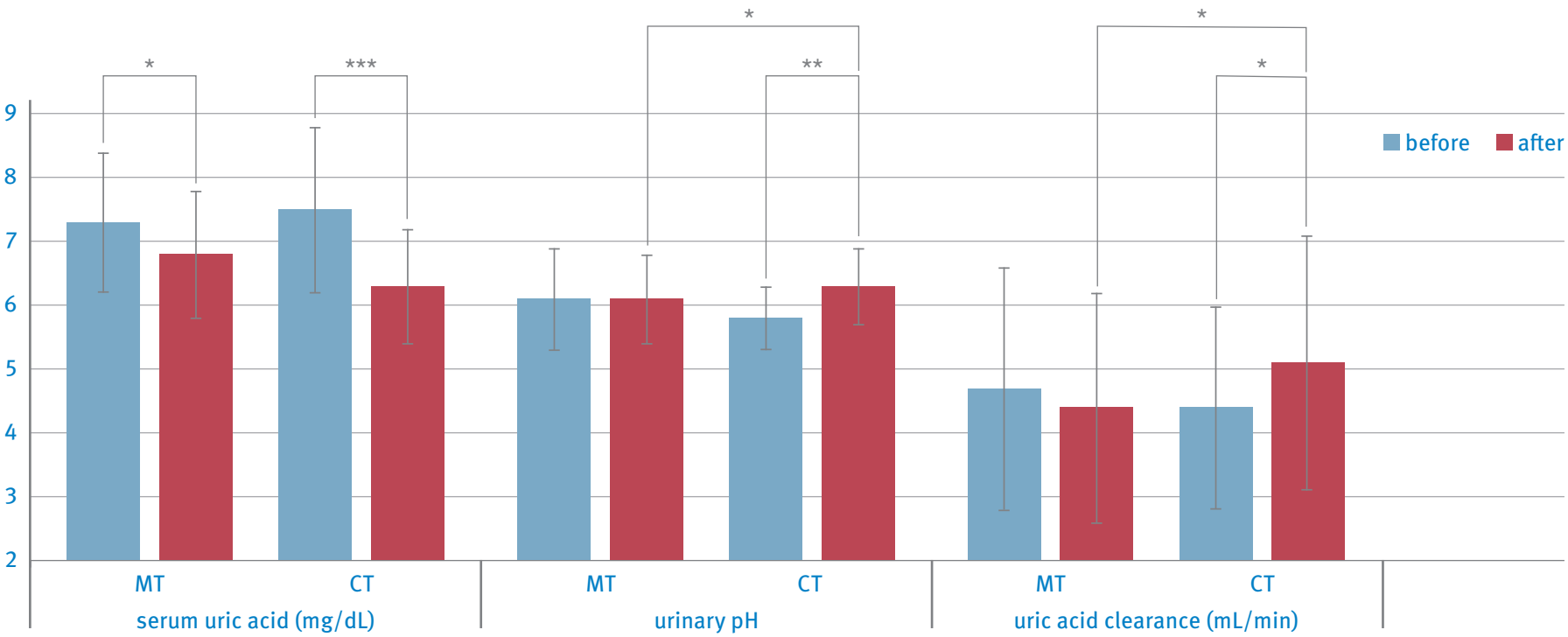

Figure 35. Positive effects of a combined therapy (CT) with Allopurinol + alkaline supplementation compared with monotherapy (MT) with Allopurinol only.
* p ‹ 0.05; ** p ‹ 0.01; *** p ‹ 0.001

OSTEOPOROSIS

Diet and other lifestyle factors contribute to bone and muscle loss. Osteoporosis is an important health problem for the aging population. In adults who are unable to excrete the daily dietary acid load, the excess acid is buffered by bone.

The mechanisms by which excess of acid affects bone have been well defined[95]:

- Decrease of activity of osteoblasts (bone-building cells)
- Excessive activation of osteoclasts (bone-resorbing cells)
- Direct demineralisation of the bone

Increased acid load has pronounced negative effects on bone and bone metabolism:

- Higher NEAP is associated with lower trabecular bone score[96]
- Higher PRAL leads to 1.5–3.2% decrease in bone density in heel bone[77] and total femur[97]
- Consequently, higher PRAL leads to a 33% (in men) or 21% (in women) higher hazard of hip, wrist and spine fractures[77]
- U-shaped association between PRAL and the risk of osteoporotic fractures: high alkaline diet increased the risk by 73%, high acidic diet by 91%[97]

Positive effect of an alkaline diet on bone metabolism:

- Low NEAP has a positive effect on the bone density of the cervical and lumbar spine[98]
- An alkaline Mediterranean diet reduces risk of hip fracture by 21%[99]
- Higher alkaline vegetable intake decreases urinary acidity and bone resorption markers in overweight and obese adults[100]

Alkaline supplementation improves bone parameters:

- Alkaline citrate supplementation in women with osteopenia (early stage of osteoporosis) reduces osteoporosis-related biomarkers of bone turnover[101, 102]
- Post-menopausal women with osteopenia that received a calcium/vitamin D substitute and either the neutral salt potassium chloride or the alkaline salt potassium citrate showed a significant difference in bone density at lumbar spine, femoral neck and hip (Fig. 36), which continued to decrease in the potassium chloride group but markedly increased in the citrate group[103]
- A similar increase in bone density at lumbar spine, femoral neck, hip and total body was achieved by the addition of potassium citrate to a calcium/vitamin D substitute, even in healthy people without osteoporosis (Fig. 37)[104]
- Meta-analyses show that alkaline supplementation results in improved calcium balance, reduced bone resorption, and significantly increased BMD in femoral neck, lumbar spine, and total hip[105, 106]

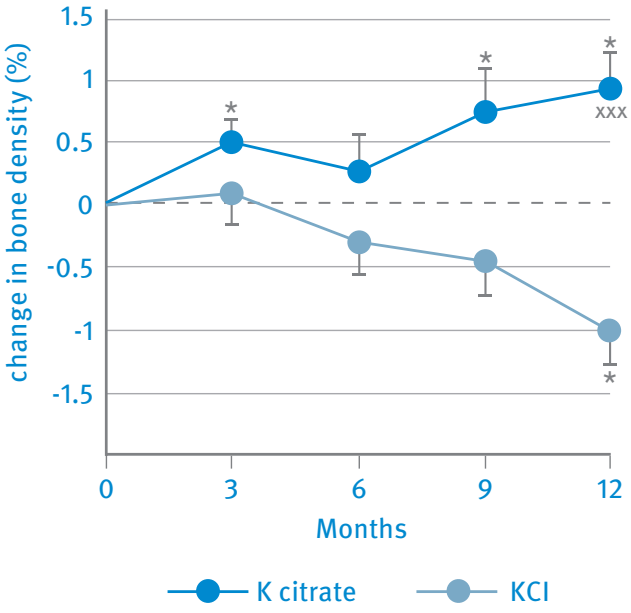

Figure 36. Increase in bone density at lumbar spine (L2–L4) in women with osteopenia after taking a K citrate supplement for one year.[103]
* p < 0.05 compared to month 0; xxx p < 0.001 compared to placebo

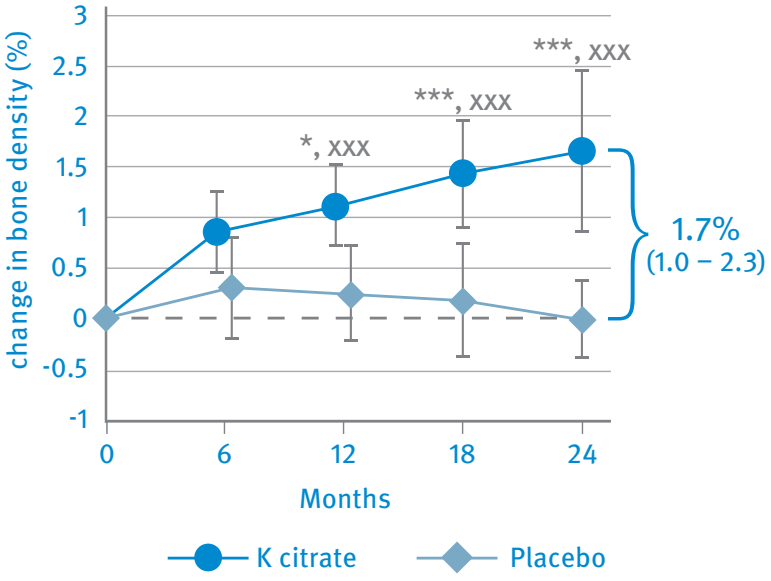

Figure 37. Increase in bone density at lumbar spine (L2–L4) in healthy men and women after taking a K citrate supplement for 2 years.[104]
* p < 0.05, *** p< 0.001 compared to month 0; xxx p < 0.001 compared to placebo

STRESS, TIREDNESS AND EXHAUSTION

Poor general well-being, with complaints such as tiredness and exhaustion, can be caused by chronic acidosis.

- → The pH value shifts towards the acidic range and exhausted buffer systems are not optimal "working conditions" of enzymes, which are required for proper functioning of all metabolic processes, including energy production
- → Metabolic imbalance caused by chronic acidosis manifests itself as tiredness, diminishing concentration and reduced performance

Higher dietary acid load is associated with:

- → low physical activity and exhaustion in older women[79]
- → higher concentration of potentially bioactive glucocorticoids (cortisol, cortisone) in lean women[107]
- → higher glucocorticoid secretion and potentially bioactive free glucocorticoids in healthy children[23]

Alkaline supplementation reduces tetrahydrocortisol (THF) levels (Fig. 38).[108]

