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Dietary Acid Load and Relationship with Diseases

Sedef Güngör

Department of Nutrition and Dietetics, Atilim University of Health Sciences, Ankara, Turkey.

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ABSTRACT

The acid-base balance of the human body is influenced by the nutritional intake and dietary composition of individuals. It is of paramount importance to maintain this equilibrium for the optimal health of humans. The body receives acid or alkaline precursors from dietary intake. In general, the consumption of animal-based foods results in an acid load, whereas the consumption of plant-based foods contributes to an alkaline load. Diets high in dietary acid load cause a state of diet-induced metabolic acidosis, which is associated with the development of cardiometabolic diseases. The significance of dietary acid-base balance in the context of cardiometabolic diseases, which have emerged as a significant contributor to global morbidity, is now being acknowledged in the literature. The objective of this review is to examine the existing evidence concerning the relationship between dietary acid load and chronic diseases and metabolic disorders, as well as the potential mechanisms underlying their development.

Keywords: Dietary acid load, non-communicable diseases, potential renal acid load, net endogenous acid production

INTRODUCTION

Non-communicable diseases (NCDs) are usually chronic diseases and are the result of genetic, physiological and environmental factors. They are the leading causes for illness and death worldwide. NCDs are responsible for 74% of all deaths worldwide [1]. Cardiovascular diseases (CVD), chronic respiratory diseases and diabetes, as well as cancer, are the main types of NCDs. A person's chances of developing a disease are influenced by various controllable and uncontrollable risk factors. Lifestyle factors (e.g. smoking, physical activity and diet) are modifiable risk factors that need to be addressed to prevent NCDs[2,3]. Among these risk factors, changing dietary habits is one of the important strategies in preventing or delaying NCDs.

Dietary patterns are used to examine the relationship between dietary habits and NCD risk. Dietary patterns take into account long-term consumption of nutrients. It is important to evaluate dietary patterns because the relationship with chronic diseases is long-term[4-6]. Through the intake of acid or base precursors, nutrient intake affects acid-base status. Western-style diets are high in animal protein and processed foods. These contribute significantly to the dietary acid load (DAL). In contrast, fruits and vegetables, which have an alkalising effect and are generally low in DAL, are consumed in insufficient quantities[7,8]. High dietary acidity is linked to a poor cardiometabolic risk factors profile, including hypertension, obesity, high triglycerides, high LDL cholesterol and diabetes[9-14]. Based on the available evidence, it has been suggested in recent years that high DAL may influence chronic diseases[15,16].

Acid-base balance

The acid-base balance refers to the balance of the concentration of positively charged hydrogen ions (H^+), which are the active component of all acids, in the extracellular fluid[17]. The pH of blood reflects the net production, buffering and elimination of all acids and bases within the system. The pH level considered normal has a range[18]. The pH of blood is approximately 7.40. While the pH of blood is maintained within the range of 7.35 to 7.45, the body employs buffer systems to prevent the occurrence of acidosis (pH below 7.35) or alkalosis (pH above 7.45), which refers to any change in this value. This is because maintaining blood pH within a certain range is critical for maintaining metabolic homeostasis[19]. A complex buffering system, involving the lungs and kidneys, is responsible for maintaining the body's acid-base balance and blood pH within the optimal range.

The organs involved in acid-base balance play many roles, but the main function of the lungs is to remove carbon dioxide (CO_2). The kidneys reabsorb filtered bicarbonate (HCO_3^-) and remove ammonia (NH_4^+) in the urine. However, plasma bicarbonate and pH fall if your body produces more acid than it can eliminate by lung and kidney. As a result of metabolic processes, an arterial pH of 7.35 or less and/or a low HCO_3^- concentration produces what is clinically described as chronic metabolic acidosis, a state of stress for the body[20,21]. The lungs are the primary organ used to neutralize acute metabolic acidosis and respond more rapidly. However, chronic acid-base imbalance is mainly regulated by the kidneys and they are slower to react, taking hours or even days to respond[22].

