Emerging non-pharmacological interventions in ADPKD

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Emerging non-pharmacological interventions in ADPKD: an update on dietary advices for clinical practice

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Purpose of review
Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) reach kidney failure at a median age of 58 years. There has been a strong interest in medical interventions to improve prognosis. With increasing understanding of the underlying pathophysiology, there is also a rationale for non-pharmaceutical interventions. However, these have received little attention. This review, therefore, focuses on dietary interventions in ADPKD.

Recent findings
Recent studies regarding salt, protein and water intake, caloric restriction, BMI, caffeine and alcohol are discussed in this review. In general, these studies suggest that advices do not need to be different from those in chronic kidney disease (CKD). On the basis of research in the general population and CKD, these advices will likely decrease cardiovascular morbidity and mortality. With respect to delaying ADPKD progression, evidence for salt restriction is growing. For increasing water intake and targeting glucose metabolism by intermittent fasting, preclinical studies are promising. Long-term randomized human intervention studies are, however, lacking.

Summary
In ADPKD, advices regarding dietary interventions can, in general, be the same as in CKD to decrease cardiovascular morbidity and mortality. Whether these interventions also delay disease progression needs further study.

Keywords
autosomal dominant polycystic kidney disease, diet, protein intake, salt intake, vasopressin

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a hereditary disease characterized by the formation of numerous cysts in both kidneys [1] leading to kidney failure at a median age of 58 years [2]. The last two decades, science has gained more insight into the underlying pathophysiological mechanism how gene defects result in cyst formation. We now know that patients with ADPKD have in the far majority of cases a mutation in the *PKD1* or *PKD2* gene [3], resulting in decreased presence or functionality of polycystin proteins. This in turn results in a disturbance of cell homeostasis and signaling pathways [4]. This knowledge has identified several targets for therapy. With increased intracellular cyclic AMP playing a pivotal role, pharmacological therapies directed at lowering cAMP have been tested. So far, vasopressin V2 receptor antagonism is the only therapy that has been proven renoprotective [5–7]. Disadvantages of this treatment are the aquaretic adverse effects, high costs and lack of access for all ADPKD patients. In recent studies, a glucose dependency of cyst cells has been shown, opening the possibility of low caloric and ketogenic diets in ADPKD [8▪▪]. Also for other dietary interventions, as increased water intake and restriction of caffeine, a pathophysiological rationale is present. Recently, various reviews have

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KEY POINTS

- Dietary advice in ADPKD is in general the same as for chronic kidney diseases. Main advices are summarized in Table 2.
- With respect to increasing water intake to decrease urinary osmolality, the advice should be dependent on kidney function.
- Research is necessary to investigate whether dietary interventions also influence disease progression.
- Of interest are especially the preclinical studies on metabolic reprogramming that open the intriguing possibility to decrease the rate of disease progression in ADPKD by a diet that enhances ketosis.

focused on medical interventions in ADPDK, whereas attention for nonmedical interventions has been limited, This review, therefore, focuses on recent advances in knowledge on dietary interventions in ADPKD.

SALT INTAKE

In chronic kidney disease (CKD), there is general consensus that daily salt intake should be less than 5 g per day in patients with high blood pressure and CKD [9▪▪], which is approximately equivalent to less than 2 g/day sodium or less than 90 mmol sodium/day). Too high intake of salt is thought to cause an increase in cardiovascular disease and mortality [10,11], whereas a decrease in salt intake has been shown to result in a decrease in SBP [12], proteinuria [13], and renal and cardiovascular events [14,15]. To gain insight in salt intake, 24 h urine sodium excretion can be measured.

In ADPKD, patients often have hypertension. Hypertension might be causally related to disease progression, for an intervention study in which blood pressure was decreased showed a reduction of 14% in cyst growth [16]. Salt restriction could be beneficial in ADPKD for it might enhance the favorable effect of renin angiotensin aldosterone system (RAAS) blockade and decrease deleterious vasopressin levels. Increased vasopressin levels have a deleterious role in the process of cyst growth and renal function decline by activating the vasopressin V2 receptor and increasing intracellular cAMP. High vasopressin levels are associated with disease progression [17], thus inducing a vicious circle. To escape from this vicious circle, vasopressin needs to be blocked or lowered. Trials have shown that vasopressin V2 receptor blockade is effective in delaying disease progression [5].

