Salt, protein, phosphate and sugar: nutrition trends in kidney disease

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Abstract

Dietary modification has long been considered a modifiable risk factor for the progression of chronic kidney disease (CKD) and a key management strategy in end-stage kidney disease. This review will focus on the history of the reoccurring focus on dietary components of salt and protein, as well as the impact of consumer behaviour moving towards convenience foods, on intake of phosphate and sugar in the form of fructose.

The latest evidence in CKD supports diets low in sodium, discourages strict diets low in protein and presents a strong case to turn the cycle of eating habits back to basics, in a bid to lower processed food intake and improve the health outcomes of our CKD patients.

Keywords

Nutrition, kidney disease, diet, sodium, phosphate.

Background

In this anniversary year of the *RSAJ*, it is timely to reflect on trends in research and practice for the nutritional management of kidney disease. In modern history, there is no better example that reflects history repeating itself than diet trends or 'fads' coming in and out of vogue in a cyclic nature.

When we consider patterns of research informing practice in the nutritional management of kidney disease, there is a long history of reoccurring focus on salt and protein intake, and a new focus on the role of processed and convenience foods in dietary management of chronic kidney disease (CKD).

Dietary salt restriction

Public health recommendations for restricting salt intake has been rather controversial over the last 40 years since it was first promoted in the *Dietary Goals for the United States* as a health promotion strategy (US Senate Select Committee, 1977). Its time course for recommendation in kidney disease management follows a similar, yet less controversial path. The initial impetus for this recommendation came from observational studies. Since this time, large scale observational studies such as INTERSALT (Intersalt Cooperative Research Group, 1988), followed by intervention studies TOHP I and II (Cook *et al.*, 2007) and the DASH study (Appel *et al.*, 1997), have highlighted benefits for lowering sodium intake on blood pressure (BP) management in the general population. However, there has been ongoing criticism of this approach, with suggestions that the science of salt is not scientific but political (Graudal & Jürgens, 2013), and as such, the cyclic nature of a 'low-salt diet' in CKD has followed. An overview of the current evidence for sodium restriction in CKD, which up until recently was drawn primarily from data from non-CKD populations, is provided below.

Salt is a substance in great abundance in the food supply. There is a clear imbalance between physiological need for sodium, guideline recommendations and actual sodium intakes, particularly in Western and Asian countries (Elliott & Brown, 2007). The physiological need for salt is thought to be in the order of up to 1.0 g/day (Morris, Na, & Johnson, 2008) whereas guidelines state up to 2.3 g/day is acceptable (Chan & Johnson, 2013). Further, current intakes are well above both of these, in the order of 3.5–4.6 g/day (Elliott & Brown, 2007).

Salt plays a key role in homeostasis of fluid and blood volume. This is achieved by action of the renin-angiotensin aldosterone system (RAAS) (Kobori, Nangaku, Navar, & Nishiyama, 2007). In the event of increased blood volume and/or blood pressure, inhibition of RAAS is triggered, resulting in an increased excretion of sodium and fluid via the kidneys (Kobori *et al.*, 2007). In the case of CKD, however, the responsiveness of RAAS is compromised, which results in fluid imbalance and issues of BP regulation, most commonly hypertension. In addition to this physiological disturbance, patients with CKD are thought to be particularly salt-sensitive, which further exacerbates the issue (Doulton & MacGregor, 2004).

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Sodium is recognised as a modifiable risk factor for cardiovascular disease (CVD) and key for the management of BP and albuminuria, which are, in turn, cornerstones of CKD treatment (Ritz & Mehls, 2009). In addition, a variety of metabolic consequences of high sodium intake have been hypothesised, including a direct effect on endothelial function, mediated through increasing oxidative stress and inflammation. These factors further exacerbate the effect of a high-salt diet in CKD (Ritz, Dikow, Morath, & Schwenger, 2006).

Meta-analyses of randomised-controlled trials (RCT) in the general population support reducing dietary sodium intake, thereby reduced BP (Feng J He, Li, & MacGregor, 2013). Variations in the results of these trials are generally due to different amounts of dietary sodium reductions between interventions. This verifies the concept from observational trials, which demonstrate the dose-dependent effect of sodium reduction on BP changes (He & MacGregor, 2008). This has been shown to be the case for normotensive as well as hypertensive individuals, although the latter to a lesser extent. However, the major issue with these trials for nephrology practice is the exclusion of patients with kidney disease. Therefore, from the above investigations, it is unclear how much our patients would benefit from sodium intervention.

