Lees, J. S. and Mark, P. B. (2021) Fruit for thought: lifestyle interventions to reduce the risk of future chronic kidney disease. *Nephrology Dialysis Transplantation*, 36(6), pp. 963-965. (doi: 10.1093/ndt/gfaa266)

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Deposited on 13 October 2020

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Fruit for thought: lifestyle interventions to reduce the risk of future chronic kidney disease

Jennifer S Lees and Patrick B Mark

Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Avenue, Glasgow, G12 8TA, UK

Email:

jennifer.lees@glasgow.ac.uk

Twitter:

@jennifer_s_lees

@drpaddymark

The major worldwide risk factors for chronic kidney disease (CKD) and end-stage kidney disease (ESKD) - diabetes mellitus and hypertension - are associated with obesity and the metabolic syndrome, and potentially may be addressed by lifestyle modification.

In this issue of NDT, Okado and colleagues describe the association between markers of 'healthy lifestyle' and the incidence of dipstick proteinuria and progression of kidney disease over 2 years. The study was prospective and observational in nature, conducted in over 450,000 participants living in Japan and attending annual employer-provided health checks. Each participant with complete lifestyle data over 2 years was included. Proteinuria was recorded on dipstick test at 0 and 2 years, as was eGFR (calculated by Japanese eGFR from enzymatic serum creatinine). Only participants without any evidence of proteinuria at baseline were included.

Healthy lifestyle was assessed according to factors previously identified i.e. smoking status, healthy eating behaviours (late dinner, snacking and skipping breakfast <3 times/week for all), within normal weight parameters (by body mass index), undertaking regular exercise and consuming alcohol below a threshold of 20g/day. Exercise and alcohol intake were not associated with risk of proteinuria and eGFR decline, and so scores were allocated as 0 (least healthy) to 3 (most healthy) according to whether participants met criteria for other healthy lifestyle factors.

The authors found that those who met all 3 healthy lifestyle criteria were less likely to develop incident trace/positive proteinuria over 2 years and were less likely to experience rapid eGFR decline ($\geq$ 20% decline in eGFR over 2 years). Importantly, those following a healthy lifestyle also had lower blood pressure, were less likely to be taking antihypertensive medications, had lower HbA1c and LDL cholesterol and higher HDL cholesterol. They were also more likely to undertake regular exercise, and consumed less alcohol. This was despite being, on average, 5 years older.

Is prevention better than cure in people at risk of CKD?

The global prevalence of CKD has been estimated at up to 15%[1], though these estimates are higher when using more sensitive measures such as cystatin C to detect early stage CKD[2]. Only a tiny proportion of these patients will go on to develop ESKD. However, even the earliest stages of CKD are associated with a substantial increase in risk of cardiovascular disease and early mortality[2]. CKD is associated with development of non-traditional risk factors for cardiovascular disease, such as uraemic cardiomyopathy, vascular stiffness and calcification, leading to heart failure and propensity to arrhythmia. Once established, there are no evidence-based treatments to reverse these processes, and traditional treatments for atherosclerotic cardiovascular disease are less effective. Early identification of those at risk of developing CKD is vital to reduce the costs of excess disease associated with chronic kidney disease, and to improve quality of life for these patients.

The effect of diet on risk factors for CKD

Okado et al describe the association of healthy eating behaviours with reduction in *de novo* proteinuria or eGFR decline[3]. Following a healthier diet has the potential to impact future renal and cardiovascular health substantially. In a meta-analysis including over 630,000 participants with no pre-existing kidney disease[3], adherence to healthy dietary intake (relative higher consumption of whole grains, vegetables, fruit, legumes, nuts and fish, and proportionately less red and processed meat, sodium and sugar-sweetened drinks) was associated with 23% lower odds of incident albuminuria and 30% lower odds of incident CKD. eGFR decline was not uniformly defined and described only in four studies (7377 participants), but there was a trend towards a reduction in kidney disease progression (OR 0.70, 95% CI 0.49-1.01)[3]. A Mediterranean diet specifically (compared to low-fat diet) is recommended in the KDOQI Clinical Practice Guideline for Nutrition in CKD (2020 update) to improve lipid parameters in non-dialysis CKD[4]. Furthermore, amongst patients with established CKD, healthy diet is associated with 27% lower risk of all-cause mortality over 4 years or more[5].