Maintenance of acid-base homeostasis is important. A multitude of biochemical processes involve the generation or consumption of acids and bases. In biological systems, acids are divided into volatile acids and endogenous acids, which are non-volatile acids that are the result of diet or metabolic processes within the organism. Net endogenous acid production (NEAP) is described as the difference between alkaline substances obtained from the gastrointestinal tract and endogenous acid production. NEAP is also used to define DAL[23].

Dietary acid-base balance

Nutrients and endogenous metabolic processes either produce or consume hydrogen ions and thus acids and bases. Under normal physiologic conditions, diet is the main determinant of net endogenous acid production and changes in diet can have various consequences for acid-base balance[23,24]. Short-term DAL may cause transient acid-base imbalance, but is rapidly compensated and has no clinical effect. Prolonged consumption of diets high in DAL may cause blood pH levels to fall within the optimum range of the spectrum but towards the lower end of the spectrum. However, these decreases are not beyond the physiologic range. In fact, when blood pH falls below 7.4, there is usually acid retention and low-grade metabolic acidosis in the body. Nevertheless, the pH of blood does not decline below the normal range until the severity of metabolic acidosis reaches a critical point. Diet-induced acidosis is different from clinical metabolic acidosis. Clinical metabolic acidosis is often triggered by a deficiency in the system's ability to neutralise the effects of blood pH fluctuations caused by non-dietary factors. This frequently culminates in a blood pH below 7.35. Although the pathophysiological implications of clinical metabolic acidosis are known, the exact impact of diet-induced metabolic acidosis is not known[25-27].

When the contents of foods are analysed, it is seen that most of the foods contain acid precursors, while fruits and vegetables contain base precursors. The main source of endogenous acids in the body are volatile acids produced as a result of reactions during the oxidation of macronutrients. In a steady state, these reactions is balanced by their continuous production and

consumption, preventing the accumulation of acid. However, in the event of incomplete oxidation of these macronutrients, an overabundance of H^+ is generated, leading to increased production of endogenous acids[18,23].

Following the digestion of food, the stomach secretes H^+, while the pancreas provides the digestive tract with alkali. Following oxidation, these amino acids release protons (H^+) and organic acids release alkalis, thereby affecting the acid-base balance and ultimately being excreted by the kidneys. Although the intestines do not directly contribute to acid or base production, they influence acid and base formation as a consequence of metabolism and absorption[24].

Diet has the potential to influence acid-base status by providing acid and alkaline precursors from food[18]. Foods rich in sulphate, phosphorus and protein such as meat, poultry, fish, cheese, cereals and rice are the determinants of DAL, while foods high in potassium, magnesium and calcium such as legumes, fruits and vegetables are the determinants of alkaline load. DAL is therefore a balance between foods that provide acid and foods that provide base precursors[24,28,29].

The recent Western dietary pattern is characterised by excessive intake of highly processed and refined foods, high levels of added sugars, salt and high levels of (saturated) fats and proteins from animal products, and low levels of alkalising plant foods[30,31]. Today's diets are poor in magnesium, potassium and fiber and rich in saturated fatty acids, simple sugars, sodium and chloride compared to the diets practiced by our ancestors. Therefore, today's diets are net acidic, whereas the diets of our ancestors were net alkaline. Acid-base balance can also be affected by changes in diet over time[32,33].

Dietary formulas for estimating the acid or alkaline effects of nutrients have been developed based on this information. The use of dietary intake estimates avoids the need to measure the net acid excretion from the kidneys. However, these formulas require quantitative analysis of both dietary cations (potassium, calcium, magnesium) and anions (sulfate, phosphate). Formulas may also include factors related to ion absorption from the intestine[18].

