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ARTICLE

Effects of dietary protein-load and alkaline supplementation on acid–base balance and glucose metabolism in healthy elderly

Michael Boschmann[1,2] · Nikoletta Kaiser[1] · Anja Klasen[1] · Lars Klug[1,2] · Anja Mähler[1,2,3] · Andreas Michalsen[4] · Juergen Vormann[5] · Tanja Werner[6] · Rainer Stange[4]

Abstract

Background/Objectives Metabolism is controlled by macro- and micronutrients. Protein-rich diets should lead to latent acidosis at tissue level with further negative implications. Food supplements with alkaline salts are available and popular pretending to prevent these changes.

Subjects/Methods Within a randomised double-blind placebo-controlled trial we tested the hypotheses that (1) a 4-week protein-rich diet induces a latent tissue acidosis and (2) an alkaline supplement can compensate this. Acid–base balance and important metabolic parameters were determined before and after 4 weeks of supplementation by peripheral blood samples, indirect calorimetry and muscle microdialysis before and after a protein-rich test meal.

Results Fourty volunteers were randomised 1:1 to either verum or placebo supplements. Protein-rich diet by itself did not significantly affect acid–base balance. Alkaline supplementation increased plasma bicarbonate concentration without changing pH. Postprandial increases in serum glucose and insulin tended to be lower for verum vs. placebo. Resting and postprandial energy metabolism, and carbohydrate and fat oxidation did not differ significantly before and after supplementation in both groups. In muscle, postprandial glucose uptake and aerobic glucose oxidation were significantly higher for verum. In addition, verum significantly increased serum magnesium concentrations.

Conclusions Four weeks of protein-rich diet did not significantly influence acid–base balance. However, alkaline supplementation improved systemic and tissue acid–base parameters and oxidative glucose metabolism.

Introduction

Acid–base balance (ABB) has an important role in nutrition sciences, internal and specifically emergency and intensive care medicine, but also in complementary and integrative medicine (CM, IM). ABB deserves attention, when significant systemic disturbances are observed, for example, ketogenic acidosis in type 1 diabetes, severe renal or respiratory insufficiency. However, within IM, it is claimed that more- subtle disturbances of ABB might have a promoting influence on chronic degenerative or inflammatory diseases. It is assumed that a Western style diet, a lack of physical activity and possible toxic influences finally lead to chronic latent acid overload, which might affect tissues even if blood parameters of ABB are still unchanged.

Western style diet (WD) is beside others characterized by high intake of animal rather than plant-derived proteins. Animal-derived proteins are rich in sulfur containing amino acids leading to generation of acidic sulfates during digestion and metabolism. In addition, WD is characterized by a

✉ Rainer Stange
r.stange@immanuel.de

1 Experimental and Clinical Research Center (ECRC) – a joint cooperation between Charité - Universitätsmedizin Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany

2 Berlin Institute of Health, Berlin, Germany

3 DZHK (German Centre for Cardiovascular Research), Berlin, Germany

4 Department for Internal and Integrative Medicine, Charité - Universitätsmedizin Berlin and Immanuel Krankenhaus, Berlin, Germany

5 Institut für Prävention und Ernährung, Ismaning, Germany

6 NuOmix Research k.s. Applied Nutriomic Research, Martin, Slovakia

large consumption of highly processed foods rich in phosphates, delivering protons while metabolized [1, 2]. In contrast, fruits and vegetables have higher contents of organic mineral salts (citrate or malate), which deliver bicarbonate as alkalizing agent when being metabolized [2].

Different algorithms have been suggested to estimate the overall nutritive acid–base load [3–5]. The concept of PRAL (potential renal acid load) has been well established to calculate acid–base load of single food items [6, 7]. PRAL estimates the need for urinary excretion of fixed acids. PRAL together with the endogenous production of organic acids defines net acid excretion (NAE). This algorithm is independent of the maintenance of blood pH mainly via carbon dioxide exhalation. Mean PRAL values have been estimated to +19.6, −1.5 and −15.2 mEq/d for omnivores, vegetarians and vegans, respectively, indicating an alkalizing effect of the last one. So far, PRAL has been correlated to the risks for type 2 diabetes, osteoporosis and progression of chronic kidney disease (CKD). It has been shown in at least seven RCTs and one systematic review, that supplementation with alkalizing additives comparable to the one used in this trial, is able to slow down progression of CKD [8, 9].

NAE is usually defined as the total ability to metabolize acidic load. It has been shown that NAE rapidly decreases in healthy persons after the age of 50 [10]. Thus, the hitherto unproven assumption in IM, that acid overload contributes to chronic disease, could have a scientific basis in the decrease of NAE, while at the same time, acid load by WD is not diminished with age.

