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The effect of energy restriction on development and progression of chronic kidney disease: review of the current evidence

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Abstract

Energy restriction (ER) has anti-ageing effects and probably protects from a range of chronic diseases including cancer, diabetes and chronic kidney disease (CKD). Specifically, ER has a positive impact on experimental kidney ageing, CKD (diabetic nephropathy, polycystic kidney disease) and acute kidney injury (nephrotoxic, ischaemia–reperfusion injury) through such mechanisms as increased autophagy, mitochondrial biogenesis and DNA repair, and decreased inflammation and oxidative stress. Key molecules contributing to ER-mediated kidney protection include adenosine monophosphate-activated protein kinase, sirtuin-1 and PPAR-γ coactivator 1α. However, CKD is a complex condition, and ER may potentially worsen CKD complications such as protein–energy wasting, bone–mineral disorders and impaired wound healing. ER mimetics are drugs, such as metformin and Na–glucose co-transporter-2 which mimic the action of ER. This review aims to provide comprehensive data regarding the effect of ER on CKD progression and outcomes.

Key words: Energy restriction: Chronic kidney disease: Energy restriction mimetics: Autophagy: Mammalian target of rapamycin pathway

Chronic kidney disease (CKD) has reached epidemic proportions as is predicted to become the fifth global cause of death by 2040[1]. Treating CKD and ameliorating its symptoms are important healthcare issues. However, today there are few therapeutic options including blood pressure control, control of circulating glucose and lipid levels and protein restriction (PR) and salt restriction. Although these measures have clearly improved CKD outcomes, they are not completely effective and CKD is still a major and growing health issue. Thus, novel preventive and therapeutic strategies are needed for CKD management[2,3]. One of these strategies is energy restriction (ER) or diet restriction (DR) although they are not the same. ER is specifically defined as a reduction in energy intake well below the amount of energy that would be consumed *ad libitum* which in most cases entails a 20–40 % reduction of food consumption relative to normal intake. In this definition, ER obligates some kind of DR. However, the contrary is not true and specific types of DR can be accomplished without ER by balancing nutrient intake (same amount of energy may be maintained during DR by increasing energy intake from other sources). ER can be mild or severe and describes an acute or chronic reduction of total energy intake without causing malnutrition and essential nutrient deprivation. Accumulating evidence suggests that ER may improve health and lifespan. After long-term ER, 'metabolic adaptation' is thought to occur which reduces the metabolic rate below the baseline value, thus supporting longevity[4]. Indeed, ER is the only manoeuvre that has consistently prolonged lifespan in all the species tested so far. ER and DR have also been used as therapeutic approaches for experimental kidney disease. The beneficial effects of low-protein diets for CKD have long been known, but the importance of independent ER has only recently been recognised. Both acute and chronic ER are associated with improved kidney functions by mechanisms including improving mitochondrial dysfunction and autophagy and suppression of

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; CKD, chronic kidney disease; DN, diabetic nephropathy; DR, diet restriction; ER, energy restriction; FOXO, forkhead box O; GFR, glomerular filtration rate; mTOR, mammalian target of rapamycin; PGC1α, PPAR-γ coactivator 1α; PKD, polycystic kidney disease; PR, protein restriction; RCT, randomised controlled trial; Sirt1, sirtuin 1.

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inflammation and oxidative stress[5]. In addition, ER retards kidney ageing and ameliorates age-induced functional and structural changes such as tubulointerstitial fibrosis, glomerulosclerosis, decreased renal blood flow and loss of several tubular transport functions[6]. A 2015 meta-analysis of twenty-seven studies investigating the effects of ER on experimental rodent CKD demonstrated that compared with *ad libitum* feeding, ER is associated with lower incidence of histopathological nephropathy (defined as the development and progression of glomerulosclerosis, tubular dilatation with protein casts, development of cysts, tubular epithelial degeneration and regeneration and chronic interstitial nephritis), decreased serum creatinine, blood urea nitrogen and urinary protein excretion. However, the effect of ER on the occurrence of kidney disease was only significant with prolonged intervention and the beneficial effect of 60 % ER was greater than that of lower than 60 % ER[7]. As to the molecular mechanisms of the beneficial effects of ER, the 2016 Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi for the discovery of the molecular principles governing autophagy and ER. ER is now considered a potential solution for chronic disease such as cancer and cardiovascular disorders, and CKD is no exception. In this review, we now address the benefits, mechanisms underlying these benefits, safety and unknowns of ER in the context of kidney disease.

Evidence for a nephroprotective effect of energy restriction

There is now enough evidence that ER is beneficial to various kidney pathologies, but there are also potential drawbacks and unknowns (Table 1). Most data were derived from experiments in animals which showed that ER was beneficial to kidney ageing as well as in models of both CKD and AKI. These studies are mostly heterogeneous with respect to inclusion criteria, methodology and outcome of interest. Accordingly, we have summarised the included studies in Table 2 regarding ER, DR and macro–micronutrient intake and main outcome which are thought to be important parameters to consider in the current topic of interest.

Animal studies

Rats benefit less from lifelong ER than from carbohydrate restriction but both are superior to PR, the traditional dietary approach to CKD in the clinic[8]. In this regard, ER has been associated with improvements in kidney function similar to the well-known protection afforded by PR. It should be emphasised that PR studies are mostly performed under non-isoenergetic conditions meaning that increased consumption of carbohydrates and fats is allowed along with low-protein diet. The protective effect of ER along with carbohydrate restriction is as effective as (if not superior to) PR with regard to renal health[5].

In Fischer Brown Norway F1 hybrid rats, 40 % ER resulted in decreased glomerulosclerosis and tubular atrophy at 6 months as well as decreased interstitial fibrosis formation within 1 year and vascular wall thickening compared with *ad libitum* feeding[9]. ER of 30 % for 7–13 weeks in Otsuka Long–Evans Tokushima Fatty rats decreased urinary protein excretion and glomerulosclerosis at later life compared with *ad libitum* diet-fed rats. These findings are important implying that even short-term ER has long-lasting renoprotective effects, independent of effects on hyperglycaemia[10]. ER and PR may be combined to optimise long-term renoprotective effects. Indeed, this combination approach has been demonstrated in rats when dietary ER was induced by two different diets for 52 weeks: a commercial diet (21·4 % protein, 5·7 % fat and 4·1 % fibre) and a modified low-protein diet (13·6 % protein, 4·6 % fat and 15·7 % fibre). In both groups, ER improved chronic renal insufficiency and survival in rats, but the lower-protein diet provided higher benefits on proteinuria, and glomerular and tubulointerstitial histopathological injury[11].