Thus, a sodium restriction could be beneficial both by enhancing favorable effects of RAAS blockade as reduction of vasopressin levels. In Han:SPRD rats (a model for polycystic kidney disease), an increase in salt intake induced an increase in kidney weight and cyst ratio [18]. Also human studies have investigated the potential role of salt intake on outcome in ADPKD, unfortunately mostly observational. These studies are summarized in Table 1.

In a large, observational study including 553 ADPKD patients with a mean follow-up of 6 years, an association was found between high salt intake and disease progression [19]. Mediation analysis suggested that the effect on disease progression was primarily a consequence of a salt-induced rise in vasopressin rather than the result of salt-induced changes in blood pressure.

Unfortunately, no randomized controlled trials have been performed that investigated the effect of salt restriction on disease progression in ADPKD. The best evidence so far, comes from a post hoc study of the HALT A and B trials [20,21]. These large trials investigated the effect of intensive blood pressure control and double vs. single RAAS blockade in early and later stage ADPKD (studies A and B, respectively) [16,19]. Patients who participated in these trials, were prescribed a salt-restricted diet containing less than 6 g salt. At baseline, mean salt intake in both studies was 10 g. Although significant, the decrease in salt intake during the trial was modest (at the end of study 9.6 g salt/day in study A and 8.8 g salt/day in study B, on average, 6.5 and 14.5% reductions, respectively, with large variations between persons, Fig. 1). A post hoc study found that each decrease of 1 g salt, was associated with less kidney growth (0.43%/year) in study A, and in study B with significantly slower rate of estimated glomerular filtration rate (eGFR) decline (−0.09 ml/min/1.73 m^2/year for each gram salt reduction) and a lower risk for the incidence of the composite renal endpoint (i.e. a 50% reduction in eGFR, end stage kidney disease, or death, hazard ratio 1.08; $P = 0.01$) [22] Altogether, these data suggest that advice in ADPKD can be equal to that in CKD and should be less than 5 g per day.

PROTEIN INTAKE

In CKD in general, the KDIGO guidelines do not recommend reducing protein intake. The advice is to avoid a high protein intake (>1.3 g/kg per day) in all patients with CKD who are at risk of disease progression. Only when kidney function is reduced to an eGFR less than 30 ml/min/1.73 m^2, protein intake should be reduced to 0.8 g/kg per day to avoid uremic complaints [23]. Protein intake can be

Table 1. Studies on salt and protein intake and disease progression in human autosomal dominant polycystic kidney disease

Study	Nutrition	Design	Number of subjects	Inclusion; ADPKD	Estimated nutritional intake	FU	Main conclusion
Torres *et al.*, *cJASN* 2011	Salt and protein	Observational	241	15–46 years CrCl >70	11.0 g salt/day 72 g protein per day	6 years	Salt at baseline is associated with increase in TKV and univariately with decrease in mGFR. Protein intake was only univariately associated with increase in TKV and decrease in mGFR
Kramers *et al.*, *KI*, 2020	Salt and protein	Observational	589	>18 years eGFR >15	9.1 g salt/day and 84 g protein/day	4 years	Salt at baseline is associated with kidney function decline and this is mediated by vasopressin. Protein intake is not associated with kidney function decline
Torres *et al.*, *KI* 2017	Salt	Post hoc analysis of RCT	558 and 486	A: 15–49 years and hypertension B: 18–64 years and eGFR 25-60	10 g salt/day. Reduction to 9.6 g salt (study A) and 8.8 g salt (study B)	8 years	Increase in salt is associated with increased TKV and in later ADPKD with decreased eGFR and increased risk of reaching the composite renal endpoint
Klahr *et al*, *JASN* 1995	Protein	RCT	200 (127 in A and 53 in B)	A: GFR 25–55 ml/min B: GFR 13–24 ml/min	1.1 vs. 0.7 g/kg/day (study A) and 0.7 vs. 0.4 g/kg/day (study B)	3 years	No difference in GFR decline in study A. In study B, a trend (*P* is 0.06) towards a less steep GFR decline (4.0 vs. 4.9 ml/min per year), proportion of patients reaching renal failure; however, not different
Choukroun *et al.*, *JASN* 1995	Protein	Observational	A: 109 B: 48	A: CrCl 30-50 B: CrCl 50—60	0.9 g/kg/day	A: 6.7 ± 0.3 years B: 4 years	No association between protein intake and eGFR was found in group A or in group A and B combined

cJASN, clinical journal of the american society of nephrology; CrCl, creatinine clearance; FU, follow-up; GFR, glomerular filtration rate; JASN, journal of the american society of nephrology; KI, kidney international; mGR, measured glomerular filtration rate; RCT, randomized controlled trial; TKV, total kidney volume.

estimated by measuring urea and total protein excretion in 24 h urinary volume using the Maroni or Bergstrom formula. These are, respectively: $15 + (0.18 \times$ ureum excretion (mmol/24 h) + protein protein excretion (g/24 h) and $13 + (0.204 \times$ ureum (mmol/24 h) + protein excretion (g/24 h).