Alkaline supplements are popular among healthy people and believed to optimize metabolism and fitness and prevent chronic disease by improving acid–base balance. Protein-rich diets may end in chronic latent metabolic acidosis and impaired organ structure and function in bones and skeletal muscle.

With this trial, we tested the hypotheses that (1) a 4-week protein-rich diet affects acid–base and other elementary parameters of systemic and local (skeletal muscle) metabolism and (2) an alkaline supplementation with a commercial product (Basica® Direkt, Pharmazeutische GmbH, Ismaning, Germany) compensates this diet-induced changes.

Methods

Design

This was a double-blind, two-armed clinical trial (registered at clinicaltrials.gov as NCT04229069) where healthy probands were randomized in a 1:1 manner to either verum (alkaline supplement) or placebo. Random allocation of patients was based on a computer-generated list for multiple treatments (balanced permutation for 40 subjects). An external person not involved in the study generated the list and sequentially numbered product containers. All people involved in the study (patients, healthcare providers, data collectors and outcome assessors) were blinded to the treatment sequence [11]. Approval was given by the ethical committee of Charité - Universitätsmedizin Berlin (EA1-292-12). Written informed consent was obtained from all probands prior to randomization.

Probands

Key inclusion criteria were basically healthy women or men age 60–70 years, body mass index 20.0–29.9 kg/m², written informed consent before study entry. Key exclusion criteria were sorbitol intolerance, use of anti-acidic drugs or nutritional supplements, vegetarians or vegans, participation in weight reducing programs, specific diets, changes in body weight >2 kg within the last 3 months, higher grade renal insufficiency (CKD > stage 2, resp. serum creatinine >2.0 mg/dl), anti-coagulation, alcohol and/or drug abuse, cardiovascular, pulmonary, hepatic, metabolic, endocrine or gastrointestinal diseases, antibiotic therapy over >7 days within the last 3 months, smoker.

Protocol

Probands were instructed to stay on a protein-rich diet for 4 weeks by specific nutritional advice from a clinical nutritionist. In addition, probands should take an alkaline supplement stick of Basica® Direkt (Protina Pharm. GmbH, Ismaning, Germany) or a placebo stick twice a day. Two sticks contained 240 mg Ca (as citrate), 400 mg Mg (as citrate and oxide), 5 mg Zn, 50 µg Mo, 40 µg Cr and 30 µg Se according to manufacturer's information. Basica® Direkt (further referred as verum) and placebo, equal in weight, colour and size of granules and wrapping, were prepared by the manufacturer.

Before and after the intervention, response of acid–base parameters and systemic and muscle metabolism were tested after a protein-rich test meal (250 g curd: 720 kJ [170 kcal], 0.75 g fat [4% of total energy], 10 g carbohydrates [24%] and 30 g protein [72%]) according to manufacturer's information. For testing, probands reported in our clinical research unit at 08:00 AM after at least a 12 h overnight fast and a sleeping phase of at least 7 h. At least one day before testing, probands were asked to abstain from caffeine- and alcohol-containing beverages and foods, and from strenuous exercise. Metabolic response was measured by indirect calorimetry and microdialysis for systemic and muscle metabolism, respectively. In addition, venous and capillary blood samples were taken. For detailed information on the protocol see Fig. 1.

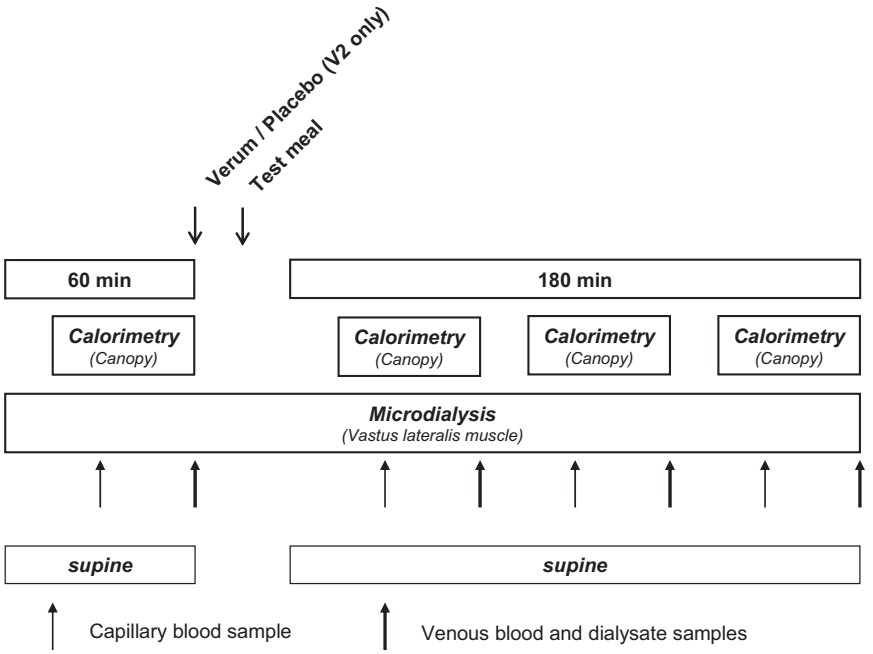

Fig. 1 Study protocol before (V1) and after (V2) 4 weeks on a protein-enriched diet and randomized supplementation of alkaline salts (verum) or placebo.

