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Review

Dietary acid load: focus on body pH homeostasis and drug responses in type 2 diabetes

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Abstract

Diabetes mellitus is a heterogeneous group of metabolic dysregulation that shares phenotype of hyperglycemia and for which genetic and environmental risk factors act synergistically. Dietary acid load and low pH of interstitial fluid are the most important, factors reducing insulin sensitivity and making the body condition worse in Type 2 diabetes mellitus (T2DM). Several pharmacological classes of oral antidiabetic drugs (OADs) are actually reachable for the treatment of T2DM. These drugs are designed especially to reduce blood glucose level but not necessary to improve insulin resistance. This latter with OADs side effects may affect the whole therapeutic strategies of T2DM. The kind of diet can deeply affect the organism by the generation of acid or base precursors. Indeed, foods such as meat, eggs, cheese, and grains increase the production of acid in the organism, while fruit and vegetables are alkalizing. However, milk, fats and sugars are considered neutral, which have an insignificant effect on acid–base balance. To save cell function, the pH of body fluids is maintained constant by various systems which became impaired with increase in age and many pathological situations. This review proposes to highlight the effect of dietary acid load on the pathogenesis and management of T2DM as well as on its influence on the heterogeneity of OADs responses observed in diabetic patients.

Keywords: Diet acid–base load, Diabetes, Potential renal acid load (PRAL), Insulin resistance, drug response.

Introduction

Diabetes is a pandemic non-infectious disease. It is a leading worldwide cause of mortality and disability [1]. The international prevalence data report that in 2017, 425 million people were diagnosed as suffering from diabetes mellitus worldwide, and the number of people with diabetes mellitus is considered to rise up to 629 million by 2045 [2]. However, more than 90% of these patients are type 2 diabetes (T2DM) [3]. The most important symptoms of T2DM are hypoglycemia, which is complicated by insulin resistance resulting from insulin hypersecretion caused by pancreatic β-cell dysfunction [4]. Chronic hyperglycemia results from glucose metabolism impairment in cells, such as hepatocytes, adipocytes, skeletal muscles, etc., frequently leading to irreversible complications like: macro-and micro-vascular complications, myocardial stroke, renal failure, peripheral neuropathy and blindness [5]. Numerous researchers are reached to develop various types of glucose lowering drugs for treatment of T2DM such as sulfonylurea, glucosidase inhibitors, biguanide, thiazolidine, dipeptidyl-peptidase (PPD) IV inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors [6]. Nevertheless, an extremely large number of people are still suffering from T2DM. This means that the above mentioned drugs are still effective from a viewpoint of reduction of blood

glucose level, but not on fully treated patients suffering from T2DM with insulin resistance [5]. Several publications have appeared in recent years documenting the implication of dietary acid load in the increasing risk of T2DM through insulin resistance [6–9]. In addition, Puddu et al. suggest that weak short-chain fatty acids (weak organic acids) produced by bacterial fermentation in distal gut may stimulate the secretion of glucagon-like peptide 1 (GLP-1) that improves insulin resistance; however, the exact molecular mechanism is still unclear [10].

Interstitial fluids provide a biochemical medium for extracellular signaling molecules such as neurotransmitters and hormones (insulin) to regulate cell function. However, variation of interstitial space composition disturbs efficiency signal transduction of this signaling molecule from extracellular cells domain to intracellular effective signal. Presence of weak pH buffering molecules in interstitial fluids makes pH homeostasis of this extracellular medium vulnerable to proton load [5]. Under anerobic conditions, glucose metabolism (glycolysis and glycogenolysis) generates protons from lactic acid (lactate–/H^+) in adipose and skeletal muscle tissues [11]. Ketone bodies (β-hydroxybutyrate–/H^+) are other major sources of protons of fatty acid in the liver cells [6, 12]. In contrast to interstitial space, blood has a powerful pH buffering such as albumin, hemoglobin, which keep the rigorous pH of blood at a range between 7.35 and 7.45. These facts mean that even if the pH of the blood stays at normal value, pH of interstitial space would deviate from the physiological range under the effects of pathophysiological metabolic conditions [5]. Disruption of pH homeostasis in intra or extra cellular space has many consequences in cells metabolism or tissues affecting mainly pH-sensitive membrane transporters, metabolic enzymes (phosphofructokinase) and hormones (insulin-receptor binding) [13].

Effective solutions are needed to slow or reverse this situation, especially by acting in variable factors, including physical activity, weight and diet. The role of lifestyle and nutrition in the management and prevention of T2DM is very clear through its effect on body weight and metabolic control [2]. Furthermore, appropriate diet and several bioactive factors involved in regulating organic acid production and proton clearance may be vital for the prevention or improvement of metabolic dysfunction linked with T2DM.

In this review article we try to highlight the influence of alkaline/acid diet load on pH homeostasis of body fluids, insulin resistance, and on drug response of T2DM. Further, this work proposes perspective therapies on the basis of regulation of body fluid pH including diet.