The idea is that a high protein diet induces hyperfiltration, leading to accelerated kidney function decline [24]. In CKD, a modest effect [−0.53 (0.08–0.98) ml/min/year] of protein restriction on disease progression has been shown in several studies [25], the most prominent one being the Modification of Diet in Renal Disease (MDRD) study [26]. This study showed that start of a low-protein diet induced a reduction in the glomerular filtration rate during the first 4 months and a slower decline thereafter. After 6 years, the hazard ratio for end-stage kidney disease and mortality were lower in the low protein groups, but after 12 years, this was not significant anymore [27], while mortality might even be increased in the very low protein group [28]. In this study, patients with various causes of kidney function decline were included.

In ADPKD, specifically, a high protein intake could not only be detrimental by inducing hyperfiltration but may also increase vasopressin level (by an increase in plasma osmolality) [29]. This

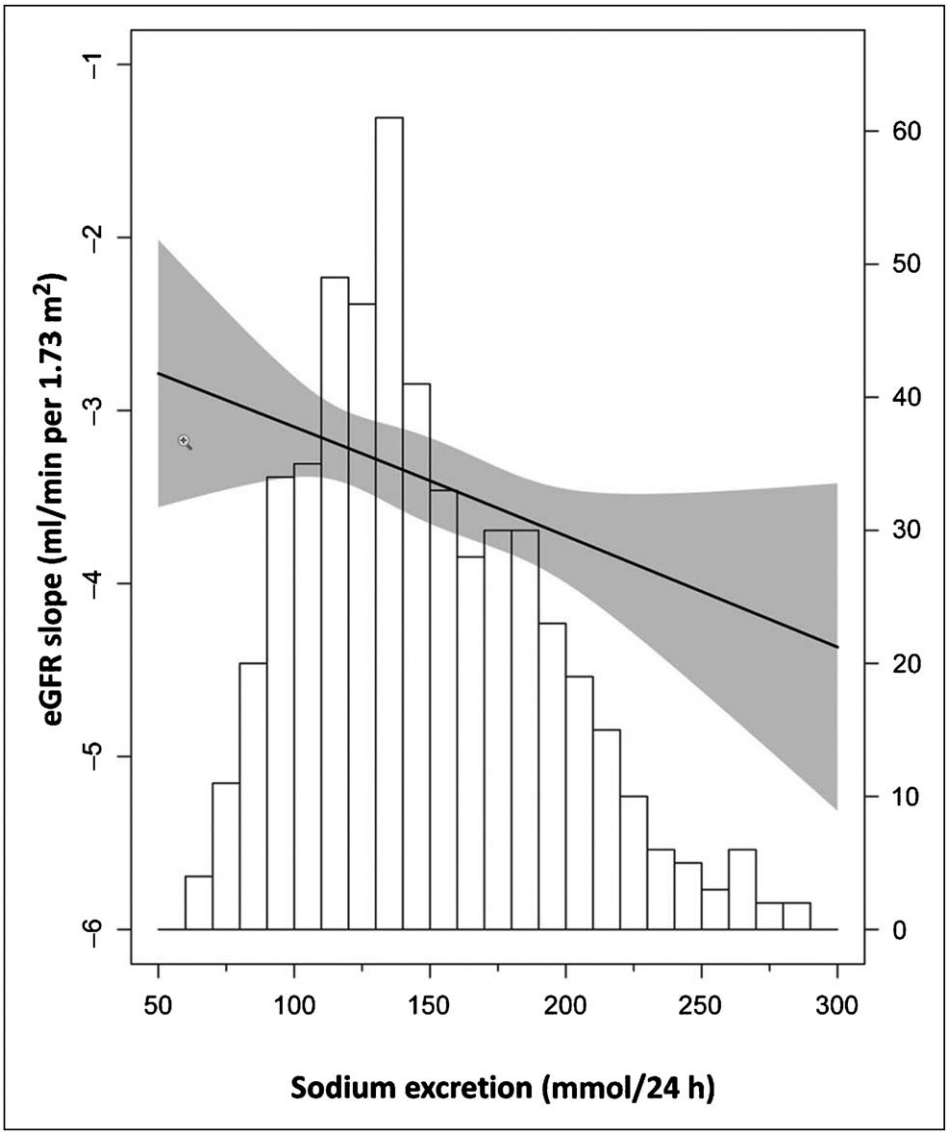

FIGURE 1. Distribution of baseline sodium excretion and its association with change in estimated glomerular filtration rate in 553 autosomal dominant polycystic kidney disease patients over a median follow-up time of 4.0 years (interquartile range: 2.6–5.0). Reprinted with permission from [32▪▪].