Calorimetry

By using a canopy calorimeter (Quark RMR, COSMED Deutschland GmbH, Fridolfing, Germany), carbon dioxide production ($\dot{V}CO_2$) and oxygen consumption ($\dot{V}O_2$) were measured for calculating resting and postprandial energy expenditure (EE) and respiratory exchange ratio (RER = $\dot{V}CO_2/\dot{V}O_2$) according to the equations by Ferrannini [12]. RER was used for assessing changes in carbohydrate and fat oxidation rates. Before starting calorimetry, the calorimeter was gas-(automatically) and flow-calibrated (manually). Intraindividual variation of $\dot{V}CO_2$ and $\dot{V}O_2$ was <5%.

Microdialysis

A microdialysis probe was implanted into the right vastus lateralis muscle. Then, probe perfusion was started with lactate-free Ringer's solution ethanol at a flow rate of 2 µl/min using a microdialysis pump (both, probe M 71 with a molecular cut-off 100,000 kDa and pump (M 107) by µDialysis AB, Stockholm, Sweden). Ethanol (EtOH, 50 mmol/l) was added to the perfusate to assess tissue perfusion (ethanol dilution technique) [11]. According to Fick's principle, a decrease in $[EtOH]_{outflow}/[EtOH]_{inflow}$ ratio is equivalent to an increase in tissue perfusion and vice versa. After starting perfusion, a 60 min period was allowed for tissue recovery and baseline calibration [11].

Assays

Blood samples were processed immediately in a centrifuge at 4.0 °C, aliquoted and stored at −80.0 °C until analysis. Blood glucose, insulin and other routine parameters were analysed according to international standards; perfusate and dialysate ethanol by a standard spectrophotometric enzymatic assay; dialysate glucose, lactate, pyruvate and glycerol by an automated colorimetric assay (ISCUS^{flex}, µDialysis, Stockholm, Sweden). In situ dialysate recovery for dialysate metabolites was about 50%, as assessed by near-equilibrium dialysis. Intraindividual variation of muscle dialysate metabolite concentrations was <3%.

Capillary blood pH, pO_2, pCO_2, HCO_3^- and dialysate pH were measured by an automated analyzer (Radiometer ABL800 flex, Radiometer Medical ApS, Bronshoj, Denmark).

Statistics

All evaluations were done as descriptive statistics with no 0-hypothesis and no correction for multiple testing. Data are expressed as means ± SD for group comparisons (baseline anthropometrics and food questionnaire, Tables 1 and 2) and as means ± SEM for repeated measurements after the test meal (Figs. 3–5). For statistical analysis of all data, standard statistical software packages were used (InStat, Version 4.0; Graphpad Software Inc., San Diego, CA, USA). For comparing baseline characteristics of patients, the non-parametric Mann–Whitney U-test for unpaired samples was used. For comparing the response curves for plasma glucose and insulin, calorimetric data, and dialysate glucose, lactate, pyruvate and glycerol between treatment groups after the test meal, global fitting was used. This test is a non-linear regression method comparing discrepancies between the fitting equation of one curve (reference or

Table 1 Anthropometric data of probands.

	Verum	Placebo
Sex (M/F)	3 /17	6/14
Age (years)	66 ± 3	66 ± 3
Weight (kg)	70.0 ± 10.0	70.6 ± 7.7
BMI (kg/m^2)	25.5 ± 2.9	25.5 ± 2.5
Waist (cm)	93 ± 8	92 ± 10
Hip (cm)	104 ± 7	102 ± 7
Waist/hip ratio	0.90 ± 0.08	0.90 ± 0.09

Data are given as means ± SD.

Table 2 Probands' daily intake of calories, macro-nutrients, magnesium, calcium and fluid before the trial, based on a food questionnaire.