Cells and interstitial pH space homeostasis

Chemical reactions in living organisms are influenced mainly by pH. This latter affects the charge of reactive groups of molecules and enzymes within extracellular and intracellular fluids (Table 1). The chemical activity or concentration of the H^+ or hydronium ion (H_3O^+) is remarkably small and stable, given the abundance of protons in body fluids [14]. Intracellular pH (pHi) is an important constant of cytoplasmic compartment which can touch approximately all aspects of cell functions. pHi changing may affect predominantly: pH-sensitive metabolic enzymes [15], such as phosphofructokinase (a key of glycolytic enzyme), polymerization, and cross-linking of cytoskeletal proteins such as actin and tubulin, the ability of muscle cells to generate tension (muscle weakness), gap junctions, many ion-selective channels, apoptosis, cell growth, and proliferation signal and osmosis. Furthermore, fluctuation of intracellular pH also leads to the change of cell responses to external informational factors, including neurotransmitters, growth factors, and hormones like insulin. For that, all cells are well-equipped with several chemical defense systems to fight against pH fluctuations. Indeed, to maintain a stable pHi, tremendous cellular buffers are implicated to regulate pHi supported by the activity of different categories of membrane bound transporters. These transporters are classified into five types: 1. Proton pumps or H^+-ATPases; 2. Cation/H^+ exchangers, for example the alkalinizing Na^+/H^+ exchanger and the acidifying K^+/H^+ exchanger; 3. Na^+-organic anion co-transporters; 4. Cl^-/organic anion exchangers; and 5. HCO_3^- dependent

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transporters, such as the (Na^++ HCO_3^-) /Cl^- and the Cl^-/HCO_3^- exchangers and Na^+-HCO_3^- co-transporters [13].

As mentioned above, to maintain the intracellular pH at physiological levels, the acids generated in the intracellular medium is extruded into the extracellular fluid (the interstitial space). The acidity of this latter is suggested to be one of the most serious pathogenesis mechanisms leading to various diseases, including tumor metastasis and diabetes mellitus [8, 9].

However, the organs directly linked to the maintenance of acid base homeostasis are lungs and kidneys, as well as a complex system of buffers. The interaction of these mentioned elements is required to save the arterial pH in physiological ranges (7.35–7.45) [7]. This equilibrium is maintained via the involvement of three interconnected mechanisms: blood and tissue buffering processes (e.g., bicarbonate), the redistribution of carbon dioxide (CO_2) from the blood to the lungs through respiration, and the excretion of excess hydrogen ions from the blood into the urine via kidneys. During every given moment, the acid-base equilibrium is mostly affected by cell metabolism (e.g., exercise), food intake, and disease patterns which it is also considered to affect either acid generation (e.g., diabetic ketoacidosis) or excretion (e.g., renal failure) [16].

Another mechanism is widely involved in acid base balance of the body which we may not ignore. Bone is a very large ion exchange buffer system which contains 99% of body calcium. Furthermore, Barzel and Massey added that 80% of the total body carbonate are in the hydration shell. Then, the water surrounding bone, are 80% of citrate and 35% of sodium, which can serve to buffer the excess acid. Bone replies to acidity by an acellular, physicochemical reaction with the immediate release of carbonate, citrate and sodium from the hydration shell. In response to

Table 1: pH of selected fluids, organs, and cell compartment.

Organ, fluid or intracellular organelle	pH	References
Skin	Natural pH is between 4 and 6.5	[16]
Urine	4.6–8	[16]
Gastric	1.35–3.5	[16]
Bile	7.6–8.8	[16]
Pancreatic Fluid	8.8	[16]
Vaginal Fluid	<4.7	[16]
Cerebro-spinal Fluid	7.3	[16]
Serum venous	7.35	[16]
Serum arterial	7.4	[16]
Breast milk	6.35–7.35	[19]
Intracellular Fluid	6.0–7.2	[16]
Cis Golgi apparatus	6.7	[20]
Medial Golgi apparatus	6.3	[20]
Trans Golgi apparatus	6.0	[20]
Secretory vesicles	5.5	[20]
Early endosome	6.5	[20]
Late endosome	6	[20]
Lysosome	<5.5	[20]
Mitochondria	7.5–8.0	[13]

chronic acid stress, such as imposed by an acid-ash diet, cellular responses mobilize bone and calcium as a buffer. An acid-ash diet is a diet that creates acid in the process of its metabolisms [17].

Therefore, under physiological conditions (anaerobic stress) a little amount of pyruvate generated by glycolysis is converted to lactate. However, the rest of pyruvate is transformed in the mitochondrial tricarboxylic acid cycle (TCA) to produce CO_2 (major sources for H^+), which is converted later into H^+ and HCO_3^- by carbonic anhydrase. Further, in a similar situation, to produce the same amount of ATP, glycolysis pathway generates more protons than the both metabolic ways (glycolysis and TCA cycle) in normal condition. This explains that glycolysis associated with mitochondrial TCA cycle impairment is more acidogenic than glycolysis followed with full functional TCA cycle. Previous studies also indicated a reduction of mitochondria function in persons with T2DM [5, 18] where the total amount of H^+ produced in these patients is much larger than that in healthy subjects with normal mitochondrial function [18].

Dietary and acid load Metabolism

Food is one of the main determinants of endogenous acid production [5]. It defines the formation of acids, alkalis or neutral biochemical species once absorbed and metabolized. Main nutrient components liberating acid precursors are presented by phosphorus and proteins (mostly the sulfur amino acids such as cysteine, taurine, and methionine, in addition to cationic amino acids like arginine and lysine). However, some minerals such as potassium, magnesium and calcium are considered to be an alkaline precursor [7].

From a practical point, the main so-called "acidifiers" foods are generally of animal origin: meat, fish, poultry, eggs, and shellfish. However, some proteins of plant origin, such as those from cereals and legumes, containing many sulfur amino acids, have also a strong acidifying power. Further, milk, by its high content of calcium (alkalizing), is considered neutral. Sugar and lipids have a weak acidifying power and a little contribution in acid-base balance [21]. Conversely, the alkalizing foods are mainly the fresh fruits and vegetables, which are particularly rich in magnesium and potassium. The alkalizing power of food is in fact appreciated by its potassium content [22]. So, the potatoes and pumpkins, are rich in K^+, and have a greater anti-acidifying effect than apples and pears. In practice, the acidifying or basifying power of diet can be approached by two methods [23]:

The First PRAL (potential renal Acid load) score was estimated using an algorithm described by Remer and colleagues [24]: PRAL (mEq/d) = 0.4888 x protein intake (g/day) + 0.0366 x phosphorus (mg/day) – 0.0205 x potassium (mg/ day) – 0.0125 x calcium (mg/day) – 0.0263 x Magnesium (mg/day). However, the NEAP (net endogenous acid load) score was calculated using the formula described by Frassetto et al., [25]: estimated NEAP (mEq/d) = [54.5 x protein intake (g/day) ÷ potassium intake (mEq/day)] – 10.2.

