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Mini-review

The role of dietary acid load and mild metabolic acidosis in insulin resistance in humans

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ABSTRACT

Type 2 diabetes is increasingly being recognised as a global health crisis (World Health Organisation). Insulin resistance is closely associated with obesity and precedes the development of type 2 diabetes. However, there is now increasing evidence to suggest that diet itself may independently be associated with type 2 diabetes risk. A diet with a high acid load (or high potential renal net acid load, PRAL) can result in a decrease in pH towards the lower end of the normal physiological range, which may in turn lead to the development of insulin resistance. Conversely, reducing dietary acid load (the so called 'alkaline diet') may be protective and prevent the onset of type 2 diabetes. Here, we explore the influence of dietary acid load on the development of mild metabolic acidosis and induction of insulin resistance. Whilst large prospective cohort studies link high dietary acid load or low serum bicarbonate with the development of type 2 diabetes, the effect of a diet with a low acid (or high alkaline) load remains unclear. Further interventional studies are required to investigate the influence of dietary composition on the body's acid/base balance, insulin resistance and incidence of type 2 diabetes.

1. Introduction

The role of nutrition in the induction of insulin resistance has received increasing attention since the recognition of the type 2 diabetes epidemic as a global health crisis by the World Health Organisation [1]. Diet plays a major role in the development of excess body weight, a key risk factor for type 2 diabetes [2]. However, there is also evidence to suggest that diet itself may independently be associated with type 2 diabetes risk [3]. The rapid rise in the prevalence of type 2 diabetes, in combination with earlier disease onset, has led to increased public health concern and a greater focus on the delineation of dietary strategies that may prevent or delay the onset of type 2 diabetes [2].

The analysis of dietary patterns has become increasingly popular in the study of diet–disease relationships. This concept considers the potential synergistic or antagonistic interaction between individual foods and nutrients within the overall diet [4,5]. Dietary patterns better reflect real-life behaviour by representing the effect of the whole diet, which may in turn reveal stronger associations with diet-related disease risk. Within the current literature, two major dietary patterns have been identified, the "Western diet" and the "Prudent diet" [6]. The Western diet is typically high in animal proteins such as those derived from red meat, processed meat and eggs, as well as processed foods including high-energy drinks, dessert foods, and French fries. The Prudent diet is comparatively rich in fruit, vegetables, legumes and whole grains [7], and is therefore rich in fibre, magnesium, potassium, folate, and vitamin B6. It is also relatively low in fat, particularly saturated fat, in contrast to the Western diet [6]. A third dietary pattern is the Mediterranean diet, which is similar to the Prudent diet, but consists of a higher dietary intake of plant based fats, and moderate consumption of alcohol (in particular red wine) [5]. It is postulated that the higher monounsaturated fat and antioxidant content of the Mediterranean diet may confer additional benefit in improving insulin

Abbreviations: GLP-1, glucagon-like peptide 1; PRAL, potential renal acid load; NEAP, net endogenous acid production; RNAE, renal net acid excretion; HOMA-IR, homeostasis model of assessment of insulin resistance.

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sensitivity, and preventing type 2 diabetes [8], cardiovascular disease and mortality [9].

1.1. Definition of diet-induced (or 'mild') metabolic acidosis

The influence of the Western diet on health and disease outcomes in terms of its effect on the body's acid/base balance, has gained increasing interest in recent years [2]. Under normal conditions, blood pH is maintained within a narrow physiological range. The pH of arterial blood is close to 7.40, with a normal range considered to be approximately 7.35–7.45. An arterial pH less than 7.35 is classified as acidaemia, whilst the underlying condition characterised by hydrogen ion retention or loss of bicarbonate or other bases, is referred to as acidosis [10]. The acidogenic Western diet is associated with an increase in the body's hydrogen ion load, and has been hypothesised to lead to chronic mild metabolic acidosis, if proceeded by the failure of compensatory processes that aim to restore the homeostatic acid/base balance [2,11]. Consumption of foods with a high acid load (e.g. animal protein) results in the net production of nonvolatile acids such as hydrogen chloride (HCl) and hydrogen sulphate (H_2SO_4). These acids are buffered through the excretion of carbon dioxide via the lungs, and the production of sodium salts from nonvolatile acids which are excreted by the kidneys, predominately in association with ammonium, as NH_4Cl and $(NH_4)_2SO_4$. The bicarbonate generated in this process is reabsorbed and returned to the plasma, to replace the bicarbonate used to buffer the nonvolatile acid [11]. If acid production in the body exceeds acid excretion from the lungs and kidneys, the plasma bicarbonate and pH decrease. Previous authors have labelled this downward shift in body pH to the lower end of the normal range as a result of dietary acid load 'latent acidosis' [12], 'diet induced acidosis' [13–15], 'low grade acidosis' [13,16], 'chronic metabolic acidosis' [2], 'subclinical acidosis' [13] or 'mild metabolic acidosis' [17–19]. For the purpose of this review, we describe this dietary associated shift in pH as 'mild metabolic acidosis'.