	Verum group	Placebo group
Energy intake (kcal/d)	1980	2050
Fat intake (g/day)	75	88
Fat intake (% energy)	33.3	33.7
Carbohydrate intake (g/d)	209	196
Carbohydrate intake (% of total energy)	43.9	41.7
Protein intake (g/d)	81	81
Protein intake (% of total energy)	17.1	16.1
Protein intake (g/d × kg BW)	1.2	1.2
Fluid intake (l/d)	2.8	2.6
Calcium (mg/d)	960	890
Magnesium (mg/d)	370	350

All data given as mean.

placebo group) and another one (active or verum group). A p-value < 0.05 was considered to indicate statistical significance.

Results

Probands

A total of 40 probands could be recruited and randomly assigned to verum or placebo. All completed the study (see Fig. 2). Probands in each group did not differ regarding anthropometric measures (see Table 1), concomitant diseases, medication (mainly thyroid hormone supplements), energy and fluid intake (see Table 2).

Acid–base balance

Capillary blood pH was 7.42 in both groups before the test meal and did not change after the test meal. The same was observed in both groups after the 4-week supplementation.

For verum and V1, HCO_3^- decreased from 23.9 ± 0.3 to 23.2 ± 0.4 mmol/L within 60 min postprandially, but returned thereafter to 23.6 ± 0.3 mmol/L. In V2, HCO_3^- was 24.2 ± 0.3 mmol/L before the test meal and did not change significantly after the test meal ($p = 0.0062$, V1 vs. V2, global fitting).

For placebo, HCO_3^--response to the test meal did not differ significantly between V1 and V2. In V1, HCO_3^- decreased from 23.8 ± 0.2 to 23.0 ± 0.3 mmol/L within 120 min postprandially and remained at that level until the end of testing. The same changes were observed in V2.

Serum glucose and insulin

For verum in V1, glucose increased within 30 min postprandially from 94 ± 5 to 100 ± 6 mg/dl, followed by return to baseline. In V2, glucose increased moderately from 87 ± 4 to 93 ± 4 mg/dl within 90 min postprandially followed by a return to baseline ($p = 0.059$, V1 vs. V2, Fig. 3). For placebo in V1, glucose increased within 30 min postprandially from 86 ± 3 to 94 ± 3 mg/dl, followed by a return to baseline. In V2, glucose followed the same pattern as before (Fig. 3).

For verum in V1, insulin increased within 30 min postprandially from 8 ± 1 to 31 ± 5 µU/ml followed by steady return to baseline. In V2, insulin increased within 30 min postprandially from 7 ± 1 to 25 ± 4 µU/ml followed by steady return (Fig. 3). For placebo in V1, insulin increased within 30 min postprandially from 6 ± 1 to 25 ± 2 µU/ml, followed by return to baseline. In V2, insulin followed a similar pattern as before (Fig. 3).

Calorimetry

Energy expenditure increased about 1.2-fold after the test meal in both groups without significant differences before and after supplementation. RER increased also in both groups without significant differences before and after supplementation. The increased values remained until the end of testing (Fig. 4).

Muscle dialysate metabolites

Baseline ethanol ratio as an indicator for tissue perfusion was 0.21 ± 0.01 and 0.22 ± 0.02 in the verum group, and 0.20 ± 0.01 and 0.22 ± 0.02 in the placebo group in V1 and V2, respectively. In the verum group, EtOH ratio increased slightly within 60 min postprandially followed by a decrease to baseline values until the end of testing in both V1 and V2 (data not shown). In the placebo group, EtOH ratio showed almost the same time course in V1 and V2 (data not shown). However, in the early postprandial phase, EtOH ratio was slightly higher in V2 ($p = 0.037$).

Baseline pH increased from 7.57 ± 0.03 at V1 to 7.63 ± 0.03 at V2 in the verum group (ns) but did not change in the placebo group (7.60 ± 0.02 at V1 vs. 7.58 ± 0.02 at V2).

Baseline glucose levels were 1.77 ± 0.10 and 1.71 ± 0.10 mmol/l in the verum group, and 1.67 ± 0.11 and 1.70 ± 0.09 mmol/l in the placebo group at V1 and V2, respectively. In the verum group, glucose increased significantly in V1 but rather moderately in V2 shortly after the test meal followed by an early return to baseline values ($p = 0.0664$, V2 vs. V1, Fig. 5). In the placebo group, glucose did not change significantly after the test meal in V1 and V2, respectively (Fig. 5).

Baseline lactate levels were 0.76 ± 0.07 and 0.80 ± 0.09 in the verum group and 0.72 ± 0.08 and 0.74 ± 0.07 mmol/l in the placebo group in V1 and V2, respectively. In the verum group, lactate increased significantly within 60 min postprandially in both V1 and V2, but remained then at that level until the end of testing with values being slightly higher in V1 vs. V2 (Fig. 5). In the placebo group, lactate increased also early after the test meal in both V1 and V2 followed by a further increase in V1 but not in V2 (Fig. 5).