The impact of ER has also been assessed in CKD caused by diabetic nephropathy (DN), obesity and polycystic kidney disease (PKD). ER was beneficial to experimental DN. In streptozotocin-induced DN in male rats, intermittent fasting preserved creatinine, albumin and HDL-cholesterol values and decreased oxidative stress, p38-mitogen-activated protein kinase cascade activation and p53 expression[12]. In diabetic Wistar fatty (fa/fa) rats, a 40 % dietary restriction for 6 months reduced urinary albumin excretion, restored creatinine clearance, reduced mesangial matrix expansion and tubulointerstitial lesions, transforming growth factor beta-1 (TGF-β1) and extracellular matrix proteins and NF-κB p65 acetylation while restoring sirtuin 1 (Sirt1) expression, the abnormal mitochondrial morphology and autophagy in proximal tubular cells[13].

The impact of maternal nutrient restriction in the early onset obesity in the offspring obesity was also studied in sheep. Pregnant sheep were randomly assigned to a normal (control, 100 %) or restricted (50 %) diet from days 30 to 80 of gestation. Offspring from dietary restricted mums had lower relative renal weight and kidney expression of some inflammatory genes at 7 d of age, and they also had milder kidney inflammation after 1 year of obesogenic diet[14]. However, no data on renal function or albuminuria were provided and histological tubular atrophy was not attenuated by maternal restricted diet, limiting the

Table 1. Benefits and potential drawbacks and unknowns of energy restriction in kidney disease

Conditions which benefit from energy restriction
Ageing kidney
Chronic kidney disease[9–11]
Diabetic nephropathy[12,13]
Obesity-induced kidney disease[21]
Polycystic kidney disease[17,18]
Acute kidney injury
Cisplatin-induced nephrotoxicity[19]
Ischaemia–reperfusion injury[21]
Current unknowns on energy restriction and kidney disease
Clinical long-term compliance?
General impact on well-being
Effect of protein–energy wasting?
Effect of wound healing?
Effect of bone mineral disorders?
Specific kidney conditions
Renal transplant recipients?
Effect on different types of glomerulopathies?
Effect on hypertensive nephropathy?

Table 2. Characteristics of included studies with regard to energy restriction (ER), diet restriction (DR) and macro- and micronutrient intake and main kidney outcomes

Study	Energy manipulation	Diet details, micro- and macronutrient intake	Main kidney outcome
Animal studies			
McKiernan *et al.*[9]	ER 40 % *v.* AL Both diets were low-protein diets (approximately 14 % by weight)	ER was enriched with caseins, fat, vitamins and minerals No specific data regarding CH and protein intake	Decreased glomerulosclerosis and tubular atrophy and interstitial fibrosis at 6 months
Nakano *et al.*[10]	30 % ER for 7–13 weeks	Four types of diet: standard chow, standard chow with 30 % ER, high-sucrose (60 %) chow, high-fat (60 %) chow No specific data regarding minerals and vitamins	ER decreased urinary protein excretion and glomerulosclerosis at later life compared with AL diet-fed rats
Gumprecht *et al.*[11]	ER and protein restriction by two different diets for 52 weeks	Commercial protein diet (21·4 % protein, 5·7 % fat, 4·1 % fibre) *v.* modified low-protein diet (13·6 % protein, 4·6 % fat, 15·7 % fibre) No specific data regarding minerals and vitamins	ER improved renal insufficiency and survival Lower-protein diet provided higher benefits on proteinuria, and glomerular and tubulointerstitial histopathological injury
Kitada *et al.*[13]	40 % DR for 6 month Food consumption was measured twice a week	No specific information about macronutrients, vitamins, minerals and how DR was achieved	DR reduced urinary albumin excretion, mesangial matrix expansion and tubulointerstitial lesions and restored creatinine clearance
Kipp *et al.*[17]	23 % reduced food intake in mouse ADPKD model	No data available regarding CH, fat and protein restriction No data available regarding minerals and vitamins	Kidney weight increased 41 % in the reduced food intake group *v.* increased 151 % in controls
Ning *et al.*[18]	40 % ER for 8 weeks Food consumption was measured every 2 weeks, and the results were used to calculate the daily food intake	Initial diet: 10·0 % water, 23·0 % crude protein, 55·0 % crude CH, 5·0 % crude fat, 4·0 % crude fibre and 7·0 % crude ash. 40 % ER was induced during the following 8 weeks	ER decreased BUN, serum creatinine and histological tubular epithelial damage in cisplatin-induced AKI in rats
Dong *et al.*[39]	40 % ER *v.* AL	Data not available regarding CH, fat and protein intake Data not available regarding vitamins, minerals	ER protected from epithelial to mesenchymal transition and kidney fibrosis
Ning *et al.*[40]	8 weeks 60 % ER Food consumption was measured every 2 weeks, and results were used to calculate the daily food intake	Initial diet: 10·0 % water, 23·0 % crude protein, 55·0 % crude CH, 5·0 % crude fat, 4·0 % crude fibre and 7·0 % crude ash. 40 % ER was induced during the following 8 weeks ER diets were enriched in vitamins, minerals and salts such that restricted animals were not nutrient deficient or salt deficient compared with the control animals	ER is associated with decreased urinary albumin excretion, mitochondrial DNA oxidative damage and increased autophagy
Wang *et al.*[47]	30 % ER for 6 months	No data regarding calculation of ER No data regarding CH, fat and protein intake Data not available regarding vitamins, minerals	ER suppressed DNA damage, inflammation and NF-κB activation
Xu *et al.*[51]	40 % ER for 8 months Food consumption was measured every 2 weeks, and results were used to calculate daily food intake Vitamins, minerals, and salts were added to ER group to ensure balance	Initial diet; 10·0 % water, 23·0 % crude protein, 55·0 % crude CH, 5·0 % crude fat, 4·0 % crude fibre and 7·0 % crude ash with 3·42 kcal/g* At 16 months of age, the rats were divided into AL and ER groups maintained for 8 months	ER decreased inflammation and kidney fibrosis
Jiang *et al.*[55]	ER is initiated as 10 % and increased to 40 % restriction at 16 weeks	No data regarding CH, fat and protein intake Data not available regarding vitamins, minerals	ER prevented lipid accumulation by decreasing SREBF1, a mediator of lipid synthesis ER also decreased proteinuria and glomerulosclerosis
Robertson *et al.*[56]	Mice were preconditioned on experimental diets lacking total energy (0–50 % ER) or protein/essential amino acids *v.* complete diets consumed AL 1 week before IRI Intake of fat and micronutrients was held constant among all groups ER was via protein or sucrose restriction	Semi-purified diets (research diets) were purchased in powdered form for customisation with sucrose, casein or crystalline amino acids The resulting complete diet contained 34 % protein (casein) and 34 % CH (sucrose) by weight	ER decreased IRI PR also decreased IRI Adding essential amino acids abrogated the protection observed during protein restriction Combination of ER and PR is additive in prevention of IRI