The values of the first equation describe the acid or alkaline load produced by each food, it is expressed by mEq/100 g. However, the second formula result from the acidifying effect of sulfuric amino acids such as cysteine and methionine contained in protein food and alkalizing action of the mineral salts, anions of weak organic acids and cationic amino acids mainly present in vegetable foods [7, 26].

The calculated PRAL and NEAP scores obtained using the above equations were well evaluated against both the PRAL and NEAP scores assessed from 24-hour urine collections. In fact, when the PRAL value for a type of food is less than 0, it is considered that this food enhances the pH of body fluids (alkalinity) and, when it is more than 0, that food tends to increase the production of acids in the body (acid load). Usually, foods such as eggs, meat, cheese and grains increase the production of acids in the body, while fruit and vegetables are alkalizing diets [22] (Table 2). The amount of discharged acid of proteins is widely linked to the chemical nature and the ways which the amino acids are metabolized. Indeed, some of these are categorized as neutral, others as acidic, and certain as alkaline. For example, histidine, lysine, and arginine, are considered acidic when metabolized, they generate hydrochloric acid, just

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Table 2: Nutrient content and estimated potential, renal acid load of frequently consumed foods and beverages (related to 100 g or ml of edible portion) [28].

Food or food group	PRAL (mEq) 100 g or mL
Beverages	
Coca-Cola	0.4
Coffee, infusion, 5 minutes	–1.4
Mineral Water (Volvic)	–0.1
Mineral Water (Apollinaris)	–1.8
Tea, Indian, infusion	–0.3
Red wine	–2.4
White wine, Dry	–1.2
Fats and Oils	
Butter	0.6
Margarine	–0.5
Olive oil	0.0
Sunflower Seed oil	0.0
Fish	
Cod, fillet	7.1
Haddock	6.8
Trout, brown, steamed	10.8
Fruits, nuts, and fruit juices	
Apple juice, unsweetened	–2.2
Apricots	–4.8
Bananas	5.5
Cherries	3.6
Grape juice, unsweetened	1.0
Kiwi fruit	–4.1
Lemon juice	–4.1
Lemon juice	–2.5
Orange juice, unsweetened	–2.9
Orange	–2.7
Peaches	–2.4
Peanuts, plain	8.3
Raisins	–21.0
Strawberries	–2.2
Walnuts	6.8
Water melon	–1.9
Grain products	
Bread, rye flour, mixed	4.0
Bread rye flour	4.1

Table 2: Coninued

Food or food group	PRAL (mEq) 100 g or mL
Bread, wheat flour, whole meat	1.8
Bread, white wheat	3.7
Rice, brown	1.5
Rice, white, easy cook	4.6
Rice, white, easy cook, boiled	1.7
Spaghetti, white	6.5
Spaghetti, whole meal	7.3
Wheat flour, white, plain	6.9
Wheat flour, whole meal	8.2
Legumes	
Beans, green/french beans	–3.1
Lentils, green and brown, whole, dried	3.5
Peas	1.2
Meat and meat product	
Beef, lean only	7.8
Chicken, meat only	8.7
Corned beef, canned	13.2
Liver sausage	10.6
Rump steak, lean and fat	8.8
Turkey, meat only	9.9
Veal, fillet	9.0
Milk, dairy products, and eggs	
Buttermilk	0.5
Camembert	14.6
Cheddar-type, reduced fat	26.4
Cheese, Gouda	18.6
Creams, fresh, sour	1.2
Eggs, chicken, whole	8.2
Eggs, yolk	23.4
Milk, whole evaporated	1.1
Milk, whole pasteurized and sterilized	0.7
Yogurt, whole milk, fruit	1.2
Yogurt, whole milk, plain	1.5
Sugar, and sweets	
Chocolates, milk	2.4
Honey	–0.3

Table 2: Coninued

Food or food group	PRAL (mEq) 100 g or mL
Sugar, white	–0.1
Vegetables	
Asparagus	–0.4
Broccoli, green	–1.2
Carrots, young	–4.9
Cauliflower	–4.0
Celery	–5.2
Cucumber	–0.8
Leeks	–1.8
Lettuce, average of 4 varieties	–2.5
Mushrooms, common	–1.4
Onions	–1.5
Peppers, capsicum, green	–1.4
Potatoes, old	–4.0
Radish, red	–3.7
Spinach	–14.0
Tomatoes	–3.1
Zucchini	–4.6

as methionine and cysteine, which contain sulfur and are transformed into sulfuric acid [22, 27]. Furthermore, the alkaline nutrients are generally organic acids precursors such as citrate or bicarbonate releasers during their catabolism [23].