1.2. Previous reviews

The association of the acid/base balance with metabolic disease, including type 2 diabetes and cardiovascular disease has been the topic of previous reviews. Salas-Salvadó and colleagues [5] summarised the effect of dietary components on the risk of developing type 2 diabetes, and concluded that following either a Prudent or Mediterranean dietary pattern was the best strategy to reduce diabetes risk. The benefit of a Mediterranean diet in preventing type 2 diabetes in those with high cardiovascular risk was evidenced in the PREDIMED study [20]. Berkmeyer and colleagues [2] explored the relationship between the Western diet, acid/base balance and obesity. They concluded that a Western (or acidogenic) diet in the absence of respiratory compensation is associated with a rise in the hydrogen ion load in the body, and this effect could be attenuated by consuming fruit and vegetables, or by taking an alkaline supplement. Adeva and Souto [14] discussed how a Western diet is linked with the development of metabolic acidosis despite renal physiological alterations such as increasing renal net acid excretion (RNAE). They hypothesised that metabolic acidosis induces insulin resistance in skeletal muscle to permit protein degradation and to generate ammonium required to promote hydrogen ion excretion, resulting in an increased risk of type 2 diabetes and hypertension. They additionally suggest that metabolic acidosis may induce glucocorticoid production, and the resulting rise in plasma cortisol could in turn contribute to insulin resistance and proteolysis [21,22]. Souto and colleagues [23] further hypothesised the risk of developing renal impairment (heralded by microalbuminuria) due to metabolic acidosis induced insulin resistance, which in turn was considered to be associated with increased risk of cardiovascular disease and mortality [24]. However, a significant development in evidence since the publication of these articles has been recently provided by large prospective studies examining the link between the dietary acid load and diabetes risk [19,25].

In the present review we will explore the role of dietary acid load and mild metabolic acidosis in insulin resistance and type 2 diabetes. We will present the evidence regarding the influence of dietary acid load on the development of mild metabolic acidosis. Next, we will explore the evidence regarding the role that metabolic acidosis may play in insulin resistance and type 2 diabetes and finally, discuss evidence gathered in large cohort studies suggesting that dietary acid load predicts insulin resistance and type 2 diabetes.

2. The influence of dietary acid load on the development of mild metabolic acidosis

2.1. Quantifying the acidogenic potential of foods

The acidogenic potential of foods can be calculated using potential renal acid load (PRAL) [19,26] and net endogenous acid production (NEAP) [19]. PRAL is based on the nutrient ionic balance and intestinal absorption rates of protein, phosphorous, potassium, magnesium and calcium as well as the production of sulphate from metabolised protein [19,27]. PRAL may be calculated by the following equation [19]:

$$PRAL\left(\frac{mEq}{day}\right) = 0.49 \times Protein\left(\frac{g}{day}\right) + 0.037 \times Phosphorous\left(\frac{mg}{day}\right) - 0.021 \times Potassium\left(\frac{mg}{day}\right) - 0.026 \times Magnesium\left(\frac{mg}{day}\right) - 0.013 \times Calcium\left(\frac{mg}{day}\right)$$

Table 1
Examples of the dietary acid load score potential renal acid load (PRAL) of common foods and beverages.

Food	*PRAL (mEq/100 g)
Cheese varieties	4.3–34.2
Meat/meat products	6.7–13.2
Bread/grain products	1.7–12.5
Whole egg	8.2
Milk chocolate	2.4
Beer	−0.1–0.9
Whole milk	0.7
Coca-Cola	0.4
Red wine	−2.4
Fruit	−21–5.5
Vegetables	−14–−0.4

The higher the PRAL the higher the acid load, and vice versa [19].

$$*PRAL\left(\frac{mEq}{day}\right) = 0.49 \times Protein\left(\frac{g}{day}\right) + 0.037 \times Phosphorous\left(\frac{mg}{day}\right) - 0.021 \times Potassium\left(\frac{mg}{day}\right) - 0.026 \times Magnesium\left(\frac{mg}{day}\right) - 0.013 \times Calcium\left(\frac{mg}{day}\right)$$

Adapted from Remer et al. [26].

A positive PRAL score is reflective of an acid forming potential, while a negative score is indicative of an alkaline forming potential [19]. Table 1 lists the PRAL score of common foods. NEAP comparatively considers dietary intake of protein and potassium as the main determinants of endogenous acid production and is calculated as follows, $NEAP\left(\frac{mEq}{day}\right) = 54.5 \times Protein\left(\frac{g}{day}\right) \div Potassium\left(\frac{mEq}{day}\right) - 10.2$. For example, the NEAP score of a Western diet has previously been calculated to be in the range of 34–76 mEq/day [28], in comparison to −0.08–34 mEq/day reported for a strict vegan diet [29]. Therefore, a high acid load score is indicative of the intake of animal proteins and processed foods in quantities not sufficiently compensated for by intake of fruit and vegetables [30].

A persistently high dietary acid load can lead to a decrease in blood pH towards the lower end of the normal physiological range if not adequately compensated for by homeostatic mechanisms or dietary modification [2,13]. In healthy individuals, PRAL and NEAP have been shown to provide a reliable estimation of the diet-dependent component of daily RNAE, a physiological marker of mild metabolic acidosis [26,27,31]. Renal net acid excretion can be calculated by the formula: RNAE = $(U^{+}_{NH4}$ x V) + (U_{TA} × V) − (U^{-}_{HCO3} x V) where U is the urine concentration, V is the urine flow rate and TA is titratable acid [11]. When NEAP is equal to RNAE, systemic acid/base balance is maintained [11]. Individuals consuming a diet rich in animal proteins have a higher RNAE [31], decreased urinary pH [23,31,32] and greater sulphate excretion [32] than individuals following a vegetarian diet [32]. A 6-week study that assessed the influence of a high protein low carbohydrate diet on body acid/base balance similarly revealed a striking increase in RNAE [33].

Plant-based foods such as fruit and vegetables are a key source of potassium and magnesium [23] and have been shown to counterbalance RNAE induced by high protein intake [34]. In patients with chronic renal disease, supplementation of the diet with fruit and vegetables was found to improve metabolic acidosis, as measured by total plasma carbon dioxide, over a one year trial [35].