Potential Renal Acid Load (PRAL)

DAL can be estimated by the potential renal acid load (PRAL), which represents the acid excretion caused by a nutrient or the diet. Remer et al. proposed a mathematical model to estimate PRAL that incorporates the amounts of micronutrients present in an individual's regular diet. PRAL estimates endogenous acid production in excess of alkali production for foods consumed daily. The model takes into account the differing absorption rates of minerals and protein involved in acid and base production, as well as the quantity of sulphate derived from metabolized protein[34]. The PRAL equation used to measure the DAL of a food or diet is shown below;

PRAL (mEq/day) = (0.49 × total protein (g/day)) + (0.037 × phosphorus (mg/day)) - (0.021 × potassium (mg/day)) - (0.026 × magnesium (mg/day)) - (0.013 × calcium (mg/day))

The PRAL equation provides an estimate of the milliequivalents (mEq) of H^+ present per 100 grams of food. Animal foods generally have positive PRAL values, with the exception of milk, whose phosphorus content is compensated by the amount of calcium. Foods with a positive PRAL (PRAL > 0) increase renal acid load by producing H^+ ions. Conversely, foods with a negative PRAL (PRAL < 0) are thought to decrease renal acid load and thus increase the body's buffering capacity. Vegetables and fruits have a negative PRAL and are considered the largest dietary buffer source due to their high potassium content. Proteins found in plants have a neutral effect as they are rich in glutamate, which utilizes H+ ions[35].

Net Endogenous Acid Production (NEAP)
It is defined as a measure of the difference between the acid-producing and alkaline-producing components of a food. It is determined by the balance between the fixed acid load from protein and the alkali load from potassium in the diet[36]. Therefore, Frassetto et al. developed a model that includes the protein and potassium ratios in the diet, which can predict the net endogenous acid production of the diet[28]. The NEAP equation is shown below;
NEAP (mEq/day) = (54.4 × protein (g/day) / potassium (mEq/day)) - 10.2

Dietary Acid Load and Relationship with Chronic Diseases
As mentioned earlier, the body can effectively buffer transient elevations in DAL but chronic exposure can lead to metabolic acidosis. Such a condition is recognized to increase the risk of cardiometabolic diseases and cancer, thus significantly affecting morbidity and mortality. In addition, damage such as breakdown of muscle, connective tissue and bone can occur if buffering capacity is reduced or the acid load cannot be met[27,37].

Bone mineral density/Osteoporosis
Bone health can be affected by things like gender, alcohol, smoking, not getting enough exercise and diet. One of the dietary factors proposed to affect bone mass is DAL, which can affect plasma acid-base balance. Because of its high calcium content, bone tissue acts as an important buffer against acid loads and responds even faster than the proton excretion mechanism of the kidney. Diet-induced metabolic acidosis reduces the activity of osteoblasts and induces osteoclast-mediated bone resorption, leading to bone mineral dissolution to maintain acid-base homeostasis. Increased osteoclastic activity releases calcium and phosphorus from bone, which maintains serum pH in the normal range and increases calciuria. This process occurs during skeletal growth and the acid load in the diet can affect bone mass formation. Reduced bone mass weakens the bone and can lead to an increased risk of osteodystrophy, osteoporosis and fractures, especially later in life. For older people with reduced kidney function, this is particularly important. Since the western diets favored in recent decades are typically high in DAL, constant acid stress may affect bone mass[38-41].

During the period of childhood and adolescence, there is a pronounced increas in bone size, which results in an elevated requirement for calcium and protein. Some studies in children have indicated that there may be an inverse relationship between dietary acidity and bone mass. Studies have suggested that high DAL may be associated with decreased cortical bone area and bone density in children[41,43,44]. However, findings on the relationship between DAL and bone health in adults are controversial. High DAL has been associated with reduced bone density and bone structure in some studies[18,41,45-48]. However, other studies have failed to find any evidence of such a link[39,49,50]. This inconsistency has also been documented in observational studies investigating the association of DAL with fracture risk[51-53]. Distinctions based on protein source have also been examined in studies. Plant-based protein is thought to have less acidogenic properties compared to animal-based protein. This is because animal-based protein sources contain more sulfurous amino acids and the metabolism of these amino acids can physiologically lead to increased acidity. Over time, this can be harmful to bone strength and health. However, phytates in cereals contain phosphate. Phosphate can physiologically contribute to increased acidity[38,54]. A meta-analysis examining the effects of protein source on bone mineral density found no significant evidence that consumption of plant protein was more beneficial for bone mass than consumption of animal protein[55]. Calcium excretion has been shown to increase with high protein intake. As protein intake increases, urinary calcium may increase and a negative calcium balance