Baseline pyruvate levels were 33 ± 3 µmol/l in the verum and 36 ± 4 µmol/l in the placebo. In the verum group and V1, pyruvate increased about 1.7-fold within 120 min after the test meal. In V2, baseline dialysate pyruvate levels were already higher (43 ± 6 µmol/l) but increased also about 1.7-fold after the test meal ($p < 0.0001$, V2 vs. V1, Fig. 5). In the placebo group, baseline values and postprandial increases of pyruvate (1.7-fold) did not differ significantly between V1 and V2 (Fig. 5).

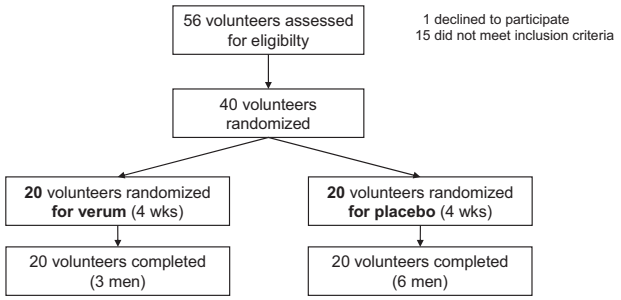

Fig. 2 CONSORT flow diagram of probands.

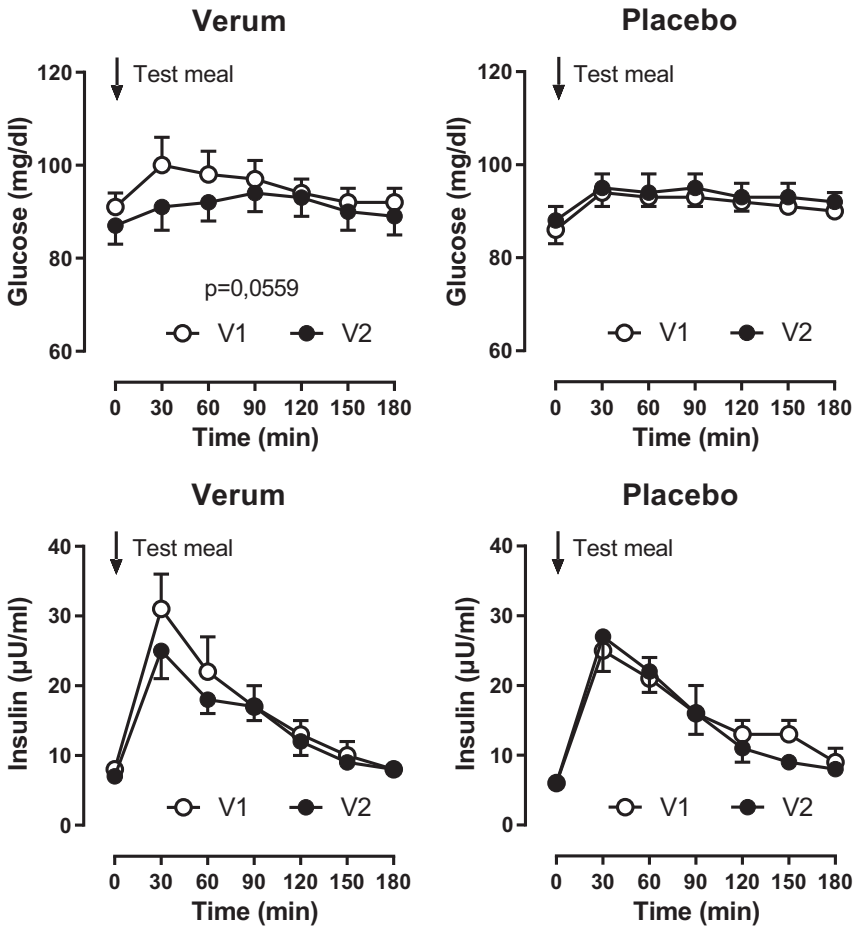

Fig. 3 Serum glucose and insulin response after a protein-rich test meal before (V1) and after (V2) 4 weeks on a protein-enriched diet and with supplementation of alkaline salts (Verum) or placebo. Data are given as means ± SE, $n = 20$ per group and all measurements.