Table 2. (*Continued*)

Study	Energy manipulation	Diet details, micro- and macronutrient intake	Main kidney outcome
Mitchell *et al.*[57]	2–4 weeks of 30 % DR DR was applied for 2–4 weeks by feeding mice 3·5 g/d	Amount of food eaten AL was approximately 3·5 g/d as determined by weighing remaining food for 1 week	DR improved insulin sensitivity, antioxidant defence and reduced inflammation and insulin/insulin-like growth factor-1 signalling
Cadenas *et al.*[58]	2 months of 60 % ER During the first week, all mice were fed AL the control diet (20 % casein, 65 % maize starch, 5 % Alphacel (non-nutritive bulk), 5 % maize oil, 3·5 % mineral mix and 1·5 % vitamin mix)	After 1 week, mice were divided into three groups: control group (C) continued to be fed AL the same diet, ER group (60 % of AL diet composed of 20 % casein, 65 % maize starch, 1·7 % Alphacel, 5 % maize oil, 5·8 % mineral mix and 2·5 % vitamin mix) and CH-restricted group (diet composed of 20 % casein, 25 % maize starch, 45 % Alphacel, 5 % maize oil, 3·5 % mineral mix and 1·5 % vitamin mix)	ER increased kidney antioxidant glutathione (GSH):oxidised glutathione (GSSG) ratio, glutathione peroxidase and cytochrome oxidase activities, and decreased *in vivo* peroxidation
Johnson *et al.*[68]	40 % ER with high protein intake	Total energy of 397·6 kcal* in AL *v*. 238·56 kcal* in ER group Casein and methionine were lower in the ER group Vitamin and mineral compositions were same	ER despite high protein intake, improved survival and delayed onset of proteinuria
Calvo-Rubio *et al.*[81]	40 % ER for 6 and 18 months	AL group had intake of 12·5 kcal*, three ER dietary groups had intake of 8·6 kcal* and diets were identical except for dietary lipid sources Diets (% total kJ/d) contained 20·3 % protein, 63·9 % CH and 15·8 % fat Dietary fat for control group was soyabean oil Dietary fats for the three ER groups were soyabean oil or lard	ER preserved podocyte foot processes and filtration slits These changes are more marked when lard was the main fat source in ER diets
Kobayashi *et al.*[83]	CH restriction with 40 % ER and no change in protein intake	Group I: AL diet in first postoperative week containing 22·5 % casein Group II: 21 % casein diet Group III: (overall food restriction without protein restriction, 60 % of energy), 35 % casein to provide the same amount of protein	ER even without protein restriction independently decreased glomerular hyperfiltration, tubular damage and kidney weight
Reisin *et al.*[84]	Low-energy diet but similar in protein To achieve low energy but similar protein, protein content of the experimental group's diet increased by 34 % and 33 % less food was given than the controls All rats received tap water AL	Experimental diet contained (in %): protein 31·4, fat 3·7, CH 38·5, K 3·1, Na 1·1, P 0·6, Ca 0·8 and 13·15 kJ/g (3·13 kcal/g) Control diet (in %): protein 23·4, fat 4·5, CH 49, K 1·1, Na 0·4, P 0·6, Ca 0·1, and 17·85 kJ/g (4·25 kcal/g)	Independent of protein, Na and K intake, low-energy diet is associated with less 24-h urinary protein excretion ER is also independently associated with less mesangial matrix expansion
Krishan *et al.*[85]	30 % ER by CH restriction for 4 weeks	Normal CH diet included maize starch 465·6 g, dextrinised maize starch 155 g, casein 140 g, sucrose 100 g CH-restricted diet included maize starch 408·4 g, dextrinised maize starch 133 g, casein 200 g, sucrose 72·2 g Cysteine was higher in CH-restricted diet compared with normal diet (2·6 *v*. 1·8 g)	CH ER resulted in lower creatinine and proteinuria, decreased oxidative stress
Human studies			
Giordani *et al.*[21]	7-d VLED (400 kcal/d*), low-Na diet to patients with type 2 diabetes	During VLED, water and salt intakes were standardised to 1·5 litres/d and <6 g/d, respectively	Diet induced an increase in GFR from 73 (SD 4) to 87 (SD 6) ml/min per 1·73 m^2 and weight reduction from 3·58 (SD 0·6) kg to 3·22 (SD 0·56) kg

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Table 2. (*Continued*)

Study	Energy manipulation	Diet details, micro- and macronutrient intake	Main kidney outcome
Ruggenenti *et al.*[22]	6 months of a 25 % ER *v.* standard diet in patients with type 2 diabetes Patients in the ER arm were provided with personalised dietary guidelines and completed a 7-d food diary using household measures to achieve 25 % ER Diaries were analysed by means of the dietary analysis software package	Nutrient composition was designed to provide 45–50 % of energy from CH, 30–35 % from fat and 15–20 % from proteins, to supply 100 % of the daily recommended micronutrient intake, >20 g/d of fibre and <300 mg/d of cholesterol	Glomerular hyperfiltration and body weight decreased in ER group compared with standard diet group
Grundmann *et al.*[23]	60 % ER *v.* AL 7 d before cardiac surgery Patients in the ER group were provided with a formula diet that contained all necessary macro- and micronutrients All participants in both groups were provided diaries and reported their food consumption on a daily basis	Calculated daily protein intake during ER was 0·6 g/kg Daily protein intake calculated from urinary urea nitrogen appearance, g/kg, was 0·8 kg in ER and 0·9 in control (statistically insignificant)	ER prevented a rise in creatinine at 48 h and resulted in decreased body weight There was a trend for lower incidence of AKI in ER group

AL, *ad libitum*; CH, carbohydrate; BUN, blood urea nitrogen; ADPKD, autosomal dominant polycystic kidney disease; SREBF1, sterol regulatory element-binding transcription factor 1; IRI, ischaemia–reperfusion injury; VLED, very low-energy diet.
* To convert kcal to kJ, multiply by 4·184.

potential benefits of the intervention. Indeed, the lower relative kidney weight of newborns of diet-restricted mothers raises the issue of potential lower kidney reserve capacity and a potential negative impact on kidney ageing, which was not addressed.

ER was also beneficial to experimental PKD[15]. Mild to moderate (10–40 %) food restriction decreased cyst growth, interstitial fibrosis and inflammation in association with suppression of the mammalian target of rapamycin (mTOR) pathway and activation of the liver kinase B1/adenosine monophosphate-activated protein kinase (AMPK) pathway[16].