2.2. Dietary acid load and bone metabolism

Increasing evidence suggests that an exaggerated acid load may also have adverse clinical outcomes on kidney and bone health as well as metabolic function. Reddy et al. [33] found that a high protein diet resulted in increased urinary acid load and urinary calcium loss, which in turn was associated with increased urinary stone formation, and a trend toward greater bone resorption. However, data in this area remains conflicting, with other studies showing that a high protein diet has no effect on calcium homeostasis and bone turnover, and increased urinary calcium excretion may be offset by increased intestinal absorption [36]. A study of 100 overweight/obese women on a high protein or high carbohydrate diet for 12 weeks found no difference in serum osteocalcin between the diet groups, suggesting no effect on bone turnover [37]. Other studies have reported that high protein diets are protective against fracture including the Framingham osteoporosis study, where increased dietary protein intake was associated with a decreased risk of hip fracture [38]. The relationship between high protein diet and bone metabolism is further complicated by the effect of dietary protein on acid/base balance. Sebastian et al. [39] demonstrated that administration of oral bicarbonate in postmenopausal women resulted in improved calcium balance, and a reduction in the bone resorption marker urinary hydroxyproline. Therefore whilst the literature in this area remains mixed, it has been suggested that an increase in fruit and vegetable ('alkaline foods') consumption, could compensate for the acid load of dietary protein, and prevent any potentially adverse outcomes in bone health.

3. Metabolic acidosis induces insulin resistance and predicts type 2 diabetes risk

In healthy adults, a decrease in pH to the lower end of the normal physiological range by ammonium chloride administration, reduced insulin sensitivity [17]. Conversely, in chronic renal failure patients, the correction of metabolic acidosis following bicarbonate treatment increased insulin sensitivity [21]. Increased RNAE, decreased urinary pH, increased sulphate excretion as well as serum markers of metabolic acidosis, including low bicarbonate, high anion gap (the difference between measured anions and cations in serum) [23,40,41] and increased lactate (a small component of the anion gap) have consistently been associated with insulin resistance [42] and type 2 diabetes risk [43,44].

3.1. Association between plasma lactate and insulin sensitivity

In a large prospective study of overweight individuals, an elevation in lactate concentration at rest was found to be an early indicator of glucose impairment [45]. This rise in lactate, an indicator of metabolic acidosis, within the normal physiological range was predictive of type 2 diabetes incidence in the Atherosclerosis Risk in Communities (ARIC) study [46]. The association between lactate and insulin resistance may be independent of body weight or adiposity, as suggested by a stronger association between plasma lactate and insulin resistance (by frequently sampled intravenous glucose tolerance test) than BMI, in a cohort of healthy lean and obese adults [42]. Consistently, in a cohort of 104 men and women, we have measured similar concentrations of plasma lactate in similarly insulin-sensitive lean and overweight/obese individuals, assessed by the gold standard measurement of peripheral insulin resistance the hyperinsulinaemic-euglycaemic clamp. Total body fat was doubled in the overweight/obese compared with the lean group. While the insulin-resistant overweight/obese group was BMI and fat matched to the insulin-sensitive overweight/obese group, plasma lactate was significantly elevated compared with both insulin-sensitive groups [47]. Similarly, in the ARIC study, adjustment for BMI and waist circumference did not attenuate the graded rise in type 2 diabetes incidence over increasing plasma lactate quartiles [46]. In the same cohort, there was a strong positive association between plasma lactate concentration and fasting blood glucose levels and prevalence of type 2 diabetes, independent of BMI [43].

3.2. Link between metabolic acidosis and insulin resistance

The mechanisms underlying the association between metabolic acidosis and insulin resistance are yet to be elucidated. In a study of cultured rat myoblasts, a decrease in extracellular pH was found to disrupt insulin binding and reduce the phosphorylation of Akt, a downstream target in the insulin signalling pathway [48]. However, the impairment was only evident with moderate acidosis (pH < 7.2), therefore its relevance in healthy individuals is questionable, and requires further evaluation. Furthermore, systemic infusion of lactate in rats was found to reduce insulin-stimulated glucose transport in muscle during a hyperinsulinaemic-euglycaemic clamp [49,50]. Similarly in humans, elevated lactate has been suggested to contribute to insulin resistance by promoting hepatic gluconeogenesis and interfering with glucose uptake in muscle [51]. The direct cause and effect relationship between a high acid load diet and body lactate production however, has not been