increased vasopressin level might lead to cyst growth and kidney function decline.

Animal experiments indeed showed that protein restriction was beneficial in ADPKD [30]. Three observational studies, however, suggested there is no major role for protein restriction in ADPKD. These studies are summarized in Table 1. In an older study, following 157 ADPKD patients, there was no association between protein intake and kidney function decline [31]. In the CRISP study, protein intake was associated with total kidney function increase and decline in measured kidney function, but this association lost significance after adjustment for important confounders [19]. In a Dutch cohort study, protein intake was also not associated with the rate of kidney function decline [32▪▪].

There is only one intervention study that looked at protein intake in ADPKD. This is a post hoc study of the above-mentioned MDRD study, investigating only the ADPKD patients who participated [33]. This considered two hundred ADPKD patients with an eGFR between 13 and 55, divided into 2 substudies (A and B). There were clear differences in protein intake throughout the study (approximately 1.1 vs. 0.7 g/kg/day in study A and 0.7 vs. 0.4 g/kg/day in study B) but no beneficial effect was found towards a renoprotective effect. Studies that investigated the effect of protein intake on kidney function in

ADPKD are summarized in Table 1.Thus, although there is a theoretical rationale to restrict protein intake and beneficial effects are seen in animal studies, this effect could not be confirmed in human studies. Advice in ADPKD is, therefore, the same as in CKD, no protein restriction but avoidance of too high protein intake.

PHOSPHATE AND NET ACID LOAD REDUCTION

In CKD, the advice is to lower elevated phosphate levels towards the normal range because of the association with accelerated kidney function decline and cardiovascular mortality and the biological plausibility that high phosphate levels are toxic. In specifically ADPKD, the additional hypothesis is that a higher phosphate intake induces tubular injury and cystic dilation of tubules, which may contribute to disease progression. Experimental studies with Polycystic kidney disease (PKD) mice and rats, showed that a low phosphate diet indeed attenuated disease progression [34▪,35▪].

Another food component of interest is net acid load. In CKD, the advice is to supplement bicarbonate when serum concentrations decrease below 22 mmol/l. PKD has been shown to be exacerbated by acidosis, and in a rat PKD model, administration of alkali had a beneficial effect [36]. Correction of acid–base imbalance could theoretically be achieved by administration of sodium bicarbonate but also by increasing fruit and vegetable intake. A pilot study showed that this was feasible and well tolerated by ADPKD patients [37]. Whether phosphate restriction and/or decreased net acid load attenuate disease progression specifically in ADPKD patients is not known, and therefore, advice beyond that for CKD in general does not seem warranted.

BMI, CALORIC RESTRICTION, INTERMITTENT FASTING, AND KETOGENIC DIET

There is increasing evidence that in ADPKD, a defective metabolism exists [8▪▪]. This defective metabolism involves a dysregulated lipid and mitochondrial metabolism but most strikingly also a defective glucose mechanism, similar to the Warburg effect in cancer [38]. This is a rewire in metabolism of cells to promote growth, survival, and proliferation. Common feature is aerobic glycolysis, leading to higher glucose need and increased lactate production. These metabolic alterations depend on the extracellular signal-related kinase (ERK) pathway and inhibit the liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) and activate the mTOR complex 1 (mTORC1)-glycolytic cascade [8▪▪]. The faster energy production (compared with oxidative phosphorylation, occurring in healthy cells) not only leads to a survival advantage for tumor cells but also to a critical dependence on extracellular glucose levels. This opens the intriguing thought that pathways that regulate glycolysis may be able to modulate cyst growth. Indeed, preclinical studies aimed at ketogenesis, either by food restriction [39,40], by time-restricted feeding, by a ketogenic diet (containing high fat but low protein and low carbohydrate) or by ketone β-hydroxybutyrate as food supplement had beneficial effects on cyst growth in preclinical PKD [41▪▪] (Fig. 2). Clinical data that test this intriguing hypothesis are scarce. Observational studies showed that overnutrition and obesity were associated with an increased growth in total kidney volume [42,43▪] and a more rapidly decreasing kidney function in one study [42] but not in another [43▪]. No intervention studies have been performed yet. An ongoing study investigates the feasibility of weight loss and periods of fasting in overweight individuals with ADPKD (NCT03342742) and another investigates the short-term effect of fasting and ketogenic diet on total kidney volume (RESET-PKD, NCT04472624).