Much of the evidence informing guidelines for dietary advice in CKD are based on observational data or small studies. However, dietary interventions have been shown to impact on risk factors which are strongly associated with outcomes in CKD. Multiple studies have shown that reducing dietary sodium intake is associated with reductions in blood pressure, the major modifiable risk factor for progression of CKD[6]. Although more restrictive, a rigidly controlled calorie-controlled diet has been demonstrated to induce remission of type 2 diabetes in a randomised controlled trial[7]. These results support that there is a role for dietary interventions in addressing risk factors for both incident and progressive kidney disease. Further randomised controlled trials are required to determine which dietary (and other lifestyle) interventions are effective in CKD.

Fruit and vegetables are essential components of a healthy diet

Addressing dietary factors for progressive CKD goes far beyond the sphere of nephrology and reflects the wider socio-economic determinants of health. Factors influencing consumption of a healthy diet include socio-economic status, food expenditure, marketing and access to healthy dietary choices[8]. Furthermore, progress has been made on sodium intake including World Health Organisation targets for salt intake for adults. In addition to continuing to adhere to targets for reducing sodium consumption to address blood pressure, we would also suggest continued focus on improving fruit and vegetable intake.

Increased fruit and vegetable intake is already recommended in non-dialysis CKD to improve parameters associated with cardiovascular risk[4]. Eating more vegetables may reduce the risk of developing CKD by 21%[9]. Furthermore, in those with established kidney disease, higher fruit and vegetable intake is associated with a lower risk of cardiovascular death[10] and of post-transplant diabetes mellitus[11]. Across mixed populations, higher fruit and vegetable consumption is associated with lower mortality[12], but most people consume less than is currently recommended[12]. Inevitably, in patients with advanced CKD, there are challenges in maintaining adequate fruit and vegetable consumption whilst restricting

potassium intake where necessary. The role of the newer potassium binding drugs has yet to be established in this setting.

Eat better, feel better

Unhealthy eating patterns lead to obesity, which is associated with chronic health conditions including depression[13] and CKD[14]. Strategies to improve eating patterns and to encourage weight loss are important targets to reduce the burden of these conditions. Most weight loss interventions in the general population have assessed low-fat diets[15]. By promoting satiety, a fibre-rich diet can also facilitate weight loss, which may be associated with improvements in mood. Fruit and vegetables are important dietary sources of fibre, and could be used to supplement dietary fibre without adding significantly to calorie intake. As an added bonus, one trial has shown that increasing fruit and vegetable consumption can have an immediate impact on psychological well-being[16], independent of body habitus.

Conclusions

The conveniences of modern life in the developed world have brought an increasing burden of poor diet, inactivity, obesity and thus chronic disease. Treating chronic health conditions (such as CKD) after they develop is more expensive and less effective than prevention at reducing complications. Lifestyle modification is seen by many clinicians and patients as an unmanageable feat. We need to establish which lifestyle interventions are effective and acceptable to patients specific to CKD risk and then translate these to become the mainstay of chronic disease prevention and management. Though this would require a drastic re-think of healthcare provision in most countries, this may provide be a more effective and sustainable way of managing chronic disease over the longer term. Supplementing the diet with fruit and vegetables (and thus fibre) is a worthy and inexpensive intervention to test in clinical trials, with potential impact on clinical endpoints including weight loss, dyslipidaemia, incident CKD, progression of CKD, cardiovascular disease and mortality risk.

Conflict of interest statement

Outside the submitted work, J.S.L. reports speaker honoraria from Vifor Fresenius, Astra Zeneca, Pfizer and Bristol-Myers Squibb. P.B.M. reports speaker honoraria from Vifor Fresenius, Astra Zeneca, Janssen, Napp, Novartis and Bristol Myers Squibb, research grants from Boehringer Ingelheim and non-financial support from Pharmacosmos.

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