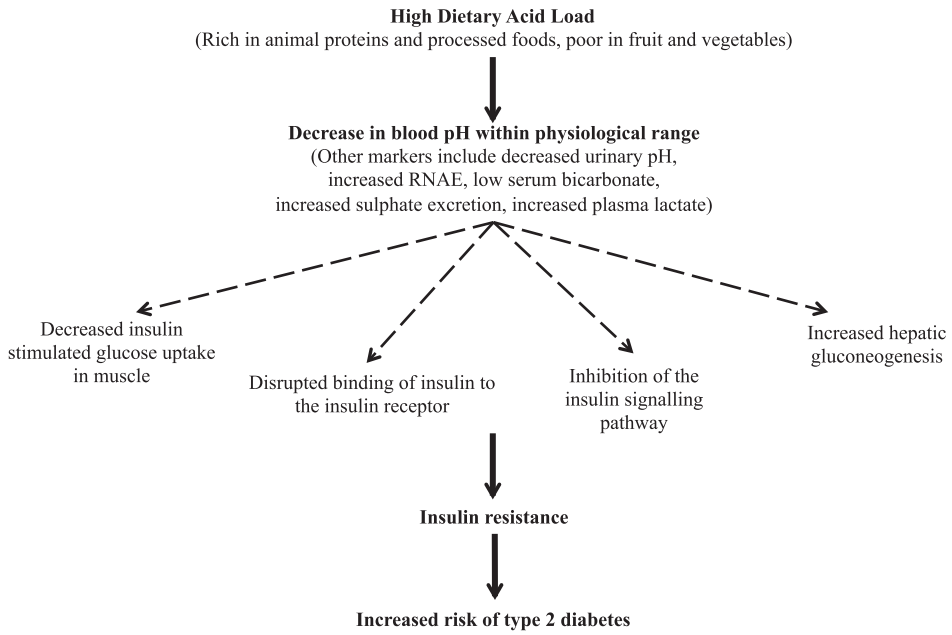

Fig. 1. Mechanisms proposed to mediate the influence of dietary acid load on type 2 diabetes risk. A diet with a persistently high acid load can result in a decrease in blood pH towards the lower end of the normal physiological range, and a change in other body acid/base markers. The mechanism(s) through which mild metabolic acidosis is thought to induce insulin resistance and increase type 2 diabetes risk is currently unclear, however various theories have been proposed. RNAE, renal net acid excretion.

established. Fig. 1 summarises the mechanisms proposed to mediate the influence of dietary acid load on insulin resistance and type 2 diabetes risk.

3.3. Association between serum bicarbonate and insulin sensitivity

A high serum bicarbonate concentration, on the other hand, is associated with a greater degree of insulin sensitivity. This was supported by Farwell et al. [40] who reported that serum bicarbonate was inversely associated with fasting insulin concentration in a study of approximately 1,500 non-diabetic adults. They found that participants with serum bicarbonate in the highest quartile had fasting insulin concentrations that were approximately 140 pmol/L (~20 mU/L) lower than those in the lowest bicarbonate quartile. In addition, data from the Nurses' Health study [41] suggested that plasma bicarbonate levels were predictive of type 2 diabetes during a 10 year follow up period. Increased plasma bicarbonate above median level was protective against type 2 diabetes, with an odds ratio of 0.76 (CI 0.6–0.96) after adjustment for BMI, renal function and hypertension. However, cause and effect cannot be established in these studies.

4. Dietary acid load predicts insulin resistance and type 2 diabetes

In healthy individuals, RNAE has been shown to be highly predictive of the protein and potassium content of the diet and is thus a reliable index of dietary acid load [16,27]. Increased RNAE, as well as other measures of mild metabolic acidosis, including low serum bicarbonate [41] high anion gap, and low urinary pH [14,40,41], have been associated with an increased risk of type 2 diabetes. Individuals who follow a plant-based diet generally exhibit a more favourable body acid/base balance as well as lower fasting blood glucose and insulin resistance by homeostasis model of assessment of insulin resistance (HOMA-IR), than those consuming a traditional Western diet [14,52]. Table 2 summarises large cohort studies addressing this area of research. In a recent prospective study of approximately 66,500 women with a 14 year follow up, Fagherazzi and colleagues [19] found that a high dietary acid load score (quantified by PRAL and NEAP, calculated on retrospective questionnaire pertaining to one year of dietary habits) was predictive of future incidence of type 2 diabetes. Interestingly, this association was even stronger in normal weight women (BMI < 25 kg/m^2) than in overweight/obese women (BMI ≥ 25 kg/m^2). In the Nurses' health study cohort [53], 702 out of 84,360 women developed type 2 diabetes in a six year follow up period. Based on prospective semi-quantitative food questionnaires calcium, potassium, and magnesium (elements of the PRAL score) were inversely associated with risk of type 2 diabetes, although there was no relationship observed between protein intake and diabetes risk. The relationship between dietary acid load and diabetes incidence was however not supported in another study of 911 elderly overweight men [25]. The strength of the latter study was the use of the gold-standard hyperinsulinaemic-euglycaemic clamp to assess insulin sensitivity. Although insulin sensitivity was shown to decrease with NEAP and PRAL increments, this did not reach statistical significance. Dietary acid load calculated from seven day prospective diet diaries, was not shown to be predictive of insulin resistance, or incidence of type 2 diabetes. However, the cohort was relatively small and accordingly only 115 incident cases of type 2 diabetes were reported during the 18 years follow up, which may limit the power of these findings. The most recent addition to the literature in this area is a cross sectional study of Japanese men and women studied by Akter and colleagues [54], who reported a positive association between PRAL and NEAP and the surrogate marker of insulin resistance HOMA-IR, although this relationship was not found with fasting glucose or HbA1c. Furthermore, after stratified analysis this association was only apparent in lean individuals with BMI <23 kg/m^2, and the long term risk of type 2 diabetes in those with high acid load scores was not assessed. It remains unclear whether differences between the cohorts of these studies, including gender, age, racial origin, or BMI, may explain the discordant results.

Table 2
Studies addressing the contribution of dietary acid load to insulin resistance or risk of type 2 diabetes in humans.

