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Adult dominant polycystic kidney disease: A prototypical disease for pharmanutrition interventions

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ABSTRACT

Background: Adult Dominant Polycystic Kidney Disease (ADPKD) is an inherited disease, associated with the development of liquid-filled cysts in the kidneys and other organs, causing renal failure. Most patients with ADPKD have mutations in either PKD1 or PKD2 genes, which encode for the two components of ion channels located in cilia and endoplasmic reticulum. These mutations cause an increase in intracellular cAMP and activate mTOR, the AMPK pathway and Jak/Stat-dependent gene transcription ultimately leading to enhanced cell proliferation and survival in cyst epithelium and to fluid release in cyst cavities. The aim of the present review is to discuss the main literature evidence suggesting that these pathologically activated transduction pathways can be targeted with an integrated pharmacological and nutritional, *pharmanutrition*, strategy.
Methods: We interrogated with no limit of publication time, the PubMed and Scopus databases using the following keywords: ADPKD, pharmacological treatment, nutritional intervention, diet, transduction pathways.
Results: In ADPKD, mTOR enhanced activity may be counteracted both with specific drugs, which have intrinsic dose-limiting toxicities, and with time-restricted feeding or ketogenic diets, and these two approaches could, theoretically, synergize. Likewise, cAMP accumulation in the cytoplasm can be counteracted pharmacologically with V2 receptor antagonists or somatostatin analogues and with nutritional interventions such as hypoosmolar diets, with or without high water intake.
Conclusions: Nutritional interventions impinge on the same transduction pathways targeted by drugs currently used or in development for ADPKD. The use of diet intervention in combination with drugs could help lowering drug dose and, consequently, dose-dependent drug toxicity.

1. Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is an inherited disorder characterized by the development of fluid-filled cysts in the kidney and, less frequently, in other organs, including the liver, the pancreas, the thyroid gland, the subarachnoid space, and the seminal vesicles [1,2]. The most relevant clinical consequence of cyst formation is the progressive impairment in renal function, which, because of the very slow growth of these lesions, appears generally only lately in the course of the disease, when patients are in their 5th or 6th decades of life. In most cases, arterial hypertension is the first clinical manifestation of the disease, which, however,ultimately leads to end stage renal disease (ESRD) and dialysis. Cysts located in other organs may also cause clinically relevant consequences. Remarkably, ADPKD is also associated with a high prevalence of intracranial aneurysms which are observed in about 40% of patients and whose rupture may cause serious intracranial hemorrhages [2].

The real prevalence of the disease, which is often underdiagnosed, is still uncertain. The classical study of Dalgaard [3] suggested that ADPKD prevalence was between 1/400 and 1/1000 individuals but later studies readjusted downwards these figures and, nowadays it is estimated the ADPKD occurs in less than 5 individuals per 10,000, the threshold for rare disease in the EU [4].

Most of the ADPKD cases are due to loss of function mutations either in the PKD1 or in the PKD2 gene, which occur respectively in 78% and 15% of patients [1]. Mutations in additional genes such as GANAB and DNAJB11 are being discovered and may account for PKD1/PKD2 negative cases that were previously considered “genetically-unresolved”

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[5].

The present narrative review is not intended to provide a comprehensive overview of ADPKD, which the readers can find in recent excellent reviews on this topic [1,6–8], but has the aim to describe how and why ADPKD could represent an exemplificative case of a disease in which drug therapy and nutritional intervention may converge in achieving similar and potentially synergistic beneficial effects, in the context of a *pharmanutrition* approach. We will show, indeed, that molecular studies on the PKD1 and PKD2 gene products and on the functional consequences of their mutations not only provided a rational basis for the pharmacological treatment of ADPKD but also disclosed how and why specific nutritional interventions may be beneficial in this disease and potentially improve the result of drug therapy.

2. Molecular pathogenesis of ADPKD and rational basis of its targeted drug therapy

In the last 20 years an enormous progress has been achieved in dissecting the molecular mechanism of ADPKD paving the way to the development of targeted pharmacological therapies for this disease, which, however, still remain mostly non approved, either because the results of randomized clinical trials in humans are still lacking or because they partially failed in randomized clinical trials (RCT) [9,10].

Most of the knowledge on the molecular pathogenesis of ADPKD was obtained by dissecting structure and function of polycystin 1 (PC-1) and polycystin 2 (PC-2), the products of the two genes mutated in this disease PKD1 and PKD2 [11].

PC-1is a large 4303-amino transmembrane protein with a long extramembranal amino-terminal, which includes extracellular adhesion domains, a receptor for egg jelly domain and a GPCR proteolysis site (GPS). The proteolytic cleavage at GPS separates the amino-terminal tail from the rest of the proteins, which consists of two structurally different portions: the 400 kDa amino-terminal portion, with structural characteristics similar to a G-coupled receptor, and the 150kDa carboxyterminal resembling to a voltage-gated ion channel but with a flexible S6 domain. The intracellular COO-tail of the protein bears a G-protein activating peptide at its the more proximal part and a coiled coil domain for interaction with PC-2, more distally [12,13]. The cleavage at the GPS site occurs early in the secretory pathway and is required for PC-1 plasma-membrane localization; it is increased by PC-2 which, consequently, enhances plasma-membrane translocation of PC-1 [14].

PC-2 is a 968 amino acid protein consisting of 6 transmembrane domains [15], which belongs to the Transient Receptor Potential channels (TRP) family and, therefore, has been renamed TRPP1 [16]. TRPP1 is a Ca^{2+}-nonselective ion channel which, depending on its binding to the intracellular chaperones phosphofurin acidic cluster sorting protein (PACS)−1 and PACS-2, can localize either in endoplasmic reticulum membranes, regulating Ca^{2+} efflux from these organelles, or in plasma membrane, regulating Ca^{2+} influx from the extracellular space [17]. TRPP1 assembles with PC-1 to form hetero-tetramers with a 1:3 PC-1:TRPP1 ratio; the formation of this tetrameric complex requires the interaction between the coiled coils located at the carboxy-terminals of both PC-1 and TRPP1 and can be disturbed by mutations occurring in these regions [18]. Recently, Su et al. [13] reported the 3.6-angstrom cryo–electron microscopy structure of the tetramers formed by the truncated human PC-1(13049-4169) and TRPP1 (2185–72). In physiological conditions tetramers are formed in localized regions of renal epithelial cells corresponding to the shaft and basal body of primary cilia where these proteins are preferentially located [19,20].

In tubular renal cells the PC-1/TRPP1 complex act as mechanosensor activated by apical fluid flow, which causes TRPP1 channel gating and Ca^{2+} influx into the cytoplasm [21,22]. Both PC-1 and TRPP1 are required for this response, which is abolished upon genetic knockout of either of them [21]. The increase of intracellular Ca^{2+} caused by the gating of this channel complex causes a decrease in intracellular cAMP, which, in kidney epithelium, is mainly synthetized in response to the activation by vasopressin (AVP) of Gs-coupled V2 receptors [23]. This effect is due to the activation of Ca^{2+}-dependent phosphodiesterases, a class of enzymes responsible for cAMP degradation. An additional mechanism that contributes to cAMP lowering is the Ca^{2+}-dependent inhibition of class 5 and 6 adenylate cylases. In ADPKD, the loss of PC-1/TRPP1 function, reduces Ca^{2+} influx and the consequent Ca^{2+}-induced Ca^{2+} release from the intracellular endoplasmic reticulum, and causes a significant increase in cAMP. This cyclic nucleotide promotes the activation of CTFR chloride channels via PKA-mediated phosphorylation with the consequent efflux into the cystic lumen of Cl^- ions. The increase in osmotic pressure caused by Cl^-efflux promotes osmotic-driven water efflux through aquaporins [24]. Intracellular cAMP also promotes cell proliferation and growth of the cystic lesions [25] by activating the extracellular signal-regulated kinase pathway [26]. The cAMP-dependent promotion of fluid secretion and cell proliferation represent a basic mechanism in the pathogenesis of ADPKD and, therefore, an efficient first strategy for the targeted therapy of this disease could be lowering the intracellular concentration of this cyclic nucleotide. As mentioned before, AVP-dependent stimulation of V2 receptors is one of the major mechanisms responsible for cAMP generation in kidney epithelial cells and, consequently, V2 receptor antagonists have been identified as rational tool for ADPKD treatment. As a matter of fact, these drugs exerted beneficial effects in animal models of the disease [27–29]. The V2 antagonist tolvaptan has been tested in humans and proved to be efficacious in decreasing kidney growth and slowing the progression to renal failure in the TEMPO 3:4 clinical trial and in the 1-year clinical trial REPRISE [30–33]. Based on these favourable results tolvaptan was approved for use in humans by EMA in 2015 and by FDA in 2018, and still is the only approved treatment for ADPKD. During clinical experimentation with this drug about 50% of the patients experienced the expected aquaretic adverse drug reactions, mainly polyuria and thirst, which led to drug discontinuation in about 8% of treated patients [30]. In addition, evidence emerged of drug-induced hepatotoxicity in about 5% of the patients receiving tolvaptan and one case report of severe liver failure requiring liver transplantation has been published [34,35]. Recently, the results of an open label extension study of the TEMPO3:4 and REPRISE trials showed that the safety of the tolvaptan therapy can be increased by performing a monthly assessment of liver transaminases for the first 18 months of therapy [36]. Another pharmacological strategy that could theoretically be used to decrease cAMP concentration in epithelial kidney cells is the stimulation of the Gi-coupled somatostatin receptors (SSTR), which inhibit adenylate cyclase and prevent AVP-induced intracellular cAMP accumulation [37]. Different SSTR isoforms are expressed in the different portion of the nephron, with SSTR1 and SSTR2 which are prevalent in the thick ascending limb of Henle, distal tubule, and collecting duct, and SSTR3, SSTR4, and SSTR5 in proximal tubules [38–40]. Importantly, SSTR receptors are also expressed in the epithelial cells lining liver cysts, a kind of lesions that may occur in the presence or not of kidney cysts [41]. Long-acting somatostatin analogues were beneficial in animal models of liver and kidney polycystic disease and showed synergic effects when given in combination with V2-antagonists [38–44]. SSTR agonists have been tested in human ADPKD with contrasting but in general disappointing results. The DIPAK1 RCT showed no benefit of lanreotide on the decline of renal function in patients with later stage ADPKD although the rate of total kidney growth was slowed [45]. Likewise, the ALADIN trial showed that after one year of treatment with Octreotide-LAR total kidney volume was significantly decreased in ADPKD patients; this effect, however, decreased progressively thereafter, and no significant difference with controls was observed after three years of therapy [46]. As in the DIPAK1 trial also in the ALADIN study, which was performed in patients with normal or minimally impaired renal function, the decline of eGFR was not slowed by the treatment. Similar results were obtained in patients with more severe renal impairment in the ALADIN2 RCT,

Table 1
Clinical trials on pharmacological interventions in ADPKD.

Drug target	Rationale	Drug	Ongoing and completed trials			
			Number	Design	Primary outcome	Status/results
V2 vasopressin receptors	The stimulation of Gs-coupled V2 receptor by vasopressin is one of the main mechanism responsible for cAMP synthesis in cyst-lining cells (see text for details).	Tolvaptan	NCT03949894	Open label, phase 4, interventional trial	TEAEs	ACTIVE, NOT RECRUITING
			NCT02729662	Single group, open Label trial	Percent TKV change	ACTIVE, NOT RECRUITING
			NCT01280721	Phase 3, multicenter, open-label extension study of Trial 156–04–251 in Japan	TKV eGFR Cys-C	COMPLETED: After 36 months, TKV and CysC increased by 22% and 26% and eGFR decreased by29% [62].
			NCT00428948 (TEMPO 3:4)	Phase 3,open-label, multicenter, parallel block (tolvaptan vs placebo) RCT	Percent annual TKV Change	COMPLETED: Annual increase in TKV was 2.8% in the tolvaptan and 5.5% in the placebo group. Tolvaptan slowed the decline in renal function [30].
			NCT01214421 (TEMPO 4:4)	Multicenter, open-label, extension study of TEMPO 3:4	Percent annual TKV Change	COMPLETED: Tolvaptan slowed TKV increase and eGFR decrease [33].
			NCT01336972	Non-Randomized, open-label, phase 2 trial; three parallel groups with different eGFR at recruitment	Change in GFR Change in Renal Plasma Flow Change in Filtration Fraction	COMPLETED: Tolvaptan did not modify renal hemodynamics in any of the eGFR groups [63].
			NCT01451827 (NOCTURNE)	Double-blind, phase 2, multicenter, four arms RCT (placebo vs Tolvaptan MR 50 mg, MR 80 mg and IR 30/60 mg)	Percent TKV Change after 3 weeks	COMPLETED: Tolvaptan MR50 and MR80 reduced TKV by about 2% whereas the effect of Tolvaptan IR30/60 was not significant [64].
			NCT02160145 (REPRISE)	Phase 3b, quadruple-mask, controlled RCT (tolvaptan vs placebo)	Mean Annualized eGFR change	COMPLETED: Tolvaptan reduced by 35% the estimated eGFR decrease over a 1-year period in patients with later-stage ADPKD [32].
Somatostatin receptors	Activated Gi-coupled SSRs inhibit adenylate cyclase and, consequently, decrease cAMP in cyst-lining cells(see text for details).	Octreotide-LAR	NCT00309283 (ALADIN)	Phase 3, Trial Randomised Placebo-Controlled, Multicentre	TKV Change at 1 and 3 years	COMPLETED: Lanreotide reduced by about 47% TKV increase after 1 year but there was no significant difference after 3 years [46].
			NCT01377246 (ALADIN 2)	Parallel-group, double-blind, placebo-controlled phase III RCT	TKV change Rate of GFR decline	COMPLETED: after 1 and 3 years, TKV was lower in the intervention group; no significant difference was observed in the rate of eGFR decline [47].
		Lanreotide	NCT02127437 (LIPS)	Open Label, parallel group, Phase 3 RCT (lanreotide vs saline)	GFR Change	COMPLETED: No Results Available
			NCT01616927 (DIPAK1)	Two arms, RCT (SC vs lanreotide)	eGFR Change	COMPLETED: There was no difference in eGFR change between groups. TKV growth rate was lower in the lanreotide group[45]
			NCT01354405 (RESOLVE)	Observational, Prospective	TLV decrease at 24 weeks	COMPLETED: Lanreotide decreased TLV by 3.1% and TKV by 1.7%[65].
		Pasireotide LAR	NCT01670110	Double-blind, RCT	% Change in TLV % Change in TKV	COMPLETED: Pasireotide reduced LTV and KTV by 1% and 3%, respectively [49].
V2 receptors and SSR	Since V2 receptors and SSR control intracellular cAMP levels acting at different levels (i.e. Gs and Gi proteins), drugs acting on these two targets could theoretically synergize.	Tolvaptan + Octreotide LAR	NCT03541447	Quadruple-mask, randomized, phase 2 crossover Trial: Tolvaptan+ Placebo vs Tolvaptan+Octreotide LAR	eGFR change	ACTIVE, NOT RECRUITING
CFTR	Chloride secretion through cAMP-activated CTFR promotes fluid accumulation in kidney cysts [66].	GLPG2737	NCT04578548	Phase 2a, double-blind,parallel group, multicenter RCT	Percent TKV change Prevalence of TEAEs	ACTIVE, not Recruiting
NRF2					Change in GFR	

(*continued on next page*)

Table 1 (*continued*)

Drug target	Rationale	Drug	Ongoing and completed trials			
			Number	Design	Primary outcome	Status/results
	Nrf2 activation reduces the oxidative stress caused by mitochondrial dysfunction and the consequent inflammation, which have a role in ADPKD progression [67].	Bardoxolone methyl	NCT03366337 (PHOENIX)	Phase 2, multicenter,open-label trial		COMPLETED: After 12 weeks Bordexolone increased GFR by about 9 mL/min/1.73 m^2. The drug was well tolerated.
PPARγ	PPARγ slows ADPKD progression by decreasing ERK/MAPK activity and TGFβ release and, consequently, tissue inflammation. It also reduces CTFR gene expression [68].	Pioglitazone	NCT02697617	Phase 2, RCT	Safety: Total Body Water Efficacy: Percent Change in TKV	COMPLETED: pioglitazone decreased total body water but did not modify TKV [69].
miR-17	miR-17 s promote the growth of cysts in ADPKD by inhibiting oxidative phosphorylation and PPARα [70,71].	RGLS4326 (anti mir-17)	NCT04536688	Multicenter,open-label, adaptive, phase 1b trial	Changes in PC1 and PC2 levels in urinary exosomes	COMPLETED: No Results Available
c-Src	ErbB2 is overactive in ADPKD and most of its signaling is conveyed via cSrc and the downstream activation of the the B-Raf/MEK/ERK signaling pathway. The pharmacological inhibition of src ameliorates ADPKD in mouse models [72].	Tesevatinib	NCT01559363	Non-Randomized, open label phase 1b/2atrial	Phase 1b: pharmacokinetics and MTD Phase 2a: Change in GFR	COMPLETED: No Results Available
		Bosutinib	NCT01233869	Phase 2, three arms,multicenter RCT: bosutinib 200 mg, bosutinib 200 mg transitioned to 400 and placebo	Change in TKV at Month 25	COMPLETED: Bosutinib reduced TKV growth rate by 82% versus placebo [73].
Mevalonate pathway	In animal ADPKD models, statins reduce cyst growth possibly by inhibiting the farnesylation of key GTPases such as ras [74].	Pravastatin	NCT00456365	Randomized, double blind, placebo control	Percent of Participants with a TKV increase > 20%	COMPLETED: 69% and 88% respectively of treated and control patients attained positive outcome
AMPK	As detailed in the main text of the article (paragraph 2), AMPK activity is reduced in ADPKD whereas its functional competitor mTOR is hyperactive.	Metformin	NCT02903511	Phase 2, parallel group (metformin vs placebo),double-blind, RCT	Safety and Tolerability of Metformin	COMPLETED: Metformin was safe and well tolerated. No difference was observed between groups in htTKV or eGFR [75].
			NCT02656017	Phase 2, parallel group (metformin vs placebo) RCT	Gastrointestinal Symptoms Drug discontinuation Serious Adverse events	COMPLETED: No Results Available
mTOR	The mTOR pathway is hyperactivated in ADPKD and maintains cyst growth through the mechanisms described in Section 2 of the text.	Everolimus	NCT02134899 (EVERKYSTE)	Open-label,multicenter randomized trial	Change in TKV	COMPLETED: No Results Available
			NCT00414440	Double-blind Phase 4, RCT, Two blocks (everolimus vs placebo)	Change in TKV	COMPLETED: Everolimus reduced TKV increase by 23% at two years [76].
			NCT01632605 (RAP)	Single group- Open-label	Slope in estimated glomerular filtration rate	COMPLETED:No Results Available
		Sirolimus	NCT00346918	Open-Label Phase 3, RCT: SC vs SC + Sirolimus	TKV	COMPLETED: No change in TKV [77].
			NCT00491517 (SIRENA)	Open Label Crossover Phase 2 Randomized trial	TKV	Sirolimus reduced TKV increase by 34% [78].
ACE/ARB	RAAS is hyperactive in ADPKD. ACE-I reduce cyst growth in animal ADPKD models possibly because they decrease AgII, which could be mitogenic for cyst cells [79].	Lisinopril, Telmisartan	NCT00283686 (HALT PKD A)	RCT, factorial design; four groups(ACE-I/ARB +Standard BP; ACE-I/ARB + Low BP; ACE-I/Placebo, Standard BP; ACE-I/ Placebo and Low BP).	Percent Annual Change in TKV	COMPLETED: Annual TKV increase was significantly lower in low than in normal BP groups with no difference between lisinopril/telmisartan and lisinopril/placebo [80].

Only the clinical trials that had been registered in the clinicaltrials.gov database (https://clinicaltrials.gov/ct2/home) till February 6th, 2022 have been reported in the table.

Abbreviations: ARB: angiotensin receptor blocker; BP: blood pressure; HtTKV: height-adjusted total kidney volume;RCT: randomized controlled trial; SC: standard care; TKV: total kidney volume; TLV: total liver volume;TEAE: Treatment-Emergent Adverse Events.

which, however, despite the absence of significant differences in eGFR in the intervention and control groups, showed that the percentage of patients progressing to ESRD was significantly lowered by Octreotide-LAR [47]. Whilst available evidence stands against the use of somatostatin analogues as tool to delay the progression of kidney disease in ADPKD, data have been reported showing their efficacy in cystic liver disease [48,49].

The PC-1 and TRPP1 complex not only senses the increase in apical flow but may also transduce its loss or decrease. This signal enhances the proteolytic cleavage of a small 17 kDa fragment from the carboxy-terminal of PC-1 which binds to Stat1 and to the coactivator P100 and, after translocation in the nucleus, promotes Stat1-dependent gene

transcription [50]. The evidence that on the one side the hyper-expression of the 17 kDa fragment was able per se to induce cyst formation in zebrafish [50] and, on the other side,PKD may be induced by a number of other genetic alterations besides PC-1 and TRPP1mutations causing the loss of ciliary function [51], strongly suggests that the loss of mechano-sensation and the activation of Stat1 dependent gene transcription could represent a general pathogenetic mechanism for this disease. The carboxy-terminal of PC-1 also inhibits the mTOR transduction cascade by activating its inhibitor tuberin (TSC2) and, consequently, preventing the assembly of the mTORC1 and mTORC2 multiprotein complexes, which control energy metabolism and cell proliferation [52]. Remarkably, mutations in the TSC2 gene are responsible for tuberous sclerosis, a disease characterized by the development not only of benign tumours in multiple organs but also of renal cysts [53]. In ADPKD, PC1-dependent TSC2 activation is lost and mTOR is hyperactivated by metabolic signals that we will describe more in detail in the next section. The activation of mTOR signalling has a major in causing cyst growth as confirmed by the evidence that both the pharmacological inhibition [52,54] and the genetic deletion of mTOR have beneficial effect on cyst formation in animal models of ADPKD [55]. A self-potentiating mechanism amplifies the effect of PC-1 loss on mTOR activation since, physiologically, mTORC1 decreases PC-1 expression [56]. It has also to be considered that the PC-1 and TSC2 genes are in a contiguous tail to tail location on DNA and that in a subset of patients with ADPKD, the mutation responsible for the disease is a combined partial deletion that involved both these genes at the same time [57]; these patients with a TSC2 haploinsufficiency might be even more susceptible to the potentiating effect of PC-1 mutations on mTOR activity. Drugs inhibiting mTOR such as sirolimus and everolimus have been also tested in human studies with disappointing results [58–60]. A possible explanation for the failure of these studies could be that effective doses couldn't be given due to the toxicity of these compounds. It has, however, also to be considered that other transduction pathways activated by PC-1/TRPP2 loss, which have been described before, contribute to cyst formation. As a matter of fact, the isolated TSC2 gene knockout in mice [56] and TSC2 mutations in patients with normal PC-1 [61] cause a milder phenotype with less and smaller renal cysts in respect to PC-1 loss of function.

In conclusion, the pharmacological inhibition of cAMP generation or mTOR activity in cystic cells represent two major targeted therapy approaches for human ADPKD. However, because of safety or efficacy concerns, these therapies are far from being optimal, and this makes necessary the development of strategies to improve them or of totally new therapeutic approaches targeting different molecular mechanisms of ADPKD. Table 1 lists the clinical trials that have been completed or are still ongoing and reports some details on additional drug targets that are currently being explored such as the cSrc signaling pathway or PPARγ receptors. In the next paragraph we will examine how pharmanutrition interventions could be helpful in the context of the therapeutic needs for ADPKD.

3. Role of nutritional interventions in the treatment of ADPKD

A wealth of experimental data suggests that nutritional interventions could exert beneficial effects in ADPKD. In this paragraph we will show that they impinge on the same molecular mechanisms targeted by some of the drugs approved or under evaluation for this disease, giving a rationale for potential combined pharmanutrition treatments.

Studies performed in animal models suggest that food restriction could improve ADPKD. Kipp et al. [81] showed that, in an orthologous mouse model of ADPKD, with mosaic inactivation of the PKD1 gene, cell proliferation of cyst-lining cells and the progression of the disease were significantly slowed by reducing food intake by only 23% with no change in the qualitative composition of the diet. Similar results were obtained by Warner et al. [82], who showed that a reduction of food intake by 10–40% reduced cyst area, cell proliferation, inflammation and fibrosis in two different mouse ADPKD models, the $Pkd1^{RC/RC}$ and the $Pkd2^{WS25/-}$ mice. Also in this study, no qualitative modification was introduced in the composition of the diet. The mechanism responsible for the beneficial effect of food restriction likely relies on the inhibition of the mTOR transduction pathway, which, as described before, is pathologically hyperactive in ADPKD and maintains cyst growth. In normal cells the Akt/PI3-K/mTOR/mTORC1 cascade acts as the main switch for activating anabolic responses and it is counteracted by AMPK, which is, instead, the main switch for catabolic responses. In conditions of nutrient deprivation, the ATP/AMP ratio decreases causing the activation of AMPK, which phosphorylates TSC2 enhancing its ability to inhibit the mTORC multiprotein complexes [83]. In ADPKD, the hyperactivity of ERK induces the LKB1-dependent phosphorylation and, consequently, the inactivation of AMPK, whereas, at the same time, it increases the activity of mTORC1 [84,85] and, therefore, the system is unbalanced in favor of mTORC1. By causing a decrease in the availability of nutrients, moderate food restriction might activate AMPK and cause an AMPK-mediated decrease in mTORC1 activity, ultimately restoring the balance between AMPK and mTORC1. As a matter of fact, Warner et al. [82] showed that, upon nutrient restriction, LKB1/AMPK were activated whereas mTORC1 was inhibited. On the contrary, no change in AMPK activity was reported by Kipp et al. [81] who, therefore hypothesized that other mechanism could account for the strong inhibition of mTOR signaling observed.

It is important to underline that those beneficial effects on ADPKD were observed by implementing a moderate food restriction, which apparently does not impact on cell metabolism in normal tissues. This raises the question of how such a disease-specific effect could be achieved. The answer to this question probably relies in the differences in cell metabolism that have been observed between ADPKD cyst lining cells and normal cells [86]. More specifically, in ADPKD glucose metabolism through oxidative phosphorylation is impaired and, as in cancer cells, this sugar is metabolized mainly through glycolysis despite the normal availability of oxygen (the Warburg effect) [84,87]. Likewise, free fatty acid oxidation is impaired in cyst lining cells [88]. Therefore, ADPKD cyst lining cells could be much more dependent on glucose and gluconeogenic substrates and more susceptible to nutrient deprivation than normal cells. In fact, the treatment with 2-deoxyglucose lower kidney size and decreases cell proliferation in animal models of ADPKD [84,87]. The high dependence from glucose of cyst-lining cells could explain why overweight or obesity, which are often accompanied by an impaired glucose tolerance, are associated with a high rate of growth of cysts in this disease [89,90].

The mechanism responsible for the metabolic anomalies in ADPKD cyst lining cells is uncertain but it has been clearly established that primary cilia, which are dysfunctional in this disease, have a role in controlling energy metabolism [91,92]. In addition, in cancer cells, mTOR, which, as described before, is activated also in ADPKD, upregulates the expression of the M2 isoform of pyruvate kinase that, when phosphorylated by tyrosine kinases, becomes inactive and promotes the Warburg effect [93,94]. Furthermore, a mitochondrial dysfunction has been documented in ADPKD and it could be explained by the impairment of PC-1/TRPP1-dependent Ca^{2+} mobilization from the endoplasmic reticulum into these organelles and of PC-1-dependent regulation of mitochondrial dynamics [86]. Since aerobic glycolysis is much less efficient than oxidative phosphorylation and lipid metabolism is impaired, ADPDK cyst-lining cells have higher nutrient request than normal cells and are highly susceptible to nutrient deprivation. Consequently, it is expected that their "starvation"-induced signaling cascades, also including AMPK could be more strongly activated than in normal cells also in response to a moderate nutrient deprivation. This is not the only expected consequence of nutrient deprivation in ADPKD cells. In fact, since these cells cannot activate efficiently the autophagic response that is activated by normal cells to survive in such conditions, they die by apoptotic death when sugar supplementation is reduced [84].

Table 2
Clinical trials on nutritional interventions in ADPKD.

Nutritional intervention	Rationale	Ongoing and completed trials			
		Number	Design	Primary outcome	Status/results
Short term fasting or ketogenic diet	In experimental ADPKD animal models, time-restricted feeding and ketogenic diets slowed disease progression by inhibiting mTOR signaling and by inducing the release of β-hydroxybutyrate (see text for more details)	NCT04472624	Non-Randomized, two arms open label trial (72 h fasting vs 14 days ketogenic diet	Change in TKV	COMPLETED: No results available
High Water Intake	High water intake causes a decrease in vasopressin release and, consequently, of V2 receptor stimulation and cAMP production in cyst-lining cells (see text for more details).	NCT03102632	Non Randomized, sequential assignment to usual and high water intake	Change in TKV	ACTIVE, not recruiting
		NCT00784030	Non randomized open-Label, two arms trial (ADPKD vs healthy controls)	Change in th Urine cAMP/ UOsm ratio.	COMPLETED: Acute water load decreased the Urine cAMP/UOsm ratio in both groups.[114]
		NCT02776241	Randomized, open Label trial (water restriction vs high water intake)	Change in TKV from baseline to 3 h	COMPLETED: No Results Available
		NCT00759369	Non Randomized Open Label	Decrease in urine osmolality	COMPLETED: Urine osmolality decreased below 285 mOsm/kg[112].
Low-osmolar diet and water adjustment	By reducing salt content in the diet, the amount of water required to effectively suppress vasopressin release can be reduced, making easier to comply to the intervention as compared with high water only diets.	NCT02225860	Two arms (1:1) RCT (low salt/high water vs normal diet)	Change in Serum Copeptin at Week 2	COMPLETED: Copeptin plasma levels and urinary total solutes decreased significantly in the intervention but not in the normal diet group.
ADPKD Diet	Excessive intake of salt and animal protein increase urinary acid excretion and promote cyst growth in experimental animal models and in patients with ADPKD[115]. An isocaloric diet, the ADPKD diet, with a low sodium and protein content and rich in fruits, vegetables, and water are expected to revert this process.	NCT01810614	Single group, open label, pre-post pilot feasibility study	Net acid excretion	COMPLETED: The ADPKD Diet induced a 20%, 28%, 20%, 37%, and 15% decrease in Urinary sodium, urea, net acid excretion, osmoles, and osmolality [116].

Only the clinical trials that had been registered in the clinicaltrials.gov database (https://clinicaltrials.gov/ct2/home) till February 6th, 2022 have been reported in the table. ABBREVIATIONS: Osm: osmolality; RCT: randomized controlled trial; UOsm: urinary osmolality.

Recently Torres et al. [95] showed that the effect of moderate food restriction can be reproduced by reducing time given to the animals for feeding, with no restriction in the total calories of the diet. As observed in moderate food restriction, also time-restricted feeding (TRF) ameliorates the course of the disease in animal models of ADPKD by reducing cyst size and growth, an effect that seems to be dependent on a decrease in mTOR and Stat signaling and, consequently, in cell proliferation and survival. Not only, cyst growth was reduced but a significant increase in apoptotic cell death was observed in cyst-lining cells. TRF induces time-limited starvation in the intervals between feeding and, therefore, it is expected to shift energy metabolism toward a ketogenic pattern suggesting that the beneficial effects of TRF in ADPKD could be dependent on the activation of ketogenesis. This hypothesis was confirmed by the evidence that a ketogenic diet, i.e. a diet intended to reproduce the effect of starvation by reducing the intake of sugars, increasing the intake of fat and maintaining the intake of proteins [96], was also successful in improving experimental ADPKD. Ketogenic diet forces the cells to use fatty acids as energy sources and, therefore, it could inhibit the mTOR pathway by potently activating AMPK, considering that less glucose is available for the inefficient aerobic glycolysis pathway, and FFA cannot be efficiently metabolized by cyst-lining cells [88,97]. Interestingly, the inability to efficiently degrade FFA could account for their accumulation as lipid droplets in the cytoplasm and, possibly, for the induction of lipotoxicity and cell death. By forcing energy metabolism towards FFA degradation, ketogenic diet causes an increase in the generation of FFA metabolites known as ketone bodies including beta-hydroxy-butyrate (BHB) [98]. Importantly, these molecules may interact with specific cell receptors and activate physiological responses to starvation. In particular, BHB interacts with GPR109A, an orphan G-protein-coupled receptor, which also binds the drug niacin, and modulates the mTOR and AMPK pathways [99]. Therefore, the effect of TRF and ketogenic diet could be, at least in part, dependent on BHB increase. As a matter of fact, BHB diet supplementation mimicked the effect of those dietary intervention in models of ADPKD.

Collectively, studies in animal models suggest that ketogenic diets with or without BHB supplementation could represent an interesting option for the treatment of ADPKD. Whilst no data have been published yet on the efficacy of such intervention in humans, the feasibility of clinical studies based on this approach has been documented and some RCT have been started. Testa et al. [100] published a pilot study on three patients with ADPKD showing that ketogenic is well tolerated and safe and significantly increases plasma ketone concentrations. They used a modified form of ketogenic diet, known as the Atkins ketogenic diet, which was developed to improve the palatability and increase the compliance of the ketogenic diet. Unlike the classical ketogenic diet, in the Atkins diet there is no calory restriction or limitation in protein intake [101]. Based on the encouraging results of the pilot study, the study protocol of a RCT with Atkins diet in ADPKD has also been published by the same group [102]. In this dietary protocol about 65% of total caloric intake comes from fat, 5% from sugars, 30% (1.9 g/IBW/-die) from proteins. Classical ketogenic diet has been chosen, instead, for the RCT ongoing at the University of Cologne, Germany whose results are expected by midst 2022 (ClinicalTrials.gov Identifier: NCT04680780; https://clinicaltrials.gov/ct2/show/NCT04680780?cond=ADPKD&draw=2&rank=1). The evidence that ketogenic diets decrease the activity of mTORC1 in ADPKD as also drugs blocking mTOR do, suggests that these two approaches could be combined to obtain synergic effects. By using such as trategy, which, however, remains to be tested, the results of the pharmacological mTOR blockade could be improved overcoming the limitations posed by the intrinsic toxicity of