may develop. However, increased calciuria does not necessarily mean calcium loss, negative calcium balance and decreased bone mass. It has also been claimed that high protein diets have no effect on calcium homeostasis. It is therefore possible that increased calcium intake may be counterbalanced by enhanced intestinal absorption[25,56]. A study of 100 obese/overweight women found no difference in serum osteocalcin levels between groups on a high carbohydrate diet or protein diet[57]. Data in this area remain conflicting, with studies, including the Framingham osteoporosis study, reporting that dietary protein intake is protective against fracture risk[58].

It has been demonstrated that adequate protein intake stimulates the action of IGF-1, which helps to build bone and increase calcium absorption. This helps build and maintain bone tissue[54]. In the elderly population, protein may be particularly beneficial in preventing bone loss and slowing the progression of osteoporosis. A systematic review of studies in the elderly suggested that protein intake above the recommended daily protein intake may play a beneficial role in reducing hip fracture risk, maintaining bone mineral density and preventing bone loss[51]. A positive association was observed between bone mineral density and total and animal protein intake compared to vegetable protein intake[59]. The existing literature on this topic exhibits considerable inconsistencies. However, a diet high in fruit and vegetables can alleviate the acid load from protein and reduce the possible negative impact on bone health. A diet with a high amount of fruit and vegetables can have a beneficial effect on bone health due to the high amount of potassium and lower acid content. A balanced diet including adequate energy and protein intake (both plant-based and animal-based) and adequate physical activity are crucial to ensure bone health. In the context of dietary interventions, it is especially important to address both the amount and type of protein consumed in older people and those with multiple comorbidities[25,54].

Sarcopenia

Decline in muscle mass and bone mineral loss are important public health problems in the aging population[60]. Muscle strength and muscle mass decline with aging; however, the decline in muscle strength is more rapid. Reduced muscle strength in the elderly may increase the risk of frailty. Several factors such as lifestyle, diet quality and eating patterns, low protein intake, obesity and physical activity can have negative effects on muscle strength[40,61].

Chronic metabolic acidosis can reduce muscle protein synthesis by causing increased cortisol production and stimulate deterioration in skeletal muscle function by increasing proteolysis. Amino acids released as a by-product of muscle breakdown can be utilised by the liver for the synthesis of glutamine and for ammonia in the kidneys. At a later stage, ammonia captures H^+ and excretes them as ammonium ions. Skeletal muscle is therefore responsible for the reduction of acidosis in order to maintain acid-base balance. However, this will lead to a decrease in muscle reserves and loss of muscle mass in individuals with a high acid load diet[40,62,63]. A positive association between lean body mass and the consumption of an alkaline diet rich in fruits and vegetables was found by Welch et al[64]. This study emphasised the importance of magnesium and potassium, in addition to protein, in maintaining muscle mass. An inverse association between skeletal muscle mass and DAL was also found in another study of overweight/obese women[62]. Faure et al.[65] found that DAL had a negative effect on total body lean mass only in elderly women.

Chronic kidney disease

There is no specific diet to help prevent kidney disease from developing or progressing. However, a disturbed balance of DAL can damage the kidneys. To neutralise the H^+ load entering the proximal

tubular cells, diets with a high acid load stimulate the production of ammonia. This results in the development of tubular hypertrophy and glomerular hyperfiltration, a condition that may be reversed during the initial stages of chronic kidney disease (CKD). The production of three substances-endothelin-1, angiotensin II and aldosterone - increases as the concentration of H^+ in the tubular cells rises. These promote the release of pro-fibrotic factors, which in turn result in a reduced glomerular filtration rate (GFR) with prolonged consumption of acid-producing foods[66,67]. A US study suggested that markers of kidney damage (increased albuminuria and decreased GFR) may increase with a diet high in DAL[68]. In a study by Rebholz et al.[66], which followed subjects for approximately 21 years, a high DAL was seen to be related to an increased risk of developing CKD. Two recent systematic reviews have confirmed associations between DAL and increased risk of CKD and reduced renal function[69,70].