Cross link between Diet acid load balance and Diabetes

As mentioned above, the endogenous acid production is mainly dependent on the metabolism of food and widely varies with its nature. The dietary acid load is eliminated by the functionally normal kidney, which thus maintains the acid-base balance. However this function of healthy kidneys becomes impaired with the increase in age. Maintaining acid-base homeostasis are ensured by neutralization of the number of milli-equivalent of non-carbonic and non-volatile acids produced with an equal amount of protons before excretion through the urine [26]. Data found that urine pH also fell with age, and sex. In fact, women are known to produce alkaline urine compared to men at all ages. Obesity and diabetes had a lower urinary pH when the prevalence of both increases with age [29]. For that, the elderly people frequently develop chronic low grade metabolic acidosis, linked to lower retention of filtrate bicarbonates, and a reduction of acid excretion, which results in a decrease in capacity response to acid charge compared to younger subjects. This low-grade metabolic acidosis, which progresses with age, is characterized by a lower limit of normal pH and plasma bicarbonates value despite a positive balance sheet of H^+ ions [30]. Chauveau et al. [26] demonstrated that a chronical uptake of high acid load food could accentuate the development of this acidosis. They added that the ingestion of alkaline diet rich in potassium salts, provided by fruits and vegetables, is able to prevent the low grade muscular metabolic acidosis observed in the elderly subjects [26] and reduces risk of developing T2DM [31].

Nevertheless, metabolic acidosis is also associated with a defect of insulin-sensitivity and an increase in the prevalence of glucose intolerance [32]. The underlying mechanisms would likely result from insulin failure to link to its peripheral receptor in interstitial space, as well as a disruption of the intracellular PI3K signalling pathway by acidosis, physiologically observed in the downstream of insulin stimulation (Fig. 1) [23].

Vegetarians have significantly lower rates of developing T2DM than do omnivores. This may be partly explained by the greater BMI of omnivores compared with vegetarians [33]. In fact, vegetable-based diets are rich in soluble fiber and low glycemic index of carbohydrates (legumes, whole grain products such as oats and barley, fruit and vegetables) characterized by slow intestinal absorption and minimal postprandial insulin secretion, avoiding hyperinsulinemia and insulin resistance. Plant-based diets also demonstrate favorable metabolic effects in other populations [31]. However, meat and processed meat intake alone was found to be an important risk factor for diabetes even after adjustment for BMI. Higher intakes of plant foods, such as vegetables, whole grain foods, legumes, and nuts, but not fruit juice,

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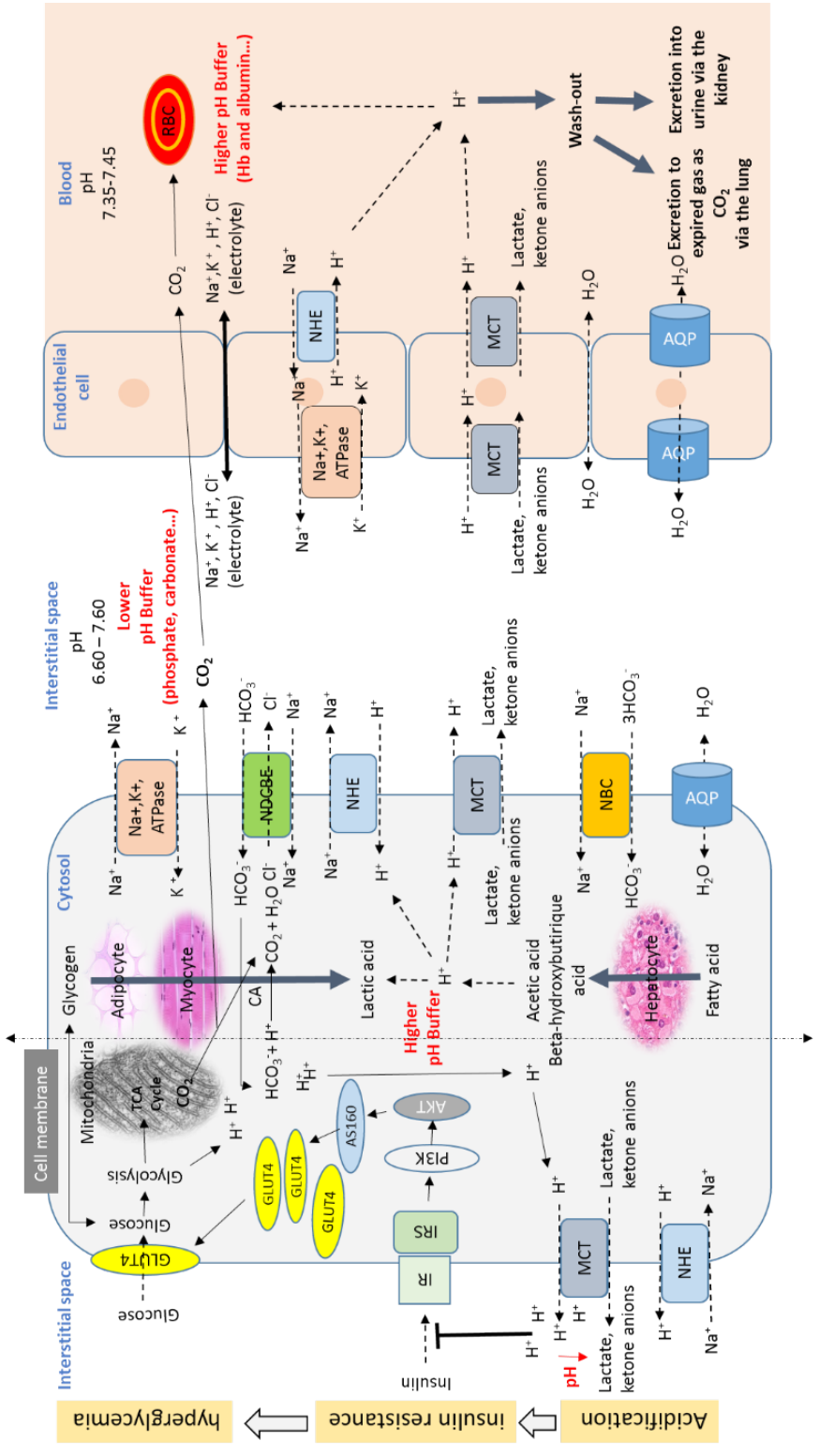