Whether intervening in energy metabolism will influence ADPKD progression is thus not known. Until such knowledge is obtained, the recommendation remains to achieve or maintain a healthy weight (BMI 20–25) to lower blood pressure and consequently improve long-term cardiovascular outcome, as suggested in the KDIGO 2012 guideline on managing CKD [23] and in the KDIGO 2015 controversies report on ADPKD [44]. Of note, it may be complicated to calculate BMI when organs (kidneys, liver) in ADPKD are very large. We suggest replacing total kidney and liver volume by a mean volume in healthy controls (for kidneys approximately 200–250 g and for liver 1300–1500 g) [45,46] and then calculate BMI.

NICOTINE, CAFFEINE, AND ALCOHOL

In CKD, intake of psycho-active substances as nicotine, caffeine, and alcohol should be moderated or stopped. Smoking cessation is advised for this is a known risk factor for development of CKD [47] and observational studies have highlighted the harmful cardiovascular effects associated with smoking [48]. In ADPKD that is characterized by a high incidence of cardiovascular disease and intracerebral aneurysms, also smoking cessation is advised in the KDIGO consensus report [49]. In addition, smoking might influence ADPK disease progression (potentially by raising vasopressin levels). Some studies

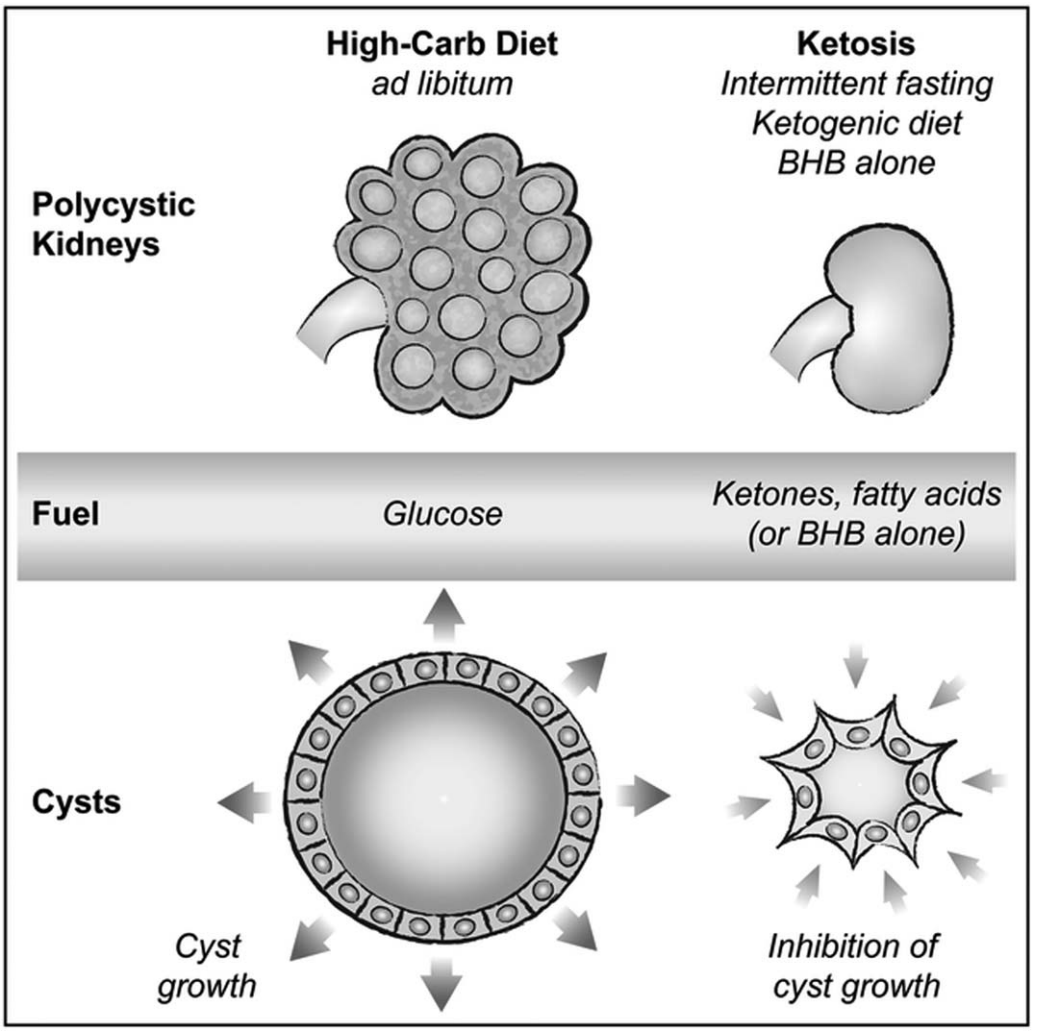

FIGURE 2. The intriguing possibility to decrease cyst growth by influencing glucose metabolism by dietary interventions. Reprinted with permission from [41▪▪].

showed this association that was, however, not significant after adjustment for potential confounders [50,51]. Nonetheless, the advice is to stop smoking also in ADPKD, because of the generally acknowledged deleterious effects of smoking on general health.

There is no formal advice on caffeine in CKD. In ADPKD, caffeine is thought to increase cAMP and accelerate progression by increasing kidney size in cultured cell studies [52] and in ADPKD mice [53▪]. An association between caffeine intake and disease progression has, however, not been found in human observational studies [54,55]. No firm recommendations can, therefore, be given but avoiding high caffeine intake seems justified as a general principle [49].