Metabolic acidosis, a complication due to decreased renal acid excretion in patients with CKD, is a modifiable risk factor for CKD progression. Once kidney damage develops, diets high in acid contribute to metabolic acidosis, accelerating disease progression and increasing the risk of end-stage renal failure (ESRD)[66,71]. In the study by Banerjee et al.[71], patients with CKD who followed a diet with a higher DAL had faster progression to ESRD. When patients with CKD have metabolic acidosis, alkali supplementation or reduced acid intake can raise serum bicarbonate, slow eGFR decline, and reduce urine albumin excretion[72].

NKF/KDOQI clinical practice guideline in CKD says eating more fruit and vegetable can slow down the decline in kidney function, body weight, blood pressure and DAL[73]. Dietary interventions or alkaline supplements can reduce acid excretion and slow disease progression. Increased fruit and vegetable intake may offer health benefits comparable to alkaline supplementation in reducing metabolic acidosis[74,75]. In accordance with findings, dietary modification to reduce DAL may be undertaken as a cost-effective, low-risk preventive strategy with the potential to prevent CKD in healthy individuals and to protect the kidneys in CKD patients.

Nephrolithiasis (kidney stone formation)

It is known that the risk of CKD or ESRD is increased by nephrolithiasis, a condition associated with the presence and formation of kidney stones. Calcium stones are the most common kidney stones. Diet is an important factor in causing kidney stones to form. Consumption of liquids, sodium and animal protein can contribute to calcium stone. Therefore, increasing fluid intake and decreasing sodium and animal proteins are generally recommended to prevent calcium stone recurrence. The risk of kidney stone formation may be affected by changes in DAL. Calcium and nutrients in vegetables and fruits (which are rich in potassium and magnesium) can increase urine pH, while animal-based proteins and components of an unhealthy diet can lower urine pH and increase calcium oxalate stone formation. In response to diet-induced metabolic acidosis, the kidneys attempt to restore acid-base balance. This promotes the formation of calcium oxalate crystals by increasing calcium and oxalate excretion and decreasing citrate excretion[7,76,77]. Studies have confirmed that as DAL increases and vegetable intake decreases, the risk of developing kidney stones increases. It emphasises that to lower the risk of kidney stones, the eating of plant foods should be encouraged to balance the acid load from animal foods[78,79].

Hypertension

Diet is likely to affect blood pressure (BP). Appropriate management of dietary components can help control or prevent hypertension[80]. People with a diet high in DAL consume less BP-lowering minerals. Urinary magnesium and calcium excretion may increase and intracellular potassium

may decrease with high acid load. A decrease in potassium leads to an increase in intracellular sodium to maintain intracellular volume and tonicity, which can exacerbate hypertension. At the same time, diet-induced metabolic acidosis can raise blood pressure by increasing cortisol and decreasing citrate excretion. When a diet high in DAL becomes chronic, renal function decreases and BP may rise[81].

Studies have reported that high DAL may contribute to high BP[10,82,83]. In a meta-analysis study, DAL was demonstrated to be a probable risk factor for hypertension[80]. Krupp et al[83]. found significant associations between blood pressure and prevalence of hypertension and potassium intake and DAL. Akter et al[82]. also obtained similar results with the previous study. A significant relationship between the incidence of hypertension and acid load was also found by Zhang et al[84]. The study by Taylor et al[85]. confirmed that factors regulating urinary citrate excretion may also be effective in hypertension. However, there are studies that have not found a link between DAL and blood pressure or hypertansion[8,86].

Insulin resistance/diabetes

Insulin resistance (IR) has been identified as an important factor causing the development of many metabolic diseases, including the development of diabetes. Lifestyle factors have proven effective in preventing or delaying diabetes. Dietary changes are also described as the first step in initiating diabetes treatment. Preferred dietary style and choice of nutrients can be influential in diabetes risk, so it is important to know dietary ingredients and their effects on diabetes[87,88]. The link between dietary acidity and diabetes has recently been highlighted[13]. Meta-analyses have concluded that DAL may be a link between IR and diabetes[89,90]. In the Korean study, a positive relationship was found between DAL and future IR development. However, they also pointed out that this effect may be influenced by various other factors such as gender, age and obesity[91]. A recent population-based study excluding individuals with diabetes and those on diabetes treatment found that higher DAL was associated with higher IR and insulin levels but not with other glycemic parameters. Beta cell function was also not affected by higher DAL[92].