Until recently, evidence for the benefit of a low-sodium diet in CKD populations was sparse and had significant methodological limitations. It is only in the past year that we have a Cochrane Review under way and dedicated trials investigating the effect of low sodium intakes on cardiovascular outcomes (McMahon, Campbell, Bauer, & Mudge, 2012). The most robust trial to date is the recent LowSalt CKD study, which represents a tightly controlled, short-term investigation (double-blind, placebo-controlled, cross-over study)(McMahon *et al.*, 2013). Although this trial showed substantial reduction in systolic BP and albuminuria, the short duration of the intervention and the somewhat artificial research environment (for example, the use of sodium tablets to mimic a high-salt diet), doesn't address the question of sustainability. DeBrito *et al.* have overcome some of these limitations in a six-month RCT demonstrating similar BP benefits with a low- versus a high-sodium diet using dietary counselling alone in Bangladeshi patients with CKD (de Brito-Ashurst *et al.*, 2013).

Adherence to dietary change is extremely challenging (McMahon, Campbell, Mudge, & Bauer, 2012), particularly in the modern food environment where sodium is abundant. Research is needed to investigate if dietary change in lowering sodium intake is sustainable, and if so, does it result in measurable changes to CKD patients' CVD risk and associated morbidity. One would suspect so; however, the trials are needed. Until then, based on changes achieved in BP and proteinuria, we can be confident that recommending a reduction in sodium intake in patients with CKD above recommendations (>100 mmol/day) is warranted.

Dietary protein restriction

The concept of protein restriction to support the management of CKD was first suggested by Addis in the 1940s (Addis, 1948), more than a century following Prevost and Dumas' discovery of the kidney's role in elimination of protein metabolic waste products, such as urea (Maher, 1989). Addis' hypothesis was based on decreasing the "workload" of the kidneys, and despite this seemingly valid concept, it wasn't until the 1980s when low and very low protein diets were given serious consideration for limiting the progression of CKD. This low protein concept was scrutinised by the landmark study, Modification of Diet in Renal Disease (MDRD), which demonstrated modest results at best, together with the increased risk of malnutrition, questioning the diet's efficacy (Kopple *et al.*, 1997).

Decades on, the focus of dietary protein's role in CKD progression has re-ignited. This time, the scientific rationale behind the diet is more robust, with our evolving understanding of protein as a precursor for key nephrovascular uremic toxins (Mafra, Barros, & Fouque, 2013). This deleterious manifestation of dietary protein has further added to its notorious role in not only the conventional "uremic" state, defined by high concentrations of urea, but also kidney stone formation, gout and hyperphosphataemia. The current Australian guidelines have maintained a conservative view of dietary protein management, with a recommendation of moderate intake in the CKD population, reflective of what is recommended for the general population (0.75–1.0 g/kg/day) (Johnson *et al.*, 2013). However, the rationale behind low and very low protein diets (defined as 0.6 and 0.3 g/kg/day, respectively) has resurfaced, particularly considering knowledge of protein's role in the generation of key uremic toxins.

Two uremic toxins in particular, indoxyl sulphate and p-cresyl sulphate, have received significant attention over the past decade for their nephrovascular properties (Meijers & Evenepoel, 2011). Both uremic toxins originate from the colonic bacterial fermentation of dietary protein-derived amino acids, where they enter the systemic circulation and are thought to target both the kidney and cardiovascular system. Both *in vitro* and animal studies have demonstrated the toxins' inflammatory and oxidative properties, promoting further kidney disease progression and heightened cardiovascular risk (Rossi, Campbell, & Johnson, 2013). Importantly, intervention studies have demonstrated the toxins' amenability to dietary protein restriction (Marzocco *et al.*, 2013).