Figure 1: pH homeostasis of the most cells involved in the physiological and pathological glucose metabolism. Living cells are actively releasing proton from the metabolism of organic acid molecules that decide the pH of body fluid. Throughout metabolic tissues such as the skeletal muscles and adipose tissues, the glycolytic metabolism of glucose and glycogen under anaerobic conditions produces lactic acid (lactate$^-$/H$^+$) while the excess of fatty acid metabolism of hepatocytes promotes the production of ketone bodies, beta-hydroxybutyric and acetoacetate acids. Cells procures many ways to remove excess proton production to maintain pH homeostasis of cytosol, interstitial liquid and blood system. These PH buffering mechanisms, are assisted by many co-transporters and proteins exchangers, Na+-driven Cl$^-$/HCO_{3-} exchanger (NDCBE) and Na+-HCO_{3-} cotransporter (NBC) participate in uptake of HCO_{3-} from interstitial space into intracellular. Monocarboxylate Transporter (MCT) and Na$^+$/H$^+$ Exchanger (NHE) remove proton from the cytosol to the extracellular space supported indirectly by Na$^+$/K$^+$ ATPase pomp. In fact, protons were transported to circulation by endothelial cell transport systems. Though, in comparison to intracellular fluid and blood (high pH buffer), the interstitial fluid may quickly become acidic due to its low pH buffering capacity such as proteins. However, in skeletal muscle cells glucose and glycogen are the main energy substrates. Excessive glucose / glycogen consumption and aerobic metabolism deficiency induces lactic acid production via the glycolysis pathway leading to interstitial pH depletion. This latter, affect the binding affinity of insulin to its receptor and the glucose uptake via Glucose Transporter 4 (GLUT4). Weak interstitial fluid pH therefore induces insulin resistance and hyperglycemia by reducing insulin sensitivity to it receptor in skeletal muscle cells. IR, insulin receptor; IRS, insulin receptor substrate; PI3 K, phosphoinositide-3-kinase; AS160, Act substrate, 160 kDa; CA, carbonic anhydrase; AQP, aquaporin.

have been associated with a substantially lower risk of insulin resistance and type 2 diabetes and improved glycemic control in either normal or insulin-resistant individuals [33] (Fig. 1).

Nonetheless, vegetables and fruits are more than an excellent alkaline diet. Indeed, legumes also supply organisms with a slow-release carbohydrate and are rich in soluble fiber and factors known to improve glycemic control and overweight such as polyphenols. In related references it was deduced that a decrease in serum HbA1C levels in T2DM is correlated strongly with decrease in body weight. In contrast, poorly planned vegetarian diets can be deficient in vitamin B12, calcium, vitamin D, zinc, iron, and long-chain omega-3 fatty acids. Vegetarians need to incorporate into their diet foods that provide adequate levels of these vitamins, minerals, and omega-3 fatty acids [33]. Additionally, concerning glycemic responses to different carbohydrate foods, there exists a relationship between the rate of digestion of starchy foods in vitro and the glycemic response to them in vivo. These differences are linked to many factors that influence the rate of digestion, including the nature of the starch, the food form, the content and type of dietary fiber, and the presence of the so-called anti-nutrients [26]. In consequence, because these factors are not adequately listed in food tables, it is not possible to predict exactly the glycemic effect or acid-base balance of a food based only on its chemical composition.

Acid load and endocrine disorders

In addition to insulin resistance, many other disturbances in endocrine metabolism have been described. In fact, metabolic acidosis is observed to increase glucocorticoid secretion and decreases the accumulation of cortisol in both plasma and urine [34, 35]. Excess cortisol in metabolic acidosis can lead to insulin resistance, proteolysis [31] and increase urinary ammonium excretion resulting from protein degradation pathway [36]. Further, a contemporary acidogenic diet is also linked to excess cortisol but bicarbonate administration is associated with a significant reduction of plasma cortisol level and free cortisol urinary excretion [31]. Likewise, diabetes acidosis is marked to decrease circulating rate of IGF-1 due to peripheral growth hormone insensitivity, but at the same time it's shown to increase plasma leptin level. This latter hormone is also known for its stimulating effect on satiety, increasing uremic anorexia syndrome and energy expenditure, and finally on reduction of cardiovascular risk [23]. Parathyroid hormone (PTH) is known to contribute to acid base balance by increasing bicarbonate excretion via inhibiting proximal bicarbonate reabsorption. This effect is demonstrated by the experiment of Arruda et al. [37]. This experiment was performed on 105 rats, which demonstrate that both PTH forms, exogenous or endogenous, play a central role in buffering of acid load via its influence on carbonic anhydrase [37]. The metabolism of different foods releases or consumes H^+ ions [23].

Acidosis and oral antidiabetic treatment responses

The increased glycemic level is not the only important sign in the pathogenesis of T2D, but is the result of insulin resistance [5]. Indeed, all oral antidiabetic drugs (OADs) are primarily designed to reduce blood glucose levels by blocking glucose production, glucose reuptake or stimulating insulin release [38], but not to essentially improve insulin resistance. For example, biguanide blocks gluconeogenesis from lactate mainly in the liver; sulfonylurea stimulates pancreatic β cells to release insulin; glucosidase inhibitors reduces the intestine breakdown of carbohydrate by inhibiting glucosidases; thiazolidine stimulates adiponectin release from adipocytes leading to glucose uptake by acting peroxisome proliferator-activated receptor (PPAR); dipeptidyl-peptidase IV (DPP-4) inhibitors preserve a high level of insulin release from pancreatic β cells by blocking break-down of incretin in the intestine. Furthermore, sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce kidney's epithelium reuptake of glucose [5] independently to insulin secretion or resistance [38].