The beneficial effects of ER in polycystic disease were replicated in an orthologous mouse autosomal dominant polycystic kidney disease model, in which a 23 % reduction in food intake decreased kidney volume growth without causing malnutrition or any apparent side effect. Kidney weight increased 41 % in the reduced food intake group *v.* 151 % in controls, and proliferation of cyst-lining cells was 8 % in the reduced food intake group *v.* 16 % in controls. Reduced food intake suppressed the two major branches of mTORC1 signalling, S6 and 4EBP1[17]. However, it should be pointed out that despite evidence of involvement of the mTOR pathway in the pathogenesis of experimental PKD, clinical trials of mTOR inhibitors in human PKD have so far failed to show benefit.

Short-term ER was also beneficial to experimental AKI. In cisplatin-induced AKI in rats, 40 % ER for 8 weeks decreased blood urea nitrogen and serum creatinine, histological tubular epithelial damage, caspase-3 activation and TUNEL-positive cells, indicative of decreased apoptosis[18]. Kidney Sirt1 as early as at 6 h after cisplatin administration peaked at day 5 and declined until day 14. The increase in Sirt1 was proportional to the severity of AKI and was paralleled by decreased acetylated histone H3 and an increased Werner syndrome protein. The increased Sirt1 likely represents a compensatory nephroprotective response, as Sirt1 transfection to human embryonic kidney 293 cells mitigated cisplatin-induced cellular damage[19]. In rats and mice, different degrees of ER for 2 weeks before kidney ischaemia–reperfusion injury resulted in better kidney function[20].

Human studies

As suggested above, human studies regarding ER in the context of CKD are scarce; however, promising data were also obtained in human studies. In fourteen patients with type 2 diabetes mellitus, morbid obesity and stage 2 CKD, a 7-d very low-energy (400 kcal (1674 kJ)/d) low-Na diet was associated with an increase in glomerular filtration rate (GFR) from 73 (SD 4) to 87 (SD 6) ml/min per 1·73 m^2 ($P = 0{\cdot}026$). Weight reduction was also observed between 3·22 and 3·58 kg[21]. However, the present study raises several issues. The sustainability of such a low-energy diet may be questioned as it decreased muscle mass. Furthermore, under these circumstances, estimation of GFR from serum creatinine is not reliable and GFR should have been measured. Additionally, hyperfiltration is considered a driver of CKD progression both in obesity and in diabetes. Thus, it is unclear whether an increase in GFR, if confirmed, would have been desirable. Finally, there was no information on the impact on albuminuria.

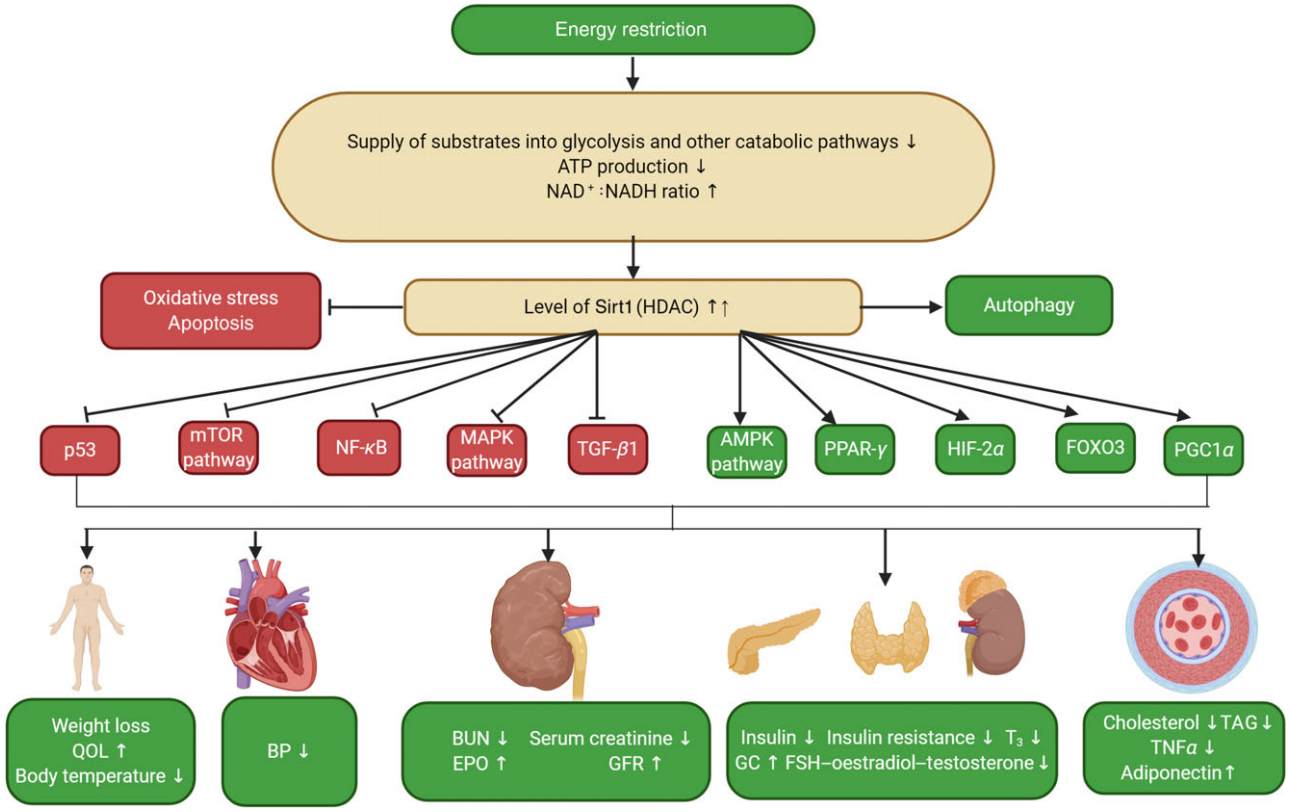

Fig. 1. Postulated mechanisms for beneficial effect of energy restriction. BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; GC, glucocorticoid; GFR, glomerular filtration rate; QOL, quality of life; FSH, follicle-stimulating hormone; EPO, erythropoietin; Sirt1, sirtuin1; T_3, triiodothyronine; HIF, hypoxia-inducible factor; FOXO3, forkhead box O-3; TGF, transforming growth factor; mTOR, mammalian target of rapamycin; AMPK, 5′ adenosine monophosphate-activated protein kinase; MAPK, mitogen-activated protein kinase; PGC1α, PPAR-γ coactivator 1α.