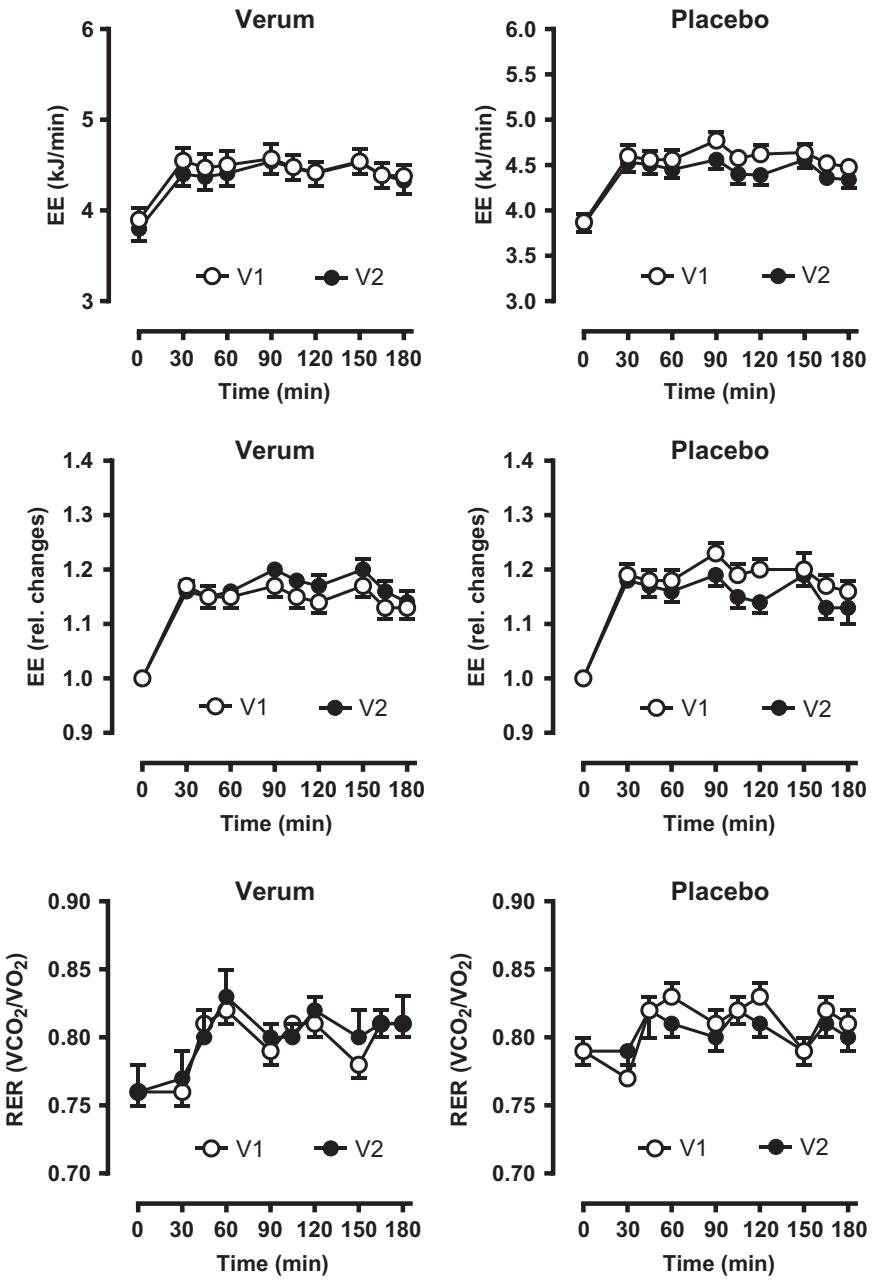

Fig. 4 Absolute (top) and relative (middle) changes in energy expenditure (EE) and also changes in respiratory exchange ratio (RER, VCO_2/VO_2, bottom) after a protein-rich test meal before (V1) and after (V2) 4 weeks on a protein-enriched diet and with supplementation of alkaline salts (Verum) or placebo. A RER of 1.00 indicates 100% carbohydrate oxidation whereas a RER of 0.7 indicates 100% fat oxidation. There were no significant differences between these parameters within the groups before and after supplementation. Data are given as mean ± SE, $n = 20$ for both groups.

Baseline dialysate lactate-to-pyruvate ratio was 25 ± 3 and 21 ± 2 in the verum group, and 22 ± 2 and 23 ± 3 in the placebo group in V1 and V2, respectively. In the verum group, this ratio did not change after the test meal in V1, however, it decreased significantly to 15 ± 2 in V2 ($p <$ 0.0001, V2 vs. V1, not shown). In the placebo group, lac-to-pyr ratio did not change significantly after the test meal, neither in V1 nor in V2 (not shown).

Baseline glycerol levels were 50 ± 3 and 55 ± 5 µmol/l in the verum group, and 48 ± 4 and 49 ± 4 µmol/l in the placebo group in V1 and V2, respectively. After the test meal, dialysate glycerol decreased significantly in both groups with no significant differences between V1 and V2 in each group (not shown).