Study	Study Participants (origin)	Study design (duration)	Outcome measures	Findings
Fagherazzi et al. [19]	66,485 women (French)	Prospective (14 years)	• Dietary acid load assessed by PRAL and NEAP • Type 2 diabetes risk	• The highest PRAL quartile was associated with a significant increase in type 2 diabetes risk, compared to the lowest quartile (HR 1.56, 95% CI 1.29, 1.9), independent of BMI. • The association was strongest amongst normal-weight women (HR 1.96, 95% CI 1.43, 2.69).
Xu et al. [25]	911 men (Swedish)	Prospective (18 years)	• Dietary acid load assessed by PRAL and NEAP • Type 2 diabetes incidence • Insulin resistance assessed by hyperinsulinaemic-euglycaemic clamp	• Dietary acid load was not associated with insulin resistance or type 2 diabetes incidence. • Although insulin sensitivity tended to decrease with PRAL or NEAP increments, this did not reach statistical significance.
Colditz et al. [53]	84,360 women (US)	Prospective (6 years)	• Dietary content of magnesium, calcium, potassium and protein	• Women reporting diets with high magnesium, calcium and potassium content had a reduced risk of type 2 diabetes. • Women in the highest quintile of potassium intake exhibited RR of 0.62 (P trend = 0.008) for diabetes, calcium 0.70 (P trend = 0.005) and magnesium 0.68 (P trend = 0.02) • There was no association observed between protein intake and risk of type 2 diabetes.
Akter et al. [54]	1732 men and women (Japanese)	Cross-sectional	• Dietary acid load assessed by PRAL and NEAP • Homeostatic model of assessment of insulin resistance (HOMA-IR)	• PRAL and NEAP were positively associated with HOMA-IR • Positive associations confined to those with BMI <23 kg/m^2 • Dietary acid load not associated with fasting glucose or HbA1c.

Currently, there are no available intervention studies that demonstrate that a high alkaline load diet improves insulin sensitivity or is protective against type 2 diabetes and therefore more research is required in this area.

4.1. Confounders in nutritional studies

While experimental manipulation of the body acid/base balance with acid or alkali agent administration altered insulin sensitivity in study participants, the effect of the diet on acid/base balance and insulin sensitivity in nutritional studies may be confounded by other components of the diet. The most obvious confounder in a low acid load diet is high intake of dietary fibre. Observational studies have shown that dietary fibre itself may be protective against type 2 diabetes [55,56], and has been hypothesised to decrease post-prandial insulin demand [57]. Potential mechanisms include slowing of glucose absorption from the intestine [58], increasing bile acid excretion which may in turn increase glucagon-like peptide 1 (GLP-1) secretion [59,60], and maintaining a favourable gut microbiota composition that has been shown to improve insulin resistance in obese insulin-resistant individuals [61].

In addition, the macronutrient proportions of dietary intake (independent of energy intake) may also have an influence on insulin sensitivity. Sluijs et al. [55] reported an association between higher consumption of animal and total protein and increased diabetes risk. Protein derived from vegetable sources was however, not found to be related to diabetes risk. Similarly, Nettleton et al. [62] demonstrated that consumption of high fat dairy and red meat was associated with a greater diabetes risk compared to a high intake of whole grain, vegetables and low fat dairy. In the Women's Health Study, the increase in diabetes risk was most pronounced amongst those with the most frequent consumption of processed meats [56]. Conversely, Valachovicova and colleagues [52] found that a vegetarian diet was associated with the maintenance of insulin sensitivity (as evaluated by HOMA-IR) over time in non-obese individuals, when compared to non-vegetarian controls with a similar intake of energy and macronutrients. Discrepant results with protein from animal or non-animal sources suggests that other dietary factors may also contribute to an increase in the risk of diabetes independent of the overall dietary pattern. However, these studies have multiple potential confounders that are difficult to control for, including variations in physical activity and lifestyle factors which may relate to consumption of animal compared to non-animal based diets.

Accumulating evidence suggests a beneficial effect of very-low-carbohydrate high-fat diets on glycaemia in type 2 diabetic children and adults [63,64]. This diet results in a significant increase in plasma ketone bodies from a very low concentration of <0.3 mmol/L to approximately 7/8 mmol/L [65]. The ketone bodies are thought to mediate the beneficial glycaemic effect irrespective of weight loss. Consistent with PRAL neutrality of dietary fats and oils (e.g. butter PRAL = 0.6, olive oil PRAL = 0 and margarine PRAL = −0.5 [66]), the ketogenic diet does not affect blood pH [65]. Future studies with glycaemic control and diabetes complications monitoring over time in type 2 diabetes patients are necessary to compare the effects of ketogenic diets and low acid load diets irrespective of weight loss.

In diets rich in animal protein, other nutrients inherent to animal protein, such as iron may also be implicated [55]. Fernandez-Real and colleagues [67] have reported that the soluble transferrin receptor (a quantitative marker of erythropoiesis) was inversely associated with insulin sensitivity, although only in lean and glucose tolerant individuals, suggesting that iron metabolism may play a role in insulin resistance. Fargion and colleagues [68] have reported that iron depletion resulted in a reduction in insulin resistance and increased insulin release, whilst iron supplementation reduced insulin binding. The authors hypothesised that removal of iron resulted in improved intracellular insulin signalling. An additional confounder that deserves consideration is the satiating effect of low acid load diets that may contribute to an overall decrease in energy intake, weight loss and thereby improvement in insulin sensitivity.

5. Conclusions

As the worldwide prevalence of type 2 diabetes continues to rise rapidly, the need for dietary intervention to address this epidemic becomes paramount. Traditional non-surgical weight loss measures are ineffective in sustaining weight loss and metabolic health

in the long term, thus feasible dietary intervention strategies need to be formulated. There is mounting evidence to suggest that a diet with high acid load increases body acidity and predicts insulin resistance and type 2 diabetes. It remains unknown however, whether a low dietary acid load (or alkaline diet) can buffer mild metabolic acidosis, improve insulin sensitivity and reduce diabetes risk. If future study proves that this is the case, dietary recommendations should promote a diet that results in metabolically favourable acid/base balance.

Conflict of interest

The authors declare no conflict of interest.

References

[1] K.F. Petersen, S. Dufour, D. Befroy, R. Garcia, G.I. Shulman, Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes, N. Engl. J. Med. 350 (2004) 664–671.