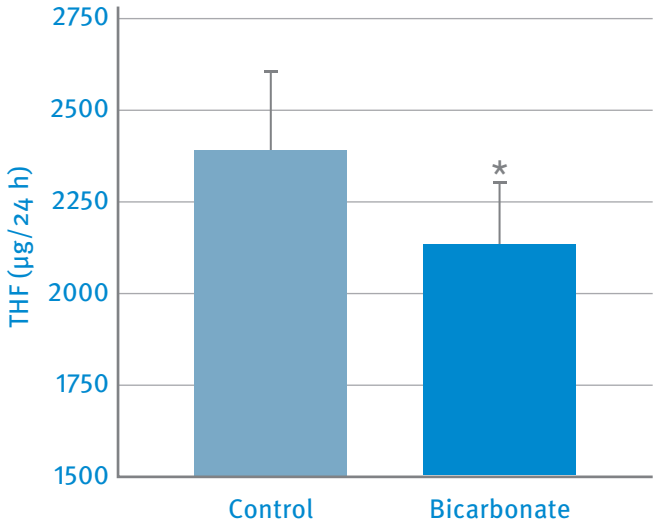

Figure 38. Significant decrease in the THF concentration in 24-hour urine following alkaline supplementation[108] * $p < 0.05$

Alkaline supplementation (Basica® Direct) improves oxidative carbohydrate metabolism and acid-base metabolism with a positive effect on the cell energy metabolism[109]:

- → Reduction of plasma HCO_3^- concentrations after a protein-rich test meal was prevented by alkaline supplementation, due to improved buffering capacity (Fig. 39)
- → Baseline peripheral muscle pH increased from 7.57 ± 0.03 to 7.63 ± 0.03 after 4 weeks' supplementation in the verum group but did not change in the placebo group (7.60 ± 0.02 vs. 7.58 ± 0.02)
- → Increase in blood glucose and insulin concentration after a protein-rich test meal was lower following 4 weeks' treatment with the alkaline supplement compared to the placebo
- → In muscle, postprandial glucose uptake and pyruvate concentration (Fig. 40) were significantly higher by alkaline supplementation improving aerobic glucose oxidation and therefore energy metabolism

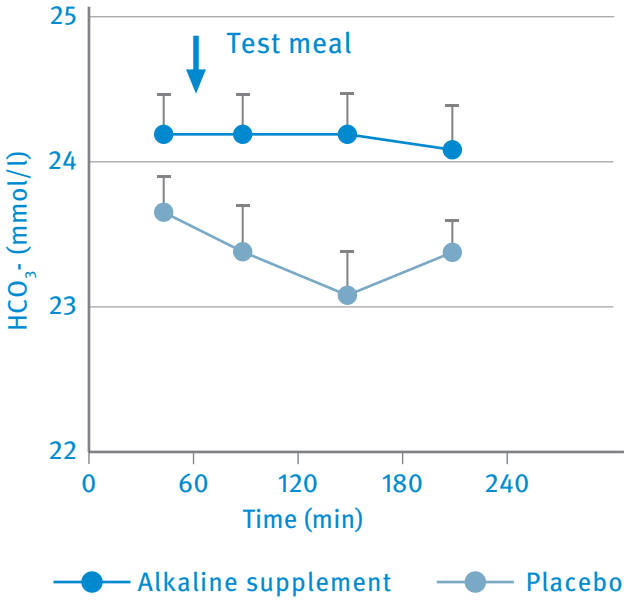

Figure 39. Significant increase in blood bicarbonate concentration following 4-week course of the alkaline supplement compared to the placebo

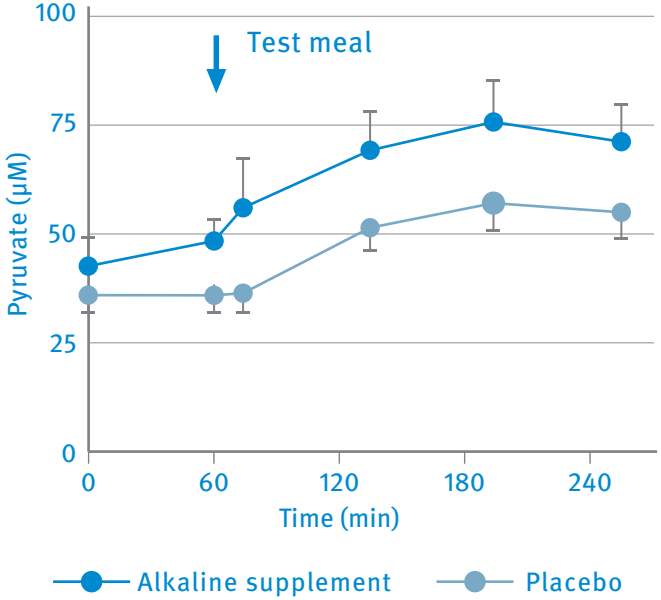

Figure 40. Significant increase in pyruvate concentration in the muscle after 4 weeks of alkaline supplementation compared to the placebo

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