Ruggenenti *et al.* in a prospective trial, randomised patients with type 2 and abdominal obesity to a 23 % ER or standard diet for 6 months at a 1:1 ratio. ER was tolerated well. Primary outcome was measured GFR (iohexol plasma clearance). At 6 months, GFR significantly decreased in the ER group and did not change in the standard diet group and changes were significantly different between the groups. GFR reduction was larger in hyperfiltering (GFR > 120 ml/min) than non-hyperfiltering patients. Body weight decreased by 4·7 (SD 5·5) kg in the ER group and by only 0·6 (SD 1·6) kg in the standard diet group. The authors concluded that in patients with type 2 diabetes with abdominal obesity, ER ameliorates glomerular hyperfiltration, insulin sensitivity and other cardiovascular risk factors, and these beneficial effects might translate into long-term nephroprotection[22].

A randomised, controlled, pilot trial study examined whether ER prevents AKI after cardiac surgery. Eighty-two patients were assigned randomly to ER (60 % of daily energy requirement) or *ad libitum* food (control) for 7 d before surgery. ER prevented a rise in median creatinine at 48 h especially in male patients and in patients with a BMI >25 kg/m^2. Median weight loss in the control group was 0·1 kg, whereas median weight loss in the ER group was 3·0 kg. There was a trend towards lower incidence of AKI in the ER group (42·0 *v.* 47·5 %, P 0·06)[23]. These promising studies should be confirmed in larger trials.

Mechanisms of the protective effect of energy restriction on kidney function

The mechanisms of the protective effect of ER on kidney function remain unclear. ER results in weight loss, and lowers blood pressure, TAG, cholesterol, fasting insulin levels, insulin resistance, insulin growth factor-1, body temperature, resting energy expenditure, oxidative stress and inflammatory mediators, changes which all potentially involve kidney protection (Fig. 1). Additionally, ER modulates several hormonal regulatory loops. Plasma glucocorticoids, adiponectin and the steroid hormone-binding protein increase[24] while anabolic hormones such as insulin, testosterone, leptin, triiodothyronine (T_3), oestradiol and follicle-stimulating hormone decrease[25–28]. Gluconeogenesis from lipids and amino acids increases on ER while glycolysis and production of advanced glycation end products decrease[29]. Thus, multiple consequences of ER may contribute to delayed ageing and to nephroprotection, although most information relates to autophagy and the AMPK/mTOR/Sirt1 pathways, mitochondrial dysfunction and oxidative stress/inflammation[9].

Disordered autophagy drives many pathological conditions such as premature ageing, CVD, neurological diseases and cancer. ER activates autophagy as a cell protective mechanism which scavenges damaged mitochondria, dysfunctional proteins and cytoplasm aggregates, recycling of cellular materials required for rebuilding essential cell structures and for generating energy[29].

Recent evidence suggests that dysregulation of autophagy is involved in the pathogenesis of a variety of kidney diseases including PKD, DN, obstructive nephropathy, focal and segmental glomerulosclerosis. The roles of autophagy in the diseased kidney have been studied mainly in proximal tubular cells and podocytes. Podocytes are terminally differentiated postmitotic cells. Therefore, their capacities for regeneration are limited and they require efficient cellular mechanisms to 'clean' themselves from protein aggregates and altered organelles that will accumulate throughout a lifetime. This task is achieved by autophagy[30]. Defective autophagy in podocytes results in proteinuria, loss of podocytes and glomerulosclerosis which are risk factors for the development of CKD[31]. Apart from podocytes and glomerular diseases, autophagy is also involved in tubulointerstitial compartment, acute kidney injury and renal fibrosis. Autophagy is now generally accepted as a renoprotective cellular response in AKI of various causes[32].

Unilateral ureteral obstruction in rodents is a classic model of progressive renal fibrosis. Autophagy markers were increased and protective in obstructed renal tubules in a unilateral ureteral obstruction model[33]. By the light of these accumulating data, inducing autophagy could be a promising therapeutic strategy for CKD although most evidence is based on rodent experiments. Nevertheless, ER seems promising in this regard given the beneficial effects on autophagy.

ER blockade of cellular energy utilisation, specifically glycolysis, is sufficient to induce autophagy via the AMPK/mTOR pathway[34]. The impact of ER on autophagy has also been observed *in vivo* and long-term, as in the case of ageing rats, in which it was associated with reduced DNA damage and ageing markers[35]. In short-term studies in rats, nephroprotection afforded by 70 % ER for 2 weeks before kidney ischaemia–reperfusion injury was associated with increased autophagy and was partially abolished by the autophagy inhibitor 3-methyladenine[20].

ER-associated decrease in ATP levels results in an increase in AMP:ATP ratio that activates the energy/nutrient sensor AMPK pathway[16,36]. AMPK is thought to be necessary for the life-prolonging effect of ER mimetics[37]. AMPK phosphorylation leads to activation of Sirt1, PPAR-γ coactivator 1α (PGC1α) and some forkhead box O (FOXO) proteins[38]. This leads to deacetylation of proteins, including key transcription factors which are important for mitochondrial health and stress defence mechanisms. Additionally, in conditions of ER, AMPK inhibits the kinase activity of mTOR, which in its activated complex mTORC1 promotes cell growth and proliferation and is an autophagy repressor[36]. In rats, ER up-regulation of AMPK along with down-regulation of mTOR signalling resulted in decreased urinary protein excretion, tubular epithelial cell senescence and epithelial to mesenchymal transition[39]. Also in rats, short-term (8 weeks) 60 % ER decreased body weight, urinary albumin excretion and TAG as well as glomerular volume, fibrosis, 8-hydroxydeoxyguanosine (mitochondrial DNA oxidative damage marker) and cell senescence. This was associated with increased autophagy markers (e.g. 3/Atg8), increased AMPK and decreased mTOR activity[40].

Sirt1 is a NAD-dependent histone deacetylase that regulates autophagy and inhibits inflammation by suppressing the transcriptional activation of the p65 NF-κB subunit[41]. The renal effects of Sirt1 are extensive[42]. For example, renal tubular Sirt1 protects podocytes in diabetes by preventing up-regulation of podocyte Claudin-1, a tight junction protein[43]. Sirt1 also inhibits TGF-β1-mediated interstitial fibrosis by decreasing TGF-β1/Smad signalling[44]. Sirt1 also deactivates several kidney apoptosis-related proteins such as FOXO3, p53, Smad7 and FOXO4, thus protecting against damage-induced apoptosis[42]. Other kidney actions of Sirt1 include suppression of inflammation, induction of autophagy, enhancing endothelial nitric oxide synthase activity and mitochondrial biogenesis by targeting PGC1α, and modulating hypoxia-inducible factor-1α (HIF-1α) and HIF-2α activity[42]. However, in the context of ER, Sirt1 promotion of autophagy is a key protective pathway[5]. Sirt1 promotes autophagy through several pathways. Thus, during ER, Sirt1 increases the expression of BCL2 interacting protein 3 (Bnip3), a driver of autophagy[45] and promotes Foxo3 deacetylation[46]. In this regard, the kidneys of aged Sirt1± mice were resistant to ER-mediated improvement in the accumulation of damaged mitochondria under hypoxia[46]. In rats, ER protection from ischaemia–reperfusion injury was associated with increased kidney Sirt1 expression and preserved kidney eNOS and PGC1α[20].