[2] S. Berkemeyer, Acid-base balance and weight gain: are there crucial links via protein and organic acids in understanding obesity? Med. Hypotheses 73 (2009) 347–356.

[3] F. Bauer, J.W. Beulens, A.D. van der, C. Wijmenga, D.E. Grobbee, A.M. Spijkerman, Y.T. van der Schouw, N.C. Onland-Moret, Dietary patterns and the risk of type 2 diabetes in overweight and obese individuals, Eur. J. Nutr. 52 (2013) 1127–1134.

[4] D.R. Jacobs Jr., M.D. Gross, L.C. Tapsell, Food synergy: an operational concept for understanding nutrition, Am. J. Clin. Nutr. (2009) 1543S–1548S.

[5] J. Salas-Salvadó, M.A. Martinez-Gonzalez, M. Bullo, E. Ros, The role of diet in the prevention of type 2 diabetes, Nutr. Metab. Cardiovasc Dis. 21 (Suppl 2) (2011) B32–B48.

[6] F.B. Hu, E. Rimm, S.A. Smith-Warner, D. Feskanich, M.J. Stampfer, A. Ascherio, L. Sampson, W.C. Willett, Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire, Am. J. Clin. Nutr. 69 (1999) 243–249.

[7] T.T. Fung, M. Schulze, J.E. Manson, W.C. Willett, F.B. Hu, Dietary patterns, meat intake, and the risk of type 2 diabetes in women, Arch. Intern Med. 164 (2004) 2235–2240.

[8] A.C. Tierney, H.M. Roche, The potential role of olive oil-derived MUFA in insulin sensitivity,, Mol. Nutr. Food Res. 51 (2007) 1235–1248.

[9] M.A. Martinez-Gonzalez, M. Garcia-Lopez, M. Bes-Rastrollo, E. Toledo, E.H. Martinez-Lapiscina, M. Delgado-Rodriguez, Z. Vazquez, S. Benito, J.J. Beunza, Mediterranean diet and the incidence of cardiovascular disease: a Spanish cohort, Nutr. Metab. Cardiovasc. Dis. 21 (2011) 237–244.

[10] M.G. Levizky, Pulmonary Physiology, Chapter 8: Acid Base Balance, McGraw-HIll Companies, United States of America, 2013.

[11] B.M. Koeppen, The kidney and acid-base regulation, Adv. Physiol. Educ. 33 (2009) 275–281.

[12] J. Vormann, T. Goedeke, Latent acidosis: acidity as a cause for chronic diseases (Latente Azidose Übersäuerung als Ursache chronischer Erkrankungen), Schewiz Zschr Ganszheits Med. 2 (2002) 90–96.

[13] I.F. Robey, Examining the relationship between diet-induced acidosis and cancer, Nutr. Metab. Cardiovasc Dis. 9 (2012) 72.

[14] M.M. Adeva, G. Souto, Diet-induced metabolic acidosis, Clin. Nutr. 30 (2011) 416–421.

[15] J. Pizzorno, L.A. Frassetto, J. Katzinger, Diet-induced acidosis: is it real and clinically relevant? Br. J. Nutr. 103 (2010) 1185–1194.

[16] L.A. Frasetto, K.M. Todd, C.M. Morris, A. Sebastian, Estimates of net endogenous non carbonic acid production in humans from diet potassium and protein contents, Am. J. Clin. Nutr. 68 (1998) 576–583.

[17] R.A. Defronzo, A.D. Beckles, Glucose intolerance following chronic metabolic acidosis in man, Am. J. Physiol. 236 (1978) E328–E334.

[18] M.F. Engberink, S.J. Bakker, E.J. Brink, M.A. van Baak, F.J. van Rooij, A. Hofman, J.C. Witteman, J.M. Geleijnse, Dietary acid load and risk of hypertension: the Rotterdam Study, Am. J. Clin. Nutr. 95 (2012) 1438–1444.

[19] G. Fagherazzi, A. Vilier, F. Bonnet, M. Lajous, B. Balkau, M.C. Boutron-Rualt, F. Clavel-Chapelon, Dietary acid load and risk of type 2 diabetes: the E3N-EPIC cohort study, Diabetologia 57 (2014) 313–320.

[20] J. Salas-Salvadó, M. Bullo, N. Babio, M.A. Martinez-Gonzalez, N. Ibarrola-Jurado, J. Basora, R. Estruch, M.I. Covas, D. Corella, F. Aros, V. Ruiz-Gutierrez, E. Ros, P.S. Investigators, Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial, Diabetes Care 34 (2011) 14–19.

[21] D. Reaich, K.A. Graham, S.M. Channon, C. Hetherington, C.M. Scrimgeour, R. Wilkinson, T.H. Goodship, Insulin-mediated changes in PD and glucose uptake after correction of acidosis in humans with CRF, Am. J. Physiol. 268 (1995) E121–E126.

[22] M. Maurer, W. Riesen, J. Muser, H.N. Hulter, R. Krapf, Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans, Am. J. Physiol. Ren. Physiol. (2003) F32–F40.

[23] G. Souto, C. Donapetry, J. Calvino, M.M. Adeva, Metabolic acidosis-induced insulin resistance and cardiovascular risk, Metab. Syndr. Relat. Disord. 9 (2011) 247–253.

[24] S.F. Dinneen, H.C. Gerstein, he association of micro- albuminuria and mortality in non-insulin-dependent diabe- tes mellitus. A systematic overview of the literature, Arch. Intern Med. 157 (1997) 1413–1418.