In addition, diets high in protein, particularly meat, are associated with elevated uric acid levels resulting from their significant purine content (Choi, Atkinson, Karlson, Willett, & Curhan, 2004), as well as enhanced risk of kidney stone formation through promotion of calcium excretion and reducing urinary citrate levels (Bataille, Presne, & Fournier, 2002). Further, the primary waste product of protein catabolism, urea, once deemed inert, is now thought to play an active role in the distinctive systemic inflammation observed in CKD, through weakening of the gastro-intestinal barrier (Vaziri, Yuan, & Norris, 2013). Beyond these symptomatic conditions, low and very low protein diets have been associated with modest improvement in outcomes in the CKD population, including reduced mortality (Fouque & Laville, 2009).

Despite these attractive benefits of low and very low protein diets, it's important to reflect on why low and very low protein diets fell off trend originally. Firstly, there is the risk of malnutrition, given declines in nutritional status and energy intake coincide with low protein diets (Joel D. Kopple *et al.*, 1997). Next, when compared to the benefit of agents such as angiotensin converting enzyme inhibitors or statins on reducing the rate of decline in the estimated glomerular filtration rate (1.9 ml/min per year) to that achieved with dietary protein restriction (0.5 ml/min per year), the impact of a low protein diet appears negligible (Fried, Orchard, & Kasiske, 2001). Finally, protein restricted diets are often plagued by poor dietary compliance, with few studies achieving greater than 50% of targeted restriction (Aparicio, Chauveau, & Combe, 2001). These figures suggest the risks of malnutrition, coupled with poor compliance, may challenge any theoretical benefit association with low and very low protein diets.

Looking to the future, perhaps the resurrection of another trend could hold the answers to this unresolved issue?

Intestinal manipulation has been utilised as a treatment for kidney disease since the late 1950s (Marr, Burnell, & Scribner, 1960). Falling in and out of trend over the past half century, intestinal manipulation techniques began from primitive purgation methods, and invasive gastro-dialysis to the modern day, innocuous pre- and probiotics supplements (Di Cerbo, Pezzuto, Palmieri, & Palmieri, 2012).

Whilst still early days for this revamped trend, the concept of intestinal manipulation holds much promise, with pre- and probiotic therapy demonstrating their ability to decrease hyperuremia, kidney stone formation, uric acid levels and importantly inhibit the generation of those key nephrovascular toxins(Di Cerbo *et al.*, 2012). Simply put, alternative treatments such as pre- and probiotics may very well offer similar benefits in reducing damaging toxin load of a low protein diet without the risks of malnutrition or burden on patients' quality of life, often associated with restrictive diets (Durose, Holdsworth, Watson, & Przygrodzka, 2004).

Lastly, a focus on the type of protein, moving away from animal protein and towards vegetable sources is a new emerging trend in CKD. In fact, turning to vegetables as the main source of dietary protein holds promise for not only managing acidosis (Goraya, Simoni, Jo, & Wesson, 2013) but decreasing phosphorous absorption (due to the lower bioavailability of vegetable forms of phosphorous known as phytate) (Calvo & Uribarri, 2013). Nonetheless, this approach requires increased dietetic monitoring to ensure patients are meeting their essential amino acid requirement (as vegetable proteins tend to be lower in one or more essential amino acids) along with not exceeding their potassium restrictions (with vegetables a major source of potassium). Despite these cautions, studies have that following a vegetarian diet can be appropriate for CKD patients (Chauveau, Combe, Fouque, & Aparicio, 2013).

Eating patterns: back to basics

A modern-day challenge to dietary intervention in CKD is the layering of commercial food production with additives, which is driven by the demand for longer shelf-life and convenient meals. The predominance for convenience foods which are typically 'ultra-processed' has resulted in an increase in not only calorie intake but in food additives (Monteiro, Moubarac, Cannon, Ng, & Popkin, 2013), presenting new issues in the dietary management of CKD.

'Cardiorenal disease' was a term coined to describe the high CVD burden and synergistic relationship between kidney disease progression and CVD severity (McCullough, 2002). Novel risk factors have been the focus of much research over the past decade, with dietary intake of key food additives identified as modifiable risk factors of interest (Stenvinkel *et al.*, 2008). In particular, added sodium, phosphorus and fructose, as well as the increased production of advanced glycation end-products (or AGEs) through processing methods, has generated significant interest in the scientific literature.