On the other side, a tremendous variability in the effect of antidiabetic drugs was observed between diabetic subjects [39]. This

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heterogeneity of treatment effects refers to the differential response to the same treatment by different patients. More specifically, this definition includes different responses of patients with different characteristics. In the literature, several theories have been proposed to explain those characteristics which can include severity of the disease under study (severe versus milder forms of the same disease); socio-demographic characteristics, such as age, sex, and race/ethnicity; genetic characteristics; and health-related behaviors, such as adherence to treatment, alcohol consumption, and use of complementary or alternative medicine [40]. Additionally, biological and non-genetic factors such as intestinal absorption, liver and kidney function or pharmacokinetic drug interactions may occur [39].

Then, significant differences between patients in terms of glucose-lowering response to OADs, tolerability and drugs incidence of adverse events is also indicated [3, 41]. To highlight this latter, metformin-associated lactic acidosis is a rare but significant adverse event and it is critical to unraveling the problem. First, this potential event continues to influence treatment strategies for T2DM, especially in many high risk patients with kidney failure, those with metformin contraindications and elderly patients [42]. Lactic acidosis is the most common cause of metabolic acidosis. It is marked by an increase in the anion gap (the concentration of sodium in the blood minus the chloride and bicarbonate concentrations) [43]. As to biguanides, they have a marked effect on glucose/lactate metabolism. Its antidiabetic properties result from the blockade of gluconeogenic precursors, such as alanine and lactate, to pyruvate. This effect is missed in other classes of antidiabetic medicines. Furthermore, all biguanides are strong bases which are fully protonated at physiological pH. Their two-dimensional structures suggest close similarities between members of this class. However, the slight differences, lead to profound variances in the behavior of these molecules in solution and also in terms of their pharmacokinetics and metabolism [43].

Faerch et al. [44] demonstrate that drugs used to treat T2DM have been a marked interaction with lifestyle and patients environment; for example, the hypoglycemic drugs such as sulfonylureas, thiazolidinediones, biguanides, and as well as lipid-lowering statins, have each been shown to interact with physical activity to influence insulin secretion, insulin sensitivity, or glycemic control [44]. The influence of each factor (genetic and epigenetic) on the development of the disease is extremely important. In fact, we cannot edit the structure of our genes, but we can influence the outcomes of their expression, e.g., through epigenetic modulation of transcription (development or prevention of the disease, drug metabolism) and through our lifestyle, in order to prevent or delay the onset of abnormalities [41].

Lower insulin sensitivity is observed in lower levels of serum bicarbonate and higher levels of anions resulting from metabolic acidosis. In fact, Mandel and colleagues [45], showed in the Nurses' Health Study a relationship between rise of plasma bicarbonate levels and reduced risk of incident T2DM among women who developed the disease after 10 years of monitoring [45]. The most interesting approach to this issue has been proposed in the work of Laboux and Azar [23], which reveal that the normalization of the plasma bicarbonate level is associated with a reduction in insulin dose and OADs posology of patients with T2DM [23]. Craig [33] has also suggested, that vegan diet characterized by low fats, poor glycemic load, and rich on fiber is observed to improved considerably glycemic control of T2DM. This funding is associated with a reduction about 43% of diabetes medication after only five months of diet [33] (Fig.2). Very few publications are available in the literature that discuss the improvement of OADs responses by an alkaline diet in acidosis situations. Further experimental confirmation of this theory on the issue would be of interest.

Conclusion

Quite recently, considerable attention has been yielded to the impact of food intake and its acid load in different pathological situation. According to this review, we conclude that the fall of interstitial fluid pH (weak pH buffering capacity) observed in T2DM leads to insulin resistance