[25] H. Xu, T. Jia, X. Huang, U. Riserus, T. Cederholm, J. Arnlov, P. Sjogren, B. Lindholm, J.J. Carrero, Dietary acid load, insulin sensitivity and risk of type 2 diabetes in community-dwelling older men, Diabetologia 57 (2014) 1561–1568.

[26] T. Remer, F. Manz, Potential renal acid load of foods and its influence on urine pH, J. Am. Diet. Assoc. 95 (1995) 791–797.

[27] T. Remer, T. Dimitriou, F. Manz, Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents, Am. J. Clin. Nutr. 77 (2003).

[28] L. Zhang, G.C. Curhan, J.P. Forman, Diet-dependent net acid load and risk of incident hypertension in United States women, Hypertension 54 (2009) 751–755.

[29] A. Strohle, A. Waldmann, J. Koschizke, C. Leitzmann, A. Hahn, Diet-dependent net endogenous acid load of vegan diets in relation to food groups and bone health-related nutrients: results from the German Vegan Study, Ann. Nutr. Metab. 59 (2011) 117–126.

[30] R.H. Gannon, D.J. Millward, J.E. Brown, H.M. Macdonald, D.P. Lovell, L.A. Frassetto, T. Remer, S.A. Lanham-New, Estimates of daily net endogenous acid production in the elderly UK population: analysis of the National Diet and Nutrition Survey (NDNS) of British adults aged 65 years and over, Br. J. Nutr. 100 (2008) 615–623.

[31] T. Remer, F. Manz, Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein, Am. J. Clin. Nutr. 59 (1994) 1356–1361.

[32] N.A. Breslau, L. Brinkley, K.D. Hill, C.Y.C. Pak, Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism, J. Clin. Endocrinol. Metab. 66 (1988) 140–146.

[33] S.T. Reddy, C.Y. Wang, K. Sakhaee, L. Brinkley, C.Y.C. Pak, Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism, Am. J. Kidney Dis. 40 (2002) 265–274.

[34] J.A. Bell, S.J. Whiting, Effect of fruit on net acid and urinary calcium excretion in an acute feeding trial of women, Nutrition 20 (2004) 492–493.

[35] N. Goraya, J. Simoni, C.H. Jo, D.E. Wesson, A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate, Clin. J. Am. Soc. Nephrol. 8 (2013) 371–381.

[36] R.P. Heaney, D. Layman, Amount and type of protein influences bone health, Am. J. Clin. Nutr. 87 (2008) 1567S–1570S.

[37] M. Noakes, J.B. Keogh, P.R. Foster, P.M. Clifton, Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women, Am. J. Clin. Nutr. 81 (2005) 1298–1306.

[38] D. Misra, S.D. Berry, K.E. Broe, R.R. McLean, L.A. Cupples, K.L. Tucker, D.P. Kiel, M.T. Hannan, Does dietary protein reduce hip fracture risk in elders? The Framingham osteoporosis Study, Osteoporos. Int. 22 (2011) 345–349.

[39] A. Sebastian, S.T. Harris, J.H. Ottaway, K.M. Todd, R.C. Morris, Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate, N. Eng. J. Med. 330 (1994) 1776–1781.

[40] W.R. Farwell, E.N. Taylor, Serum bicarbonate, anion gap and insulin resistance in the national health and nutrition examination survey, Diabet. Med. 25 (2008) 798–804.

[41] E.I. Mandel, G.C. Curhan, F.B. Hu, E.N. Taylor, Plasma bicarboante and risk of type 2 diabetes mellitus, CMAJ 184 (2012) E719–E725.

[42] J. Lovejoy, F.D. Newby, S.S.P. Gebhart, M. DiGirolamo, Insulin resistance in obesity is associated with elevated basal lactate levels and diminished lactate appearance following intravenous glucose and insulin, Metabolism 41 (1992) 22–27.

[43] S.O. Crawford, R.C. Hoogeveen, F.L. Brancati, B.C. Astor, C.M. Ballantyne, M.I. Schmidt, J.H. Young, Association of blood lactate with type 2 diabetes: the atherosclerosis risk in communities carotid MRI Study, Int. J. Epidemiol. 39 (2010) 1647–1655.

[44] S.P. Juraschek, E. Selvin, E.R. Miller, F.L. Brancati, J.H. Young, Plasma lactate and diabetes risk in 8045 participants of the atherosclerosis risk in communities study, Ann. Epidemiol. 23 (2013) e794, 791–796.

[45] L.O. Ohlson, B. Larsson, P. Bjrrntorp, H. Eriksson, K. Svardsudd, L. Welin, G. Tibblin, L. Wilhelmsen, Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913, Diabetologia 31 (1998) 798–805.

[46] S.P. Juraschek, G.P. Shantha, A.Y. Chu, E.R. Miller, E. Guallar, R.C. Hoogeveen, C.M. Ballantyne, F.L. Brancati, M.I. Schmidt, J.S. Pankow, J.H. Young, Lactate and risk of incident diabetes in a case-cohort of the atherosclerosis risk in communities (ARIC) study, PLoS One 8 (2013) e55113.

[47] R.S. Williams, L.K. Heilbronn, D.L. Chen, A.C. Coster, J.R. Greenfield, D. Samocha-Bonet, Dietary acid load, metabolic acidosis and insulin resistance – Lessons from cross-sectional and overfeeding studies in humans, Clin. Nutr. (2015 Aug 12), http://dx.doi.org/10.1016/j.clnu.2015.08.002 pii: S0261-5614(15)00218-6. [Epub ahead of print].