The role of dietary phosphorus in metabolic bone disease (CKD-MBD), which is highly prevalent in the dialysis population and of increasing interest in CKD and the general ageing population, is of growing concern (Ketteler, Wolf, Hahn, & Ritz, 2012). The use of phosphorus as a food additive is increasing and the high degree of bioavailability of this form of phosphorus presents a real challenge for the management of serum phosphate and risk of CKD-MBD (Kalantar-Zadeh *et al.*, 2010). Diet interventions focused on educating dialysis patients about the presence of phosphorus additives, through strategies including how to read ingredient labels and the provision of individualised advice regarding convenience food options, resulted in a significant decrease in serum phosphate (Sullivan, Sayre, Leon *et al.*, 2009). This demonstrates the potential impact of dietetic intervention strategies on clinical outcomes. Nonetheless, this level of dietetic intervention is not only time-intensive but is limited by the patients' cognitive capacity.

Advanced glycation end-products (AGEs) are derivatives of glucose-protein or glucose-lipid interactions during food preparation and are implicated in complications associated with ageing, diabetes and CKD (Neade & Uribarri, 2008). This warrants important consideration in later stages of CKD, given serum AGE levels are associated with not only dietary consumption but also impaired renal clearance (Uribarri *et al.*, 2003). AGEs are created by the Maillard (or browning) reaction on food by reducing sugars and free amino groups from proteins and lipids (O'Brien & Morrissey, 1989). Diets rich in highly processed foods, fats and grilled or roasted meats carry a particularly high AGE-load compared with diets rich in plant foods and 'wet' cooking methods (such as casseroles and soups) (Uribarri *et al.*, 2010). Intervention studies demonstrate a 'low AGE' diet can reduce serum AGE levels (Uribarri *et al.*, 2003). Further, providing a low-AGE diet has attenuated the progression of renal disease in experimental mice studies, compared with AGE-containing diets (Thallas-Bonke *et al.*, 2013).

Fructose has been identified as a potential mediator of increased cardiovascular risk and CKD (Johnson *et al.*, 2007). Fructose is a common food additive in the United States in the form of 'high fructose corn syrup'. This is added to increase the palatability of food and is used in commonly sweetened foods such as soft drinks, and even foods not commonly sweetened such as crackers, thereby becoming rather ubiquitous in the food supply (Johnson *et al.*, 2007). High fructose intake has been associated with increased risk of metabolic syndrome, hypertension and elevated triglycerides. However, the potential impact of fructose on the stimulation of uric acid production has attracted the most attention, and is hypothesised to have a key role for inducing cardiorenal disease (Johnson *et al.*, 2007). Experimental studies have identified a causal effect of fructose consumption on the development of features of the metabolic syndrome (Nakagawa *et al.*, 2006), in addition to the deterioration of renal function, increased glomerulosclerosis and proteinuria in rats fed a high fructose diet (Teff *et al.*, 2004). However, intervention studies in human populations are still needed to identify if the experimental findings are likely to translate to clinical practice.

Given the above, there is an important impetus to promoting the cycle turns back to less processed food in not only the CKD population but also those at high risk of CKD. Fortunately, worldwide there has been a trend in the demand for local, sustainable and organic food production (Kearney, 2010). In fact, Australian food trend predictions for 2014 (Weber Shandwick, 2014) suggest a 'back to basics' approach in line with global, Western trends as a result of rising food costs. Further, consumers are looking to market gardens and buying fresh and local produce, to not only curb costs but increase their feeling of control over where their food comes from. Unlike many other diet trends, this trend, moving away from packaged and processed food consumption patterns, aligns with emerging recommendations for CKD diet management.

Summary

As highlighted in this review, dietary management of CKD patients evolves over time, often following cyclic trends. Enabling dietary change is associated with a range of considerations, including the requirement for cooking skills, the ability to read and comprehend food labels and, importantly, food security, including cost and availability of fresh food to all parts of Australia. Therefore, utilising a multidisciplinary approach, including the expertise of an appropriately qualified dietitian (Accredited Practising Dietitian in Australia or Registered Dietitian in other countries), in addition to public health advocacy is key to supporting patients through the challenge of dietary management in CKD, recognising fact from fad or fiction.

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