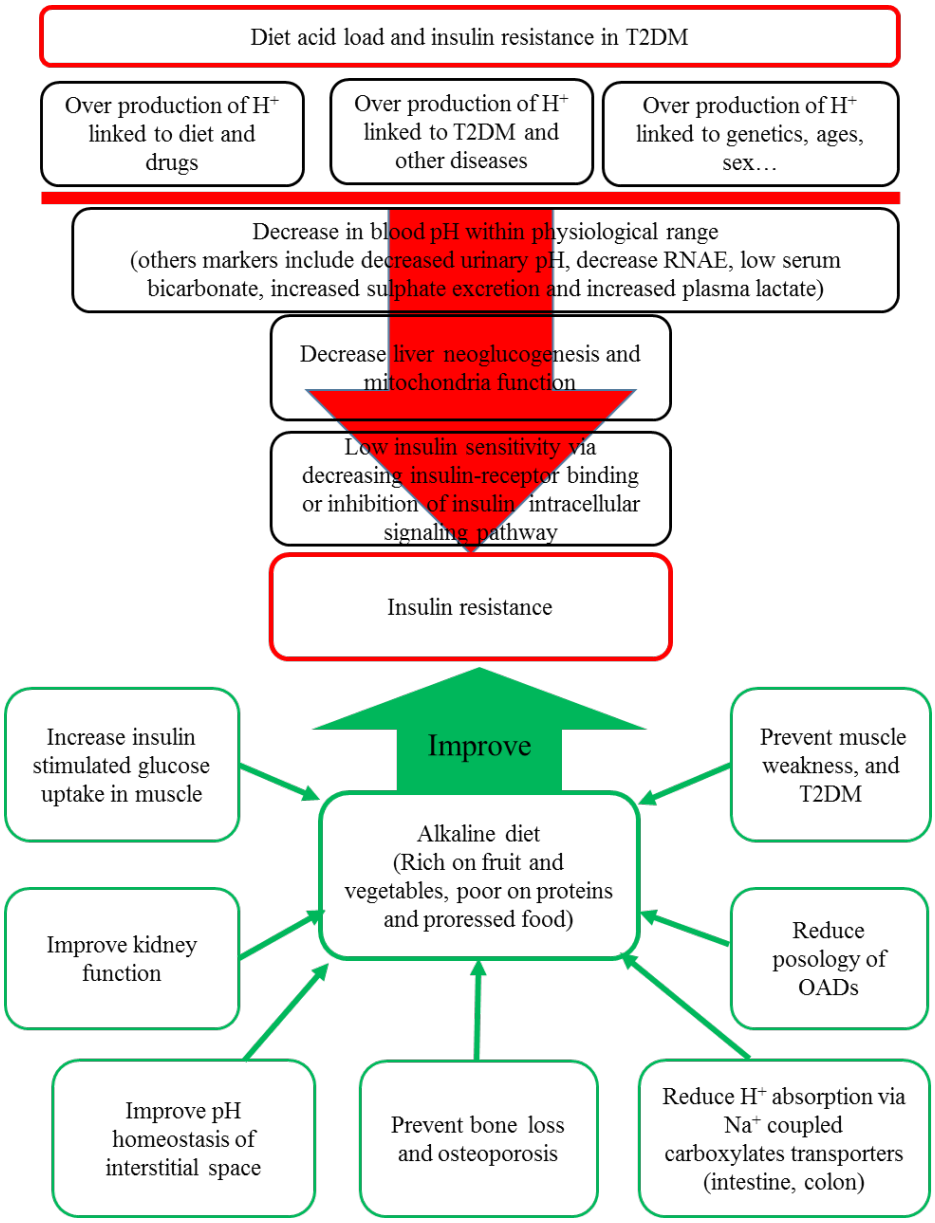

Figure 2: Summarizes dietary alkaline-acid load effects on body metabolism and insulin resistance in humans.

via reduced insulin-receptor binding affinity or via the reduction of insulin affinity with its receptor or via the impairment of intracellular insulin signaling pathway and mitochondria metabolism. Then, considering the evidence in the literature, we can believe that alkaline diets (fruits and vegetables) notably rich in vegetal proteins, soluble fiber, and low glycemic index associated with poor processed food can reduce the level of acidic load in the body and ameliorate the response of diabetic's patients to OADs. Thus, it could improve hyperglycemia and metabolic complications resulting mainly from disturbance of interstitial space pH buffering. Consequently, evaluation of acid diet load and the use of diet replacement feature (replacement of acidic food with another less acidic, referring to the table above of calculating PRAL) can be an important approach for future interventions in populations with a high risk for T2DM, especially for elderly persons. It may also contribute to the control of the body acidosis and reducing posology and side effects of OADs in this group. The next stage of our research will be experimental to confirm this theory concept.

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Conflict of interest

The authors declare no conflict of interest.