Magnesium

Serum concentrations showed significant increase for verum from 0.82 ± 0.05 mmol/l before supplementation to 0.86 ± 0.08 mmol/l after ($p = 0.03$). This was not observed for placebo (0.83 ± 0.08 mmol/l, resp. 0.82 ± 0.06 mmol/l, n.s.).

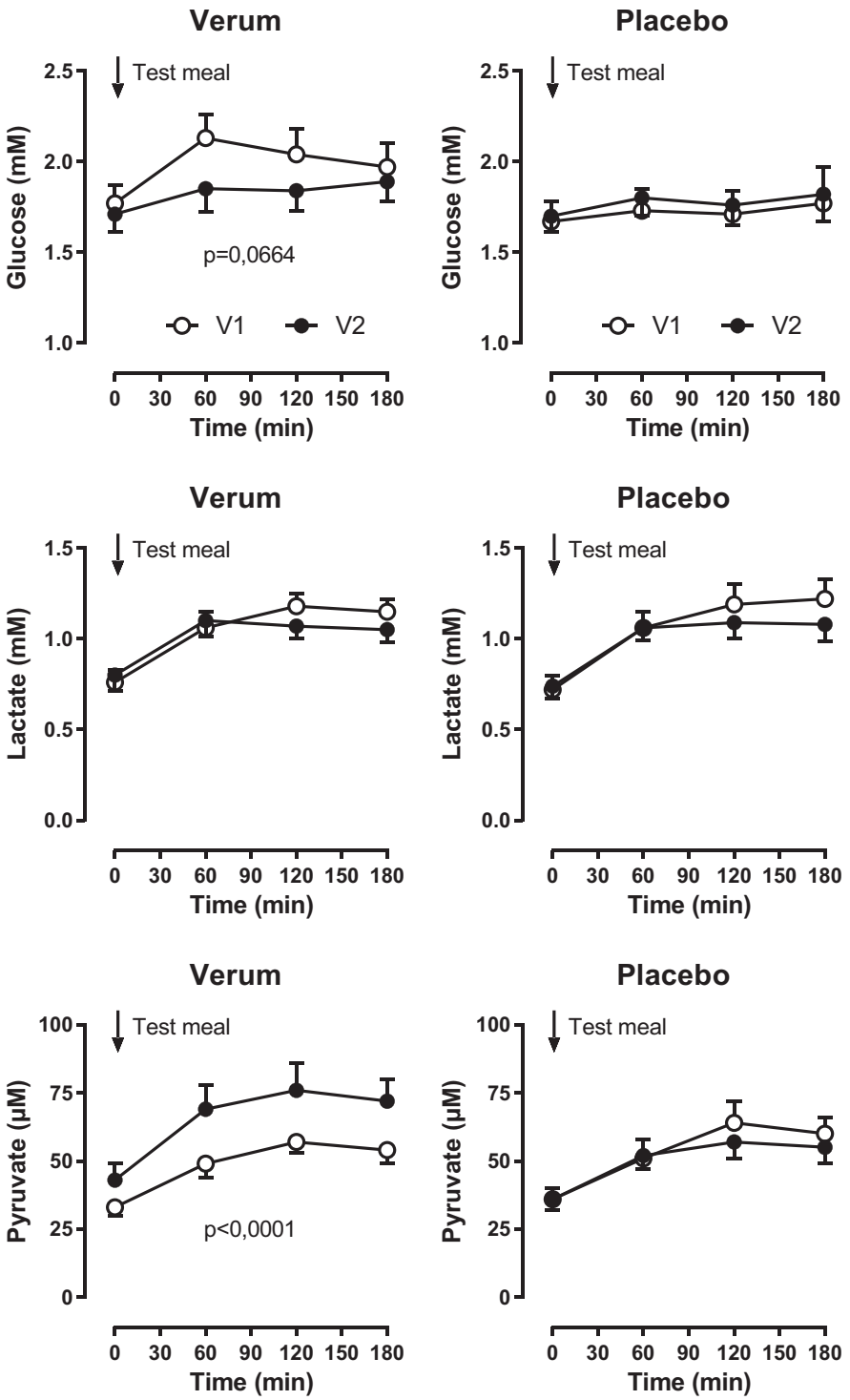

Fig. 5 Muscle dialysate glucose, lactate and pyruvate response after a protein-rich test meal before (V1) and after (V2) 4 weeks on a protein-enriched diet and with supplementation of alkaline salts (Verum) or placebo. Data are given as means ± SE, $n = 20$ per group and all measurements.

Discussion

In this study, effects of a 4-week protein-rich diet on systemic and local muscular acid–base parameters and metabolism after overnight fasting were investigated. Furthermore, it was tested with placebo control, whether an alkaline supplementation (Basica® Direkt) would affect these parameters. In addition, before and after supplementation, the response to a single protein-rich test meal was recorded.