Alcohol restriction is shown to lower blood pressure in the general population [56], but no data specific to CKD or ADPKD are known. Therefore, advice is the same as in the general population and as in CKD according to the KDIGO guidelines; moderate alcohol to maximal two standard drinks per day for men and one for women [57].

WATER AND OSMOLAR INTAKE

In CKD, intravascular depletion should be avoided. There is, however, no formal advice on what the optimal level of water intake should be.

In ADPKD, there is a urine concentrating deficit already early in the disease, leading to compensatory increased vasopressin levels [58] that are detrimental in ADPKD [59]. Increasing water intake or decreasing osmolar intake, therefore, seems an attractive option in ADPKD to lower vasopressin concentration and slow disease progression [60].

In animal ADPKD experiments, a high water intake decreased renal expression of vasopressin V2 receptors and renal cAMP levels. This high water intake reduced kidney weight and improved kidney function in most models [61,62].

Several short-term (2 weeks) human intervention studies showed that change in diet and additional water intake induced a decrease in urinary osmolality [37,63] and a decrease in copeptin (the proven surrogate measure for vasopressin) [64,65]. However, longer term suppression of vasopressin seems difficult, for another study found a decrease in copeptin after acute water loading but not anymore after 7 days of additional water intake [66]. In another study, 42 ADPKD patients were randomized to a high water intake, targeting a urinary osmolality less than 270 mOsm/l or ad libitum water. Home monitoring of urine-specific gravity was employed to promote adherence. Despite a difference in urine volume and – osmolality at week 8, copeptin values were not different at this time point [67▪].