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References

1. Akter S, Eguchi M, Kuwahara K, Kochi T et al. High dietary acid load is associated with insulin resistance: The Furukawa Nutrition and Health Study. *Clin Nutr*. 35(2):453–459, 2016.
2. Forouhi NG, Misra A, Mohan V, Taylor R et al. Dietary and nutritional approaches for prevention and management of type 2 diabetes. *BMJ*. 361:k2234, 2018.
3. Emami-Riedmaier A, Schaeffeler E, Nies A, Mörike K et al. Stratified medicine for the use of antidiabetic medication in treatment of type II diabetes and cancer: where do we go from here? *J Intern Med*. 277(2):235–247, 2015.
4. Shi G-J, Li Y, Cao Q-H, Wu H-X et al. In vitro and in vivo evidence that quercetin protects against diabetes and its complications: A systematic review of the literature. *Biomed Pharmacother*. 109:1085–1099, 2019.
5. Marunaka Y. Roles of interstitial fluid pH in diabetes mellitus: Glycolysis and mitochondrial function. *World J Diabetes*. 6(1):125, 2015.
6. Marunaka Y. The proposal of molecular mechanisms of weak organic acids intake-induced improvement of insulin resistance in diabetes mellitus via elevation of interstitial fluid pH. *Int J Mol Sci*. 19(10):32–44, 2018.
7. Osuna-Padilla I, Leal-Escobar G, Garza-García C, Rodríguez-Castellanos F. Dietary Acid Load: Mechanisms and evidence of its health repercussions. *Nefrología*. 39(4):343–354, 2019.
8. Gillies RJ, Pilot C, Marunaka Y, Fais S. Targeting acidity in cancer and diabetes. *Biochim Biophys Acta Rev Cancer*. 1871(2):273–280, 2019.
9. Aoi W, Zou X, Xiao JB, Marunaka Y. Body Fluid pH Balance in Metabolic Health and Possible Benefits of Dietary Alkaline Foods. *eFood*. 1(1):12–23, 2019.
10. Puddu A, Sanguineti R, Montecucco F, Viviani GL. Evidence for the gut microbiota short-chain fatty acids as key pathophysiological molecules improving diabetes. *Mediators Inflamm*. 2014:1–9, 2014.
11. Williams RS, Kozan P, Samocha-Bonet D. The role of dietary acid load and mild metabolic acidosis in insulin resistance in humans. *Biochimie* 124:171–177, 2016.
12. Newman JC, Verdin E. β-Hydroxybutyrate: a signaling metabolite. *Annu Rev Nutr* 37:51–76, 2017.
13. Sperelakis N. Intracellular pH regulation. In: *Cell physiology source book: essentials of membrane biophysics*. Press Academic (Ed). Canada, Elsevier, pp 303–321, 2012.
14. McNamara J, Worthley L. Acid-base balance: part I. Physiology. *Crit Care Resusc*. 3:181–187, 2001.
15. Busa W, Nuccitelli R. Metabolic regulation via intracellular pH. *Am J Physiol Regul Integr Comp Physiol*. 246(4):R409–R438, 1984.
16. Schwalfenberg GK. The alkaline diet: is there evidence that an alkaline pH diet benefits health? *J Environ Public Health*. 2012:1–7, 2012.
17. Barzel US, Massey LK. Excess dietary protein can adversely affect bone. *J Nutr*. 128(6):1051–1053, 1998.
18. El-Hattab AW, Emrick LT, Hsu JW, Chanprasert S et al. Glucose metabolism derangements in adults with the MELAS m. 3243A> G mutation. *Mitochondrion*. 18:63–69, 2014.
19. Fríguls B, Joya X, García-Algar O, Pallás C et al. A comprehensive review of assay methods to determine drugs in breast milk and the safety of breastfeeding when taking drugs. *Anal Bioanal Chem*. 397(3):1157–1179, 2010.
20. Demaurex N. pH Homeostasis of cellular organelles. *Physiology* 17(1):1–5, 2002.
21. Banerjee T, Crews DC, Wesson DE, Tilea A et al. Dietary acid load and chronic kidney disease among adults in the United States. *BMC Nephrol*. 15(1):137, 2014.
22. Angéloco LRN, de Souza GCA, Romão EA, Chiarello PG. Alkaline diet and metabolic acidosis: practical approaches to the nutritional management of chronic kidney disease. *J Ren Nutr*. 28(3):215–220, 2018.
23. Laboux T, Azar R. Dietary control of metabolic acidosis in chronic kidney disease. *Nephrol Ther*. 15(7):491–497, 2019.
24. Remer T, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. *Am J Clin Nutr*. 77(5):1255–1260, 2003.
25. Frassetto LA, Todd KM, Morris Jr RC, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr*. 68(3):576–583, 1998.
26. Chauveau P, Lasseur C, Nodimar C, Prezelin-Reydit M et al. Dietary acid load: A novel target for the nephrologist? *Nephrol Ther*. 14(4):240–246, 2018.
27. Passey C. Reducing the dietary acid load: How a more alkaline diet benefits patients with chronic kidney disease. *J Ren Nutr* 27(3):151–160, 2017.
28. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc*. 95(7):791–797, 1995.
29. Menezes CJ, Worcester EM, Coe FL, Asplin J et al. Mechanisms for falling urine pH with age in stone formers. *Am J Physiol Renal Physiol*. 317(7):65–72, 2019.
30. Frassetto L, Sebastian A. Age and systemic acid-base equilibrium: analysis of published data. *J Gerontol A Biol Sci Med Sci*. 51(1):91–99, 1996.
31. Adeva MM, Souto G. Diet-induced metabolic acidosis. *Clin Nutr*. 30(4):416–421, 2011.
32. Williams RS, Heilbronn LK, Chen DL, Coster AC et al. Dietary acid load, metabolic acidosis and insulin resistance–Lessons from cross-sectional and overfeeding studies in humans. *Clin Nutr*. 35(5):1084–1090, 2016.
33. Craig WJ. Nutrition concerns and health effects of vegetarian diets. *Nutr Clin Pract*. 25(6):613–620, 2010.
34. Maurer M, Riesen W, Muser J, Hulter HN et al. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. *Am J Physiol Renal Physiol*. 284(1):32–40, 2003.

35. Ballmer PE, Imoberdorf R. Influence of acidosis on protein metabolism. *Nutr Clin Pract*. 11(5):462–470, 1995.
36. Defronzo RA, Beckles A. Glucose intolerance following chronic metabolic acidosis in man. *Am J Physiol Endocrinol Metab*. 236(4):E328, 1979.
37. Arruda J, Alla V, Rubinstein H, Cruz-Soto M et al. Parathyroid hormone and extrarenal acid buffering. *Am J Physiol Renal Physiol*. 239(6):533–538, 1980.
38. Pillon F, Tan K, Jouty P, Frullani YJAp. Le traitement médicamenteux du diabète de type 2. 53(541):23–28, 2014.
39. Becker ML, Pearson ER, Tkáč I. Pharmacogenetics of oral antidiabetic drugs. *Int J Endocrinol*. 2013:1–10, 2013.
40. Greenfield S, Kravitz R, Duan N, Kaplan SH. Heterogeneity of treatment effects: implications for guidelines, payment, and quality assessment. *Am J Med*. 120(4):3–9, 2007.
41. Tremblay J, Hamet P. Environmental and genetic contributions to diabetes. *Metabolism*. 100:153952, 2019.
42. May M, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. *Ther Adv Endocrinol Metab*. 7(2):69–83, 2016.
43. Lalau JD. Lactic acidosis induced by metformin. *Drug Saf*. 33(9):727–740, 2010.
44. Faerch K, Hulman A, PJ Solomon T. Heterogeneity of pre-diabetes and type 2 diabetes: implications for prediction, prevention and treatment responsiveness. *Curr Diabetes Rev*. 12(1):30–41, 2016.
45. Mandel EI, Curhan GC, Hu FB, Taylor EN. Plasma bicarbonate and risk of type 2 diabetes mellitus. *CMAJ*. 184(13):719–725, 2012.

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