As expected, blood pH was not influenced by any intervention. However, reduction of plasmatic HCO_3^- concentrations after the test meal was prevented by alkaline supplementation, probably due to improved buffering capacity.

The protein-rich test meal led to a strong increase in postprandial thermogenesis. After supplementation it tended to be higher in the verum group but lower in the placebo group. Postprandial thermogenesis was accompanied by an increased RER indicating an increased carbohydrate oxidation rate, which tended to be higher under verum but lower under placebo after the intervention.

Contrary to our hypothesis, acid–base parameters were rather moderately affected by the protein-rich diet. The recommended daily protein intake during the trial was about 1.2 g per day and kg body weight, which is about 50% above the recommended daily intake. However, uptake of alkaline foods (vegetables and fruits) might have compensated the protein-associated acid load.

The beneficial effects of dietary protein on muscle health in older adults continue to be refined. Results from muscle protein anabolism, appetite regulation and satiety research support the assumption that meeting a protein threshold (~30 g/meal) represents a promising strategy for middle-aged and older adults concerned with maintaining muscle mass while controlling fat mass [13].

However, a 10-day high-protein diet (1.5 g/kg as lean meat) raised urinary nitrogen excretion in older healthy volunteers, which could be attenuated by supplementation with up to 90 mmol/d $KHCO_3$ [14]. In rats, a long-term intake of a high-protein diet induced a mild metabolic acidosis characterized by hypercalciuria, hypermagnesuria and hypocitraturia, which could also be neutralized by $KHCO_3$ [15]. Chronic mild metabolic acidosis is common among older adults, and limited evidence suggest that it may contribute to insulin resistance and type 2 diabetes mellitus [16]. In a double-blinded placebo-controlled study on 153 ambulatory, non-diabetic adults aged 50 years and older, a 3-month supplementation with bicarbonate (either as potassium or sodium salt) reduced urinary net acid excretion but had no effect on fasting glucose, serum insulin, or HOMA-IR [16].

The metabolic outcome or effects on cardiometabolic risk factors may depend also on the dietary protein source. Longer-term dietary supplementation with whey protein might have a potential to improve glucose metabolism by increasing levels in some incretins such as glucagon-like peptide 1 (GLP-1) or glucose-dependent insulinotropic polypeptide (GIP) [17]. However, whey protein plus bicarbonate supplement had little effects on structural and proteolysis marker immunopatterns in skeletal muscle disuse of young healthy men during 21 days of bed rest [18]. Also, metabolic acidosis itself can enhance the rate of muscle protein degradation, at least in patients with chronic renal failure, whereas alkaline diets favour lean tissue mass in older adults [19, 20].

The increase in plasma glucose, in turn, leads to an increased insulin secretion. Insulin, again, stimulates glucose uptake into organs such as muscle by activating glucose transporter 4 (Glut 4). This is reflected by the reduced postprandial increase in muscle dialysate (and hence interstitial) glucose after supplementation indicating an increased cellular glucose uptake.

The alkaline supplement contained 400 mg/d magnesium. It has been shown that low dietary magnesium intake and low serum magnesium concentrations are related to the development of insulin resistance and/or type 2 diabetes [21–23]. A recent meta-analysis of randomized, double-blind controlled trials showed that in type 2 diabetes oral magnesium supplementation (median dose 360 mg/d) over 4–16 weeks reduced plasma glucose concentrations [24].

Strenghts and limitations

Strength of this study is that tissue responses to the test meal before and after a placebo-controlled supplementation could be measured by microdialysis in addition to indirect measures in blood, urine or by exhalation. In addition to acid–base parameters, several metabolic parameters were measured, reflecting for the first time specifically carbohydrate metabolism under conditions of alkaline supplementation.

However, our study is limited by the small number of participants and the short period of supplementation.

Conclusion

In elderly healthy probands, a 4-week protein-rich diet might not significantly challenge resting systemic and tissue acid–base parameters after overnight fasting. However, during 3-h response after a defined metabolic stress by protein-rich test meals, alkaline supplementation improved tissue magnesium status, systemic and tissue acid–base parameters, esp. bicarbonate (HCO_3^-), as well as improved glucose utilisation in comparison to placebo.

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Author contributions MB, AMi, and RS developed the study protocol and wrote the paper; LM and AMä recruited and screened the probands; MB, NK, AK, and LK conducted the study; MB, NK, and RS analyzed the data; JV, TW, and RS reviewed and edited the paper.

Compliance with ethical standards

Conflict of interest JV received consulting fees from TW and owns equity in NuOmix k. s. The authors declare that they have no conflict of interest.

Ethical approval Approval was given by the ethical committee of Charité - Universitätsmedizin Berlin (EA1-292-12).

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