The only intervention study investigating an effect of increased water intake on ADPKD disease progression so far is the study from Higashihara *et al.* [68]. In this study, 36 ADPKD patients were investigated. Patients had a strong preference for level of water intake, and therefore, a randomized study was not possible. Patients could, therefore, choose to be in the high ($n = 18$) or the free water intake group ($n = 16$). Patients in the high water intake group were encouraged to drink 50 ml/kg per day. During this 1-year study, 24 h urine volume was higher in the high water intake group (2.7 vs. 1.5 l) and copeptin was lower. Despite the suppression of copeptin, there was a trend towards enhanced disease progression in the high water intake group, as shown by trends towards faster eGFR decline (−5.6 vs. −1.1 ml/min/1.73 m^2, $P = 0.06$) and total kidney volume (TKV) growth (9.68 vs. 5.28%/year, $P = 0.08$). This could be caused by methodological issues of this study (as the lack of randomization, use of historical data, and small sample size) and/or an increased salt intake in the high water intake group or inadequate vasopressin suppression at nonmeasured time points (e.g. at night). These inconclusive results emphasize the need for randomized controlled trials in ADPKD. Two ongoing studies investigating water intake on ADPKD progression are of interest. A smaller study including 32 participants looks at change in total kidney volume after 1 year (NCT03102632) and a larger study, consisting of 180 ADPKD patients who will be randomized to control (usual fluid intake) or intervention (individualized daily fluid intake to reduce osmolality to ≤270 mOsmol/kg) during 36 months. End points will be change in total kidney volume and estimated GFR [69]. Until results of these studies become available, the question is what to advise to ADPKD patients. Because of the strong theoretical rationale, low costs, and relatively low efforts of patients, we advise to increase the water intake and lower osmolar intake. How much water should be used is not exactly known. We propose to titrate water intake upon urinary osmolality, with different cut off values, depending on the kidney function. Importantly, because of a concentrating deficit, ADPKD patients can have a low urinary osmolality with high copeptin value especially in more advanced disease (Fig. 3a). Trying to reach a urinary osmolality below 270 mOsm/l (the value that is often mentioned), therefore, does not guarantee a suppressed vasopressin. Also the fact that urinary osmolality can decrease far below 270 mOsl/l with vasopressin V2 receptor antagonist therapy, shows that not all vasopressin activity is suppressed at this level. Furthermore, also maximal diluting capacity is decreased in patients with a lower kidney function, and thus with a lower number of functioning nephrons. Figure 3b shows that the increase in 24 h urinary volume with vasopressin V2 receptor blockade is largely dependent on kidney function. Patients in the lower GFR range will, therefore, have problems to excrete sufficient water in case of overhydration, and more water intake can easily induce a hyponatremia. It seems, therefore, well tolerated to differentiate between high and low kidney function when advising to increase water intake in ADPKD. For subjects with an eGFR greater than 60 ml/min 1.73 m^2, urinary osmolality should be decreased as much as possible in order to obtain a suppressed vasopressin level, whereas in subjects with an eGFR less than 30 ml/min 1.73 m^2, additional water intake should be limited to prevent hyponatremia [70].

SPECIAL CONSIDERATIONS

Patients and medical doctors might see dietary advices as restrictions from the normal situation. However, throughout the years, our dietary pattern has changed, adding more salt, protein, calories, caffeine, etc. Dietary advices should, therefore, not be seen as a restriction but as a return to the normal healthy situation. In fact, the present dietary advice in ADPKD (and CKD) reflects just healthy nutrition, as defined by the WHO. We think it might increase compliance to emphasize this as mind shift to patients.

To optimize compliance, it is furthermore, important to involve patients in their treatment and give them insight into their diet. Feedback will help enhance compliance and make potential adjustments. Essential for this feedback is collection of 24 h urine, to be able to calculate salt and protein intake from urinary sodium and urea excretion. A sodium excretion of 90 mmol/24 h equals 5 g of salt intake, and a urea excretion of 360 mmol/24 h