IR is a risk factor for developing diabetes including. In a cohort study conducted by Fagherazzi et al. on 66,485 women followed for 14 years, DAL was reported to be a risk factor in addition to the known risk factors for diabetes[93]. The association between diabetes and DAL was established by Kiefte-de Jong et al[13]. In a case-control study of 147 people with pre-diabetes, people with pre-diabetes had an increased acidogenic diet in comparison with a control group. It was also shown that high DAL was associated with increased prediabetes morbidity[94]. A case-control study comparing 125 people with newly diagnosed diabetes and healthy controls suggests that a high DAL may be connected to an elevated risk of incident diabetes[14]. Among older men without diabetes, high DAL were not linked to insulin sensitivity, beta-cell function or diabetes risk. Another study, from Akter at al., linked higher DAL to an increased risk of diabetes in men[95,96].

How diet-induced metabolic acidosis increases IR remains unclear. However, some mechanisms have been proposed for their relationship. The first of these mechanisms is that low blood pH has been proven to reduce both the number of insulin receptors and the activity of the reduced number of receptors. Impaired binding of insulin to receptors may result in reduced glucose uptake by muscle tissues and worsen β cell function, leading to IR and diabetes[97]. The second possible mechanism is that a high DAL causes an increase in cortisol. As the H^+ concentration increases, cortisol secretion is stimulated and chronically high cortisol levels can be the cause of IR[98,99]. The third mechanism is that low urinary citrate excretion may be correlated with IR. At high DAL, our body

excretes less urinary citrate, which may lead to IR[95,100,101]. The last possible mechanism is that the disturbance of acid-base balance affects the absorption of magnesium and calcium, which are essential for the normal function of insulin. Mild metabolic acidosis increases the excretion of magnesium and calcium from the body, which may lead to IR[102,103]. However, dietary patterns may contribute to obesity and IR. This makes it difficult to determine exactly how DAL is involved in developing IR independent of obesity.

Obesity

The relationship between obesity and the subsequent development of chronic diseases, including diabetes, IR, CVD and hypertension, has been established in literature. Given the rising prevalence of obesity-related illnesses, preventive strategies are becoming increasingly crucial. Among the strategies identified, it is of paramount importance to alter behaviours related to nutrition and diet[83,105,106]. An elevated DAL rating is associated with increased triglyceride concentrations and prevalence of obesity. A reduction in the DAL may prove beneficial in the fight against obesity[105]. Previous evidence suggests that consuming an acidogenic diet leads to the accumulation of hydrogen ions associated with weight gain. Excess intake of animal foods and meat and the adoption of westernized diets lead to higher organic acid production and fatty acid oxidation, especially in obese individuals[106]. A study of 456 children in Iran reported that children consuming a more acidogenic diet had a higher risk of general and central obesity[107]. Studies have shown that high DAL is linked to certain body measurements. A study of 207 students aged 18-25 years found that high DAL was related to higher weight, fat mass, hip circumference, and lower fat-free mass. It was suggested that this could be a link with obesity[108]. The study found that higher DAL may be negatively associated with resting metabolic rate, but directly related to higher waist circumference, IR, diastolic BP and waist-to-hip ratio in obese or overweight women[109]. Overall, obesity was associated with higher DAL. It may be feasible to mitigate the likelihood of developing metabolic disorders by focusing on the reduction of DAL in individuals with obesity.

Cardiovascular Disease and Mortality

Poor dietary habits, age, genetics, sedentary lifestyle, hypertension, obesity, diabetes, dyslipidemia and smoking are known risk factors for CVD. Identifying these risk factors in individuals is important for determining the appropriate treatment and prevention strategy. Changing dietary habits among risk factors is an important approach in the management and prevention of CVD and mortality, and can reduce mortality and increase life expectancy. A considerable body of research has been conducted to investigate the impact of DAL on cardiometabolic risk factors[15,110].