ER also suppresses inflammation. In rats, 30 % ER for 6 months decreased DNA damage and retarded the pro-inflammatory senescence-associated secretory phenotype, decreasing NF-κB activation[47]. In autoimmune susceptible mice, a high-energy diet resulted in γ-globulin deposition and increased cellular infiltration in the kidneys while ER reduced glomerulosclerosis, glomerular cell proliferation and Ig deposits[48]. In rats, 40 % ER for 8 months increased the expression of single Ig IL-1-related receptor, a key negative regulator of inflammation that improves kidney fibrosis[49–51]. This was associated with milder activation of the pro-inflammatory NF-κB transcription factor, as evidenced by lower phospho-IκBα and phospho-RelA levels[51]. In human randomised controlled trial (RCT), a 12 % ER leads to lower C-reactive protein values at 2 years[52].

There is recent interest on the role of lipids in kidney injury[53]. Thus, sterol regulatory element-binding transcription factor 1-a, a mediator of lipid synthesis and lipotoxicity, promotes kidney lipid accumulation, proteinuria and glomerulosclerosis, especially in DN[54]. Lipid metabolism is also modulated by ER. In rats, ER modified renal sterol regulatory element-binding transcription factor 1-a expression and lipid accumulation resulting in milder renal structural and functional changes associated with 24-month ageing[55].

In mice, both ER and PR for 1 week were beneficial and additive in terms of decreasing ischaemia–reperfusion injury. However, the benefits of PR were decreased when essential amino acids are added. There was an 87 % decrease in leptin, independent of energy intake and recombinant leptin administration partially offset benefits of dietary preconditioning against renal ischaemia–reperfusion injury[56]. Short-term dietary

restriction (30 %) prevented renal dysfunction and improved survival, antioxidant defence, insulin sensitivity and reduced inflammation in mice 28 d post-renal ischaemia. Surprisingly even, 1–3 d of fasting also improved the renal functional abnormalities and increased survival rates, but these beneficial findings disappeared after refeeding[57].

ER also reduces renal oxidative stress. Two months of 60 % ER in growing mice increased the kidney antioxidant glutathione (GSH):oxidised glutathione (GSSG) ratio, glutathione peroxidase and cytochrome oxidase activities and decreased *in vivo* peroxidation[58]. Increased hydrogen sulphide production and activation of the redox-sensitive nuclear factor (erythroid-derived 2) like 2 contribute to the beneficial effects of ER on oxidative stress. Previously, it was shown that 30 % ER resulted in H_2S up-regulation and decreased reactive oxygen species levels and protein carbonylation as well as delayed ageing[59]. Nuclear factor (erythroid-derived 2) like 2 activates the expression of genes encoding enzymes that fight oxidative damage. During ER, antioxidant enzymes under the control of the nuclear factor such as NQO1 (NAD(P)H dehydrogenase, quinone 1) are increased[60]. Interestingly, nuclear factor (erythroid-derived 2) like 2 activators such as bardoxolone consistently increase GFR, although at least in certain populations, the adverse effects profile is not favourable[61]. ER also positively influences mitochondrial structure and function, at least in part by promoting the expression of the master mitochondrial biogenesis regulator PGC1α[20,62]. PGC1α is a key part of the endogenous nephroprotective response which is down-regulated during AKI, and PGC1α down-regulation promotes kidney inflammation[63,64]. During ATP generation in mitochondria, some superoxide radicals are also formed[65]. Mitochondrial ageing increases baseline reactive oxygen species production while mitochondrial antioxidant defence enzymes (e.g. SOD2) and ATP generation decrease, thus further contributing to oxidative stress[66,67].

Energy *v.* protein *v.* carbohydrate *v.* fat restriction

ER may be achieved by restriction of different nutrient families. However, there is limited comparative evidence on dietary energy *v.* carbohydrate *v.* protein *v.* fat restriction on CKD progression. There is also some confusion with definitions such as caloric restriction, energy restriction and DR. In some studies, dietary restriction is considered equal to ER, indicating an overall decrease in food consumption. Most dietary restriction studies impose a 20–40 % ER, and the duration of this restriction ranges from a few weeks to an entire lifespan[7].

ER appears to be the most important component at least in some species. For example, 40 % ER in spite of high protein intake improved survival and delayed the onset of proteinuria in lupus-prone (NZB × NZW) F1 (B/W) mice[68]. However, there is conflicting evidence regarding relative contribution of reduced energy *v.* reduction of specific nutrients. While some studies suggest that both PR and energy restriction are beneficial[69], others showed a negligible influence of the source of energy (fat, protein)[70] and still others showed that the primary reduction of protein is more important than ER[71].

PR in the context of CKD merits special consideration, as it is widely practiced, and CKD patients spontaneously decrease protein intake as CKD progresses. PR is classically accepted as a measure for kidney protection. In a recent meta-analysis regarding the PR in CKD, patients showed that there was reduced risk of kidney failure (OR 0·59, 95 % CI 0·41, 0·85) and end-stage renal disease (OR 0·64, 95 % CI 0·43, 0·96) with low protein intake. In addition, PR reduced the rate of GFR decline and proteinuria[72]. The underlying beneficial mechanisms of PR are not completely understood, but there are some longstanding hypotheses. PR decreases glomerular hyperfiltration which is associated with pathological albuminuria and with CKD progression. Indeed, current nephroprotective drugs such as renin angiotensin-system blockers and Na–glucose co-transporter-2 inhibitors work by decreasing glomerular hyperfiltration[73,74]. A high protein intake has long been known to increase intraglomerular pressure and glomerular hyperfiltration, leading to glomerular damage and glomerulosclerosis[75]. PR may also have additional advantages. Short-term (3 d) PR increased the expression of FOXO3, hepatocyte nuclear factor 4 and high mobility group A1 in kidneys and decreased ischaemia–reperfusion injury-induced AKI[76]. This effect appears independent from any contribution to CKD progression.

PR may be used to restrict energy intake and, thus, down-regulate the mTOR pathway which is closely related to senescence and kidney damage as suggested above[56]. However, part of the impact of PR may depend on specific amino acids as some amino acids are thought to be more detrimental than others with regard to kidney injury. For example, methionine supplementation increased tubulointerstitial damage[77], whereas methionine restriction decreased mitochondrial reactive oxygen species production and oxidative stress[78]. Methionine and cysteine supplementation also decreased H_2S production which is an important antioxidant mechanism[79]. However, not all studies confirmed that PR is beneficial for CKD progression or the risk of dialysis and death[80].

Lipid restriction is also another way of ER, and there are studies showing that lipid restriction with ER is also beneficial for the kidney. However, the type of fat may be relevant. A 40 % ER for 6 and 18 months in mice decreased age-associated glomerular basement membrane thickness and preserved podocyte foot processes and filtration slits, and these changes were more marked when lard was the main fat source in ER diets than when soyabean oil or fish oil was the fat sources. The age-associated increase in mitochondrial volume was also less marked in the ER lard group[81].

Carbohydrate restriction is another mode of ER. Indeed, it has been long before demonstrated that carbohydrate restriction may be protective for renal damage. Kleinknecht *et al.* studied the renal effects of carbohydrate restriction in uraemic rats. Carbohydrate-restricted rats (starch and glucose) showed slower increase in plasma creatinine, lower mortality rate and less histological renal damage compared to *ad libitum* rats with best survival rates as observed in glucose-restricted rats. The authors suggested that carbohydrate restriction may preserve the renal parenchyma, and restriction of 'simple' rather than 'complex' sugars may be more beneficial[82].

In another study, Kobayashi *et al.* showed that carbohydrate restriction with 40 % ER and despite no change in protein intake resulted in decreased glomerular hyperfiltration, tubular damage and kidney weight[83]. Reisin *et al.* demonstrated that low-energy diet achieved by carbohydrate restriction without PR resulted in higher creatinine clearance, lower 24-h urinary protein excretion, lower mesangial expansion index in spontaneously hypertensive rats independent of PR or Na and K content[84].

Cadenas *et al.* showed that 2 months of carbohydrate restriction reduced renal oxidative stress by increasing glutathione (GSH)/oxidised glutathione (GSSG)[58]. Krishan *et al.* showed that a 30 % ER by carbohydrate restriction in streptozotocin-induced type 1 diabetes in rats for 4 weeks resulted in better glycaemia control, milder changes in blood urea nitrogen, creatinine and proteinuria, decreased oxidative stress and preserved kidney glutathione and preserved kidney expression of HIF-1α[85].

Overall, these studies suggest that not only ER but also the specific type of restriction (protein *v.* carbohydrate *v.* lipid) and the source of nutrients may independently modulate renal protection in experimental animals. These findings further complicate the choice of diet for eventual RCT aiming at reproducing basic research data.

Safety of energy restriction in chronic kidney disease

ER may have side effects potentially relevant to CKD. One important issue is the fact that protein–energy wasting and hypoalbuminaemia are common in CKD and related to morbidity and mortality[86]. Thus, ER may further exacerbate protein–energy wasting. However, therapeutic ER aims to be balanced, so as to prevent a catabolic process. A protein-restricted diet supplemented with keto analogues can be successfully implemented in advanced CKD without any harm, even with benefits[87]. In any case, any future RCT of energy restriction for CKD should carefully evaluate safety.

One of the peculiar aspects of ER in CKD is the obesity paradox, a survival advantage in obese patients on dialysis. The obesity paradox implies that obesity increases long-term cardiovascular mortality; however, it may decrease short-term mortality associated with malnutrition, inflammation and protein energy wasting[88]. However, in kidney-transplanted patients, obesity increases the risk of mortality and graft loss, as compared with normal-weight patients[89]. Thus, ER may not be appropriate when looking from the 'obesity paradox' perspective. However, ER as discussed above has many beneficial effects. Thus, the safety of ER for CKD patients may be CKD stage specific. For example, a patient with diabetes, obesity and stage 1 CKD may get benefit from ER as an obese patient on renal transplant waiting list in contrast to a dialysis patient with decreased albumin, BMI and muscle mass. These conflicting issues regarding ER in CKD patients need to be highlighted in further studies. There are also no data of ER in patients receiving renal transplant. ER implementation before kidney transplantation needs to be studied with respect to duration, amount of ER and type of ER protocols.

Hypertension is a prominent feature in CKD patients and the prevalence of hypertension increases as CKD progresses[90]. In CKD, fluid overload is common and most patients were hypervolaemic[91]. Thus, a reduced salt intake is strongly recommended and has been shown to decrease blood pressure and proteinuria[92]. However, in a recent study, ER inappropriately activated aldosterone production in rats with normal kidney function. This response was magnified by salt restriction so as the lower blood pressure observed in ER- or salt-restricted rats was no longer observed when both ER and salt restriction were combined. This raises questions about the impact of combined salt restriction and ER in the CKD context[93]. This issue is especially important for advanced CKD and dialysis patients who are hypervolaemic and reduction in salt intake is recommended for them. There is a need to explore the impact on blood pressure of combined ER and salt restriction in CKD patients. Fortunately, the degree of Na restriction achieved in experimental rats is unlikely to be achieved in persons with CKD.

Decreased bone mineral density with potential for increased osteoporosis and fracture risk may be other complications of ER[94]. In CKD patients, there is already an increased risk for osteoporosis and fracture risk associated with CKD mineral bone disorder[95]. While bone pathophysiology in the CKD patients is very different from the general population, until specific studies have addressed the impact of ER on bone health in the CKD context, this represents a further potential risk of ER in CKD patients.

Other potential side effects of ER are immunosuppression, impaired wound healing, delayed sexual maturity and social exclusion[29]. These are also well-known concerns in CKD patients. Thus, one must consider all these aspects when considering ER in CKD patients. It is clear that one size does not fit all and clearly RCT are needed that clearly establish the benefit: safety balance for CKD patients with different CKD stages, comorbidities, CKD mineral bone disorder parameters, psychological state and others.

Energy restriction mimetics

A key issue in ER research is long-term adherence. Benefits of ER depend on adherence and especially long-term adherence may be problematic. Adherence may be more difficult for CKD patients who are already on a very strict diet. To overcome adherence issues, ER mimetics may be of value. ER mimetics are drugs that induce metabolic, hormonal and physiological changes that are similar to the effects of ER, that is, they induce a ER-like stress response without significantly influencing long-term dietary intake[29]. ER mimetics are expected to achieve the same benefits of ER, such as prolonging lifespan and reducing age-related diseases[96].

Compounds with ER mimetic properties include resveratrol, spermidine: hydroxycitric acid, aspirin, (poly)phenols, metformin, Na–glucose co-transporter-2 inhibitors and rapamycin[4]. Both upstream-type ER mimetics that inhibit glycolysis and downstream ER mimetics that regulate or genetically modulate intracellular signalling proteins are recognised[97]. However, CKD limits the use of some of these agents. Thus, despite recent trends to be more tolerant of the use of low dose metformin in

advanced CKD, the safety of such approach has been questioned[98,99]. By contrast, Na–glucose co-transporter-2 inhibitors, until recently limited to individuals with preserved GFR, were shown in RCT to preserve renal function and reduced cardiovascular events even in individuals with decreased GFR[100]. In any case, except for Na–glucose co-transporter-2 inhibitors, there is a paucity of data supporting the use of ER mimetics for kidney protection.

Unknowns and areas for further study

The effects of ER in human health are just only being recognised[101]. However, most research has been performed in experimental animals.

There may be several reasons for the lack of the data in humans, so the interpretation must be made carefully. First, although similarities exist, animal models may not fit 100 % to human physiology. Second, experimental conditions do differ from daily conditions and every day practice. For example, in experimental studies, there is usually a certain period of time to focus which differs from real-life experiences. Indeed, experiments regarding ER are mostly performed in a certain limited period of time. However, the effects of ER may extend for long-time periods and long-term observations may be more reliable in real-life settings. Third, studies regarding ER in humans may be difficult to design due to adherence issues. Some experiments used during ER are far from practical and some of them limit ER to very low levels which is not possible to be adhered by humans. Lastly, although similarities exist, kidney disease pathophysiology differs between rodents and humans. Although this assumption is correct for all experimental rodent models, this may be even more pronounced in the context of ER. There are various *in vitro* and *in vivo* models for CKD in animal experiments including spontaneous models, vascular injury models, genetically engineered models and acquired models. However, these models do not fit 100 % with human CKD. For example, some models are highly strain specific (e.g. 5/6 nephrectomy model) and do not represent the whole species. Another drawback is that the genes that yield the phenotype in a given model in certain inbred strains may only represent a small subset of the genes that produce the phenotype in complex human diseases[102].

With regard to observation of pathophysiological changes during CKD, there is often a mismatch between the detailed outcomes measured in animal research but not in human trials. For example, in the context of fibrosis and progression of CKD, animal models measured multiple histological, histochemical and biochemical parameters at the same time, whereas in humans the more restrictive end points of mortality, glomerular filtration or proteinuria are commonly used. Whether these multiple surrogate markers measured in the animal models can be readily extrapolated to the human condition is questionable[103]. Thus, due to these limitations, there is lack of large RCT, regarding the potential impact of ER on human CKD; however, limited, short-term studies in humans suggest a benefit. In one of these studies, Giordani *et al.* showed that a 7-d of very low-energy diet increased GFR from 73 (SD 4) ml/min per 1·73 m^2 to 87 (SD 6) ml/min per 1·73 m^2 in diabetic patients[21]. These findings were similar to those 12 weeks very low-energy ketogenic weight reduction diet in six obese diabetics with eGFR < 40 ml/min per 1·73 m^2[104]. A 12 % weight reduction was associated with lower albuminuria and lower levels of the filtration markers serum creatinine and cystatin C, but GFR was not measured and it is unclear whether benefit may have been obtained in non-obese individuals. In a slightly longer study, low-energy diet for 5 months decreased weight by 4 % and urinary protein excretion in thirty patients with proteinuric nephropathies both with and without diabetes[105]. However, no impact on eGFR was observed. Thus, larger, longer studies are needed that expand to other causes of CKD, including hypertension, specific glomerular diseases, hereditary kidney diseases and kidney involvement in rheumatological diseases. A potential major drawback is compliance, especially in countries with a high prevalence of obesity, in which an inability to limit energy intake at the society level is one of the key drivers of the current obesity epidemic. A recent US phase 2, RCT in healthy young people illustrates both the challenges and promise of ER[52]. The trial aimed for a 25 % energy reduction for 2 years but could only achieve a 12 % decrease. However, this was enough to result in benefit, as demonstrated by weight loss, lower LDL-cholesterol, blood pressure and C-reactive protein and improved insulin sensitivity index. Unfortunately, kidney outcomes were not assessed.

CKD is associated with a very early decrease in kidney production of the anti-ageing factor Klotho. This may be driven by albuminuria or local kidney inflammation[106,107]. Genetic deficiency of klotho is associated with vascular calcification, senescence, muscle atrophy and renal dysfunction, and acquired Klotho deficiency during CKD is thought to contribute to these features[108]. Whether ER improves Klotho levels in CKD is unknown.

ER has also been associated with intestinal microbiota changes. This is not surprising since the diet also feeds the gut microbiota. A high-fat dietary pattern leading to obesity in rodent models is associated with changes in the microbiota. The possibility that energy restriction may impact colonic health and cancer risk via changes in the structure or function of microbiota is also under study[109]. In mice, compared with an *ad libitum* control and moderate-fat diet, lifelong 30 % ER reduction was associated with attenuated immune- and inflammation-related gene expression in the colon and an increase in certain beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*[110]. In this regard, there appears to be bi-directional relationship between CKD and the microbiota, by which CKD influences the microbiota and the microbiota may influence CKD progression[111]. However, too little is known at this point about the clinical relevance of the ER–microbiota interaction for kidney health.

Lastly, not only restriction of lipids, proteins and carbohydrates but also the pattern of ER may be also important. There are various fasting protocols aiming ER including skipping meals, 24 h fasting, 36 h fasting alternate day fasting, etc. It should be pointed out that ER is not same with DR. ER with various types of DR exists (Table 2). Besides, inadequate intakes of one or more nutrients might have effects on development and progression of CKD that are additional to effects of energy restriction *per se*. Unfortunately, there are no sufficient data

British Journal of Nutrition

regarding which one of these fasting protocols is best protective for kidneys. However, although not a scope of this review we want to mention that a special kind of fasting has been already carried out by Muslim people named 'Ramadan fasting' as an example.

Ramadan fasting during the holy month is one of the pillars of Islam and abstains Muslims from eating, drinking, smoking from dawn to sunset. Fasting duration may change according to geographic location and season; while some fast for 8–9 h, others fast for 18–20 h. There are studies performed to investigate the effects of Ramadan fasting on renal function with inconsistent results, some showing benefit and others showing harm. The contradictory findings may be due to difference in fasting time, underlying disease and the type of diet pattern during fasting. Thus, more studies are needed regarding fasting protocols with kidney outcomes.

Conclusion

Pioneering studies showed that ER might have a beneficial role in development and progression of CKD. However, these data are largely derived from experimental rodent models and there are only few human studies present until now. This raises questions about the direct transformation of experimental data to humans. Various mechanisms regarding the protective role of ER are suggested including autophagy and improved mitochondrial function, decreased oxidative stress and mTOR pathway. CKD itself is a very stressful condition with various co-morbid conditions. Thus, compliance to ER will likely be challenging in CKD patients who already have restrictive dietary requirements, and ER may potentially exacerbate CKD complications such as protein–energy wasting and CKD mineral bone disorder. Future studies should clarify whether ER is a valid alternative for routine nephrology care and the role of ER mimetics in CKD patients.

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