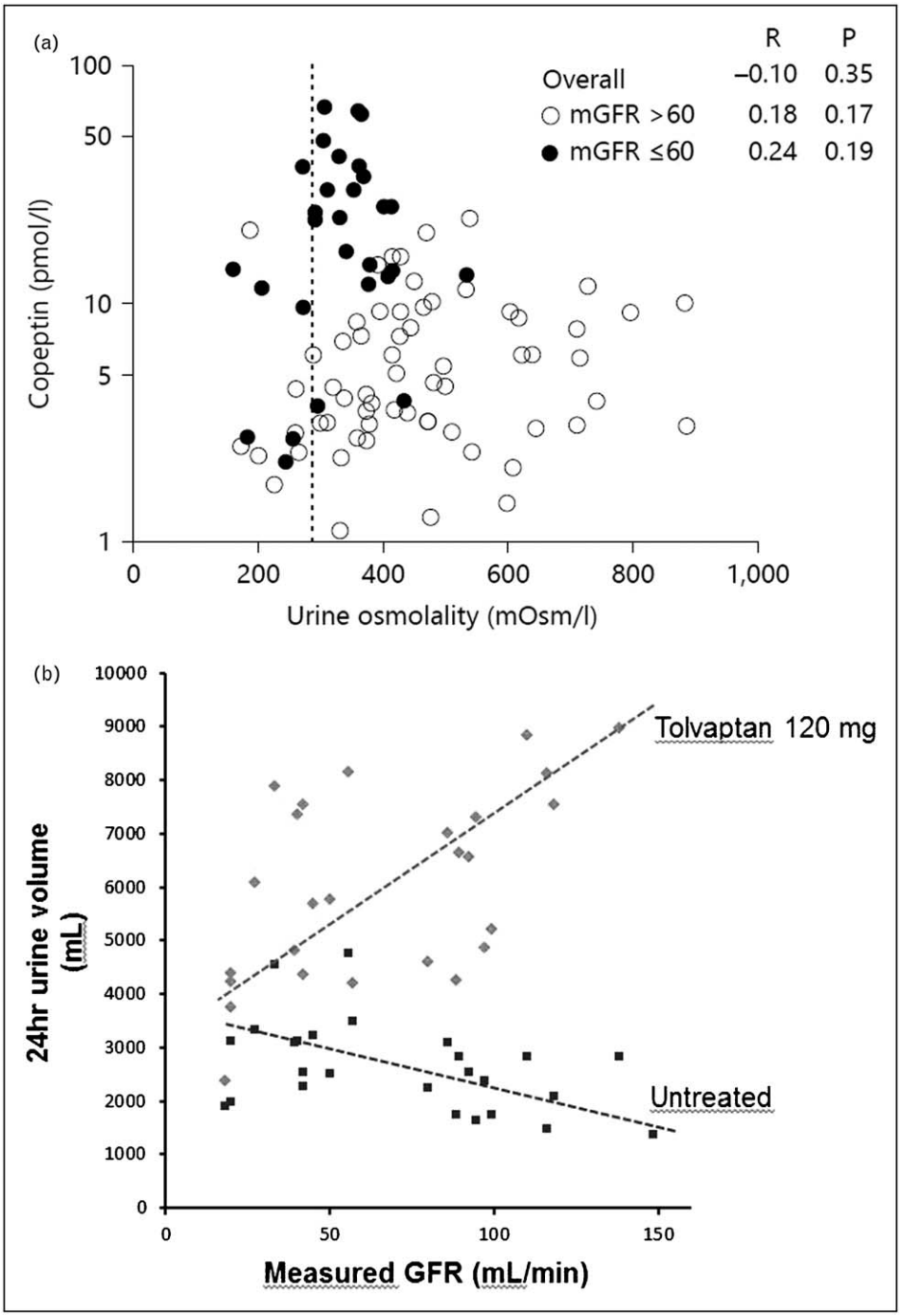

FIGURE 3. (a) A urinary osmolality below 270 mOsm/l does not guarantee a suppressed copeptin, for this is already present in patients with autosomal dominant polycystic kidney disease who eat and drink at libitum, especially when the measured glomerular filtration rate (mGFR) is below 60 ml/min. Reprinted with permission from [71]. (b) Response to vasopressin V2 receptor antagonist treatment is dependent on kidney function. Data from [72] and adapted from [73].

represents a protein intake of 1 g protein/kg body weight for a 80 kg weighing male individual who has no significant proteinuria (Maroni formula). To achieve treatment targets and to avoid dietary shortages, patients should be referred to a specialized dietician with expertise in renal care.

CONCLUSION

After reviewing the literature, we believe that dietary advices in ADPKD can in general be equal CKD in general. These advices are summarized in Table 2 and include a dietary salt intake of 5 g/day or less (or 2 g sodium or 90 mmol sodium) and avoiding a

Table 2. Summary of dietary advices in autosomal dominant polycystic kidney disease

Restrict dietary salt intake to ≤5 g/day (or ≤2 g sodium or ≤90 mmol sodium per day)
Avoid a protein intake ≥1.3 g/kg/day (only restriction to ≤0.8 g/kg/day in case eGFR declines <30 ml/min per 1.73 m^2
Stop or do not start smoking
Pursue a healthy weight (BMI 20–25 kg/m^2).
Moderate caffeine and alcohol intake
Target for a low urinary osmolality, as low as possible when eGFR >60 ml/min per 1.73 m^2. When eGFR is <30 ml/min per 1.73 m^2 additional water intake should be limited to avoid hyponatremia

eGFR, estimated glomerular filtration rate.

protein intake at least 1.3 g/kg/day. Patients are furthermore advised not to smoke, eat a healthy diet, maintain a BMI between 20 and 25, moderate caffeine and alcohol intake, and keep hydrated. Hydration should be dependent on kidney function. For subjects with an eGFR greater than 60 ml/min per 1.73 m^2, urinary osmolality should be decreased as much as possible in order to obtain a suppressed vasopressin level, whereas in subjects with an eGFR less than 30 ml/min per 1.73 m^2, additional water intake should be limited to prevent hyponatremia. With the current interest in metabolic reprogramming in ADPKD and the promising therapeutic potential of related dietary interventions, future studies are anxiously awaited.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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