High DAL has been associated with an undesirable cardiometabolic risk profile[9,10,13,93,99]. A study of 11,601 patients in Korea found that a high DAL was associated with an increased risk of CVD, even when obesity and IR were taken into account[111]. In a cross-sectional study of 371 women, Mozaffari et al[112]. reported that women with high DAL tended to have higher weight, waist circumference and triglyceride concentrations. Nevertheless, no association was observed between DAL and CVD incidence or risk factors in the Polish and Iranian studies[113,114].

CVD is today the most prevalent cause of mortality worldwide. A diet with too much acid in it is linked to more chronic diseases, so a higher DAL is likely to raise the risk of CVD, hypertansion and death. In 454 people who had previously undergone coronary artery bypass grafting surgery, they reported that a higher DAL was associated with an increased 10-year mortality risk[15]. The Japanese study revealed a statistically significant correlation between a high DAL level and an elevated probability of

mortality from all causes and CVD[96]. Xu et al[115]. found a U-shaped relationship between DAL and mortality. Both high alkaline diets and high acid diets were associated with higher mortality. The lowest mortality rate was seen in those adopting an acid-base balanced diet.

Despite the lack of clarity surrounding the precise mechanism through which DAL is linked to CVD, several potential explanations have been put forth. These include increased body weight, IR, high blood pressure and effects on lipid metabolism. A high DAL may elevate the risk of IR by impeding the capacity of insulin to interact with its receptor, but high acid load may increase CVD risk independently of IR through several pathways, including impaired coronary microcirculation and increased arrhythmogenesis[96,116,117]. Another mechanism is that the increased metabolic acidosis associated with high DAL increases cortisol production, ammonia formation and renal acid excretion. This may lead to hypertension[114]. The final mechanism is that elevated cortisol concentrations can stimulate lipase activity, resulting in elevated free fatty acid concentrations in the bloodstream and augmented production of very low-density lipoproteins (high TG concentrations) in the liver[111,112].

The Mediterranean diet has been demonstrated to have a beneficial effect on cardiovascular health and metabolic health. It is rich in bioactive nutrients and their combination contributes to the health-promoting effects of the Mediterranean Diet. A study of 448 adults found that adherence to the Mediterranean diet was not associated with a reduction in the estimated risk of CVD and metabolic syndrome. Nevertheless, a high DAL was associated with a greater prevalence of metabolic syndrome and an elevated risk of CVD[118].

Steatotic liver disease associated with metabolic dysfunction (MASLD)/ non-alcoholic fatty liver disease (NAFLD)

In June 2023, NAFLD, also known as MASLD, was officially redefined. MASLD was defined within the steatotic liver disease construct as an umbrella term that facilitates the classification of various liver disorders with abnormal fat accumulation. This new term includes a more metabolic-oriented definition and two stigmatizing terms (non-alcoholic and fatty) have been removed from the definition of the disease[119,120].

MASLD is associated with many lifestyle and nutrition-related risk factors, including metabolic syndrome, dyslipidemia, diabetes, obesity and IR. Diet is a significant contributing factor in the development of MASLD. Different dietary patterns and habits can prevent or enhance the progression of MASLD[121,122]. In the context of the development of chronic diseases, it can be posited that high DAL may be an effective factor. Therefore, we hypothesized that DAL has a potential association with MASLD. A cross-sectional population study showed a moderate association between NAFLD and DAL[123]. A positive association between DAL and NAFLD was reported in a cross-sectional study including 18,855 individuals in the US[124]. A prospective cohort study, an independent and non-linear association between acidic diet and NAFLD was found[125]. A recent case-control study, the relationship between DAL and NAFLD was found to be U-shaped[126].

NAFLD is a form of the metabolic syndrome that affects the liver. Although the precise mechanism by which DAL exerts its influence on the pathogenesis of NAFLD remains elusive, the correlation between high DAL levels and multiple components of the metabolic syndrome, including elevated BP, IR and obesity, suggests the possibility of underlying mechanisms. Furthermore, it has been demonstrated that reduced levels of growth hormone (GH) and IGF-1 are correlated with an elevated prevalence of NAFLD amongst adults. Diet induced metabolic acidosis suppresses GH secretion and the IGF-I response, leading to resistance. It is

postulated that high DAL may contribute to hepatic triglyceride accumulation, potentially through their effect on the GH-IGF-I system[123,127,128].

Cancer

Globally, cancer represents a significant cause of morbidity and mortality. Exposure to risk factors has been demonstrated to exert a pivotal influence on the biological characteristics of the majority of cancer types. The etiology of most cancer types is complex, including lifestyle, environmental and genetic factors. The identification of modifiable risk factors is of significant importance in the context of cancer prevention. Diet can influence the body's hormonal, metabolic and inflammatory responses and can be an important factor in cancer prevention strategies[129,130]. In general, a diet rich in vegetables and fruit reduces the risk of cancer, while a high intake of animal products, especially red and processed meat, can increase cancer risk. Similarly, studies have identified a positive association between the consumption of a Western-style diet, which is characterized by a high intake of animal products and processed foods, and the development of different types of cancer. It is postulated that diet-induced metabolic acidosis contributes at least partly to the increased risk of developing this condition[131,132]. Two recent meta-analyses have found an association between a DAL and an increased risk of cancer, as well as an unfavourable prognosis for cancer, and have concluded that it is a significant risk factor for this disease[129,133]. This state of diet-induced metabolic acidosis may be considered a systemic stress, with the potential to induce severe metabolic alterations that promote cancer. The main mechanism between cancer and DAL is thought to be through IR. However, indirectly acid-base imbalance can stimulate carcinogenesis or metastasis[134]. An acidic diet can reduce adiponectin levels, causing an increase in insulin and therefore an increase in IGF-1. Insulin and IGF-1 are thought involved in the development of cancer by inhibiting apoptosis. At the same time, increased IGF-1 may also trigger angiogenesis and metastasis. In another possible mechanism, elevated cortisol due to an acidic diet may suppress the immune system, prevent apoptosis of cells with mutations, and cause increased DNA damage[133,135].

A large-scale study conducted in Uruguay provided epidemiological evidence based on ten case-control studies involving 3736 cancer cases and 9534 controls. Studies of many types of cancer have been part of this review. It found that dietary intake of DAL was related to cancer risk, and that cancer risk was also related to amount of methionine in animal food relative to DAL. The researchers suggested that reducing high levels of methionine could help reduce the risk of cancer caused by high levels of DAL[135]. In a prospective cohort study by Shi et al.[136], DAL was positively associated with pancreatic cancer. A case-control study in Korea involved 923 patients with colorectal cancer. As has been the case in other studies, an acidic diet has been shown to have a positive effect on cancer risk. The positive association was also found to be stronger for women than men. It was also highlighted that acidogenic diets should be given special consideration, especially in the setting of cancer prevention in women[137]. Data from a total of 43,750 participants in the Sister Study were analysed in a prospective cohort study that was conducted in the US. The study found a positive link between DAL and breast cancer risk. Evidence also suggests that diets rich in fruit and vegetables can help prevent breast cancer[138]. However, unlike these studies, a case-control study of 150 Iranian women with breast cancer found that DAL was not associated with breast cancer incidence[139].

CONCLUSION

In conclusion, the results of various studies have indicated that DAL may be an effective intervention in the occurrence or development of cardiometabolic diseases.

The Western-style dietary patterns currently observed are associated with an increased risk of cardiometabolic diseases. This may be, at least in part, due to the high content of DAL observed in these diets. Nevertheless, research exploring the correlation between high DAL and negative health outcomes is predominantly observational. The direction of causality in the association between adverse health outcomes and other factors remains unclear. Consequently, longitudinal cohort and dietary intervention studies are required in order to ascertain the relationship between high DAL and diseases and metabolic outcomes.

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