[48] H. Hayata, H. Miyazaki, N. Niisato, N. Yokoyama, Y. Marunaka, Lowered extracellular pH is involved in the pathogenesis of skeletal muscle insulin

resistance, Biochem. Biophys. Res. Commun. 445 (2014) 170–174.
[49] R. Vettor, A.M. Lombardi, R. Fabris, C. Pagano, I. Cusin, F. Rohner-Jeanrenaud, G. Federspil, B. Jeanrenaud, Lactate infusion in anesthetized rats produces insulin resistance in heart and skeletal muscles, Metabolism 46 (1997) 684–690.
[50] C.S. Choi, Y.B. Kim, F.N. Lee, J.M. Zabolotny, B.B. Kahn, J.H. Youn, Lactate induces insulin resistance in skeletal muscle by suppressing glycolysis and impairing insulin signaling, Am. J. Physiol. Endocrinol. Metab. 283 (2002) E233–E240.
[51] A. Consoli, N. Nurjahan, J.J. Reilly Jr., D.M. Bier, J.E. Gerich, Mechanism of increased gluconeogenesis in noninsulin-dependent diabetes mellitus, J. Clin. Invest. 86 (1990) 2038–2045.
[52] M. Valachovicova, M. Krajcovicova-Kudlackova, P. Blazicek, K. Babinska, No evidence of insulin resistance in normal weight vegetarians. a case control study, Eur. J. Nutr. 45 (2006) 52–54.
[53] G.A. Colditz, J.E. Manson, M.J. Stampfer, B. Rosner, W.C. Willett, F.E. Speizer, Diet and risk of clinical diabetes in women, Am. J. Clin. Nutr. 55 (1992).
[54] S. Akter, M. Eguchi, K. Kuwahara, T. Kochi, R. Ito, K. Kurotani, H. Tsuruoka, A. Nanri, I. Kabe, T. Mizoue, High dietary acid load is associated with insulin resistance: the Furukawa nutrition and health study, Clin. Nutr. (2015).
[55] I. Sluijs, J.W. Beulens, A.D. van der, A.M. Spijkerman, D.E. Grobbee, Y.T. van der Schouw, Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study, Diabetes Care 33 (2010) 43–48.
[56] Y. Song, J.E. Manson, J.E. Buring, S. Miu, A Prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women, Diabetes Care 27 (2004) 2108–2115.
[57] J. Montonen, P. Knekt, T. Harkanen, R. Jarvinen, M. Heliovaara, A. Aromaa, A. Reunanen, Dietary patterns and the incidence of type 2 diabetes, Am. J. Epidemiol. 161 (2005) 219–227.
[58] G. Livesey, H. Tagami, Interventions to lower the glycemic response to carbohydrate foods with a low-viscosity fiber (resistant maltodextrin): meta-analysis of randomized controlled trials, Am. J. Clin. Nutr. 89 (2009) 114–125.
[59] H. Ma, M.E. Patti, Bile acids, obesity, and the metabolic syndrome, Best. Prac. Res. Clin. Gastroenterol. 28 (2014) 573–583.
[60] Y. Yokoyama, N.D. Barnard, S.M. Levin, M. Watanabe, Vegetarian diets and glycemic control in diabetes: a systematic review and meta-analysis, Cardiovasc Diagn Ther. 4 (2014) 373–382.
[61] A. Vrieze, E. Van Nood, F. Holleman, J. Salojärvi, R.S. Kootte, J.F.W.M. Bartelsman, G.M. Dallinga–Thie, M.T. Ackermans, M.J. Serlie, R. Oozeer, M. Derrien, A. Druesne, J.E.T. Van Hylckama Vlieg, V.W. Bloks, A.K. Groen, H.G.H.J. Heilig, E.G. Zoetendal, E.S. Stroes, W.M. de Vos, J.B.L. Hoekstra, N. M, Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome, Gastroenterology (2012) 913–916.
[62] J.A. Nettleton, L.M. Steffen, H. Ni, K. Liu, D.R. Jacobs Jr., Dietary patterns and risk of incident type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA), Diabetes Care 31 (2008) 1777–1782.
[63] C.V. Mobbs, J. Mastaitis, F. Isoda, M. Poplawski, Treatment of diabetes and diabetic complications with a ketogenic diet, J. Child. Neurol. 28 (2013) 1009–1014.
[64] R.D. Feinman, W.K. Pogozelski, A. Astrup, R.K. Bernstein, E.J. Fine, E.C. Westman, A. Accurso, L. Frassetto, B.A. Gower, S.I. McFarlane, J.V. Nielsen, T. Krarup, L. Saslow, K.S. Roth, M.C. Vernon, J.S. Volek, G.B. Wilshire, A. Dahlqvist, R. Sundberg, A. Childers, K. Morrison, A.H. Manninen, H.M. Dashti, R.J. Wood, J. Wortman, N. Worm, Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base, Nutrition 31 (2015) 1–13.
[65] A. Paoli, A. Rubini, J.S. Volek, K.A. Grimaldi, Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets, Eur. J. Clin. Nutr. 67 (2013) 789–796.
[66] T. Remer, F. Manz, Potential renal acid load of foods and its influence on urine pH, J. Am. Diet. Assoc. 95 (1995) 791–797.
[67] J.M. Fernandez-Real, J.M. Moreno, A. Lopez-Bermejo, B. Chico, J. Vendrell, W. Ricart, Circulating soluble transferrin receptor according to glucose tolerance status and insulin sensitivity, Diabetes Care 30 (2007) 604–608.
[68] S. Fargion, P. Dongiovanni, S. Guzzo, L. Colombo, L. Valenti, A.L. Francanzani, Iron and insulin resistance, Aliment. Pharmacol. Ther. 22 (Suppl. 2) (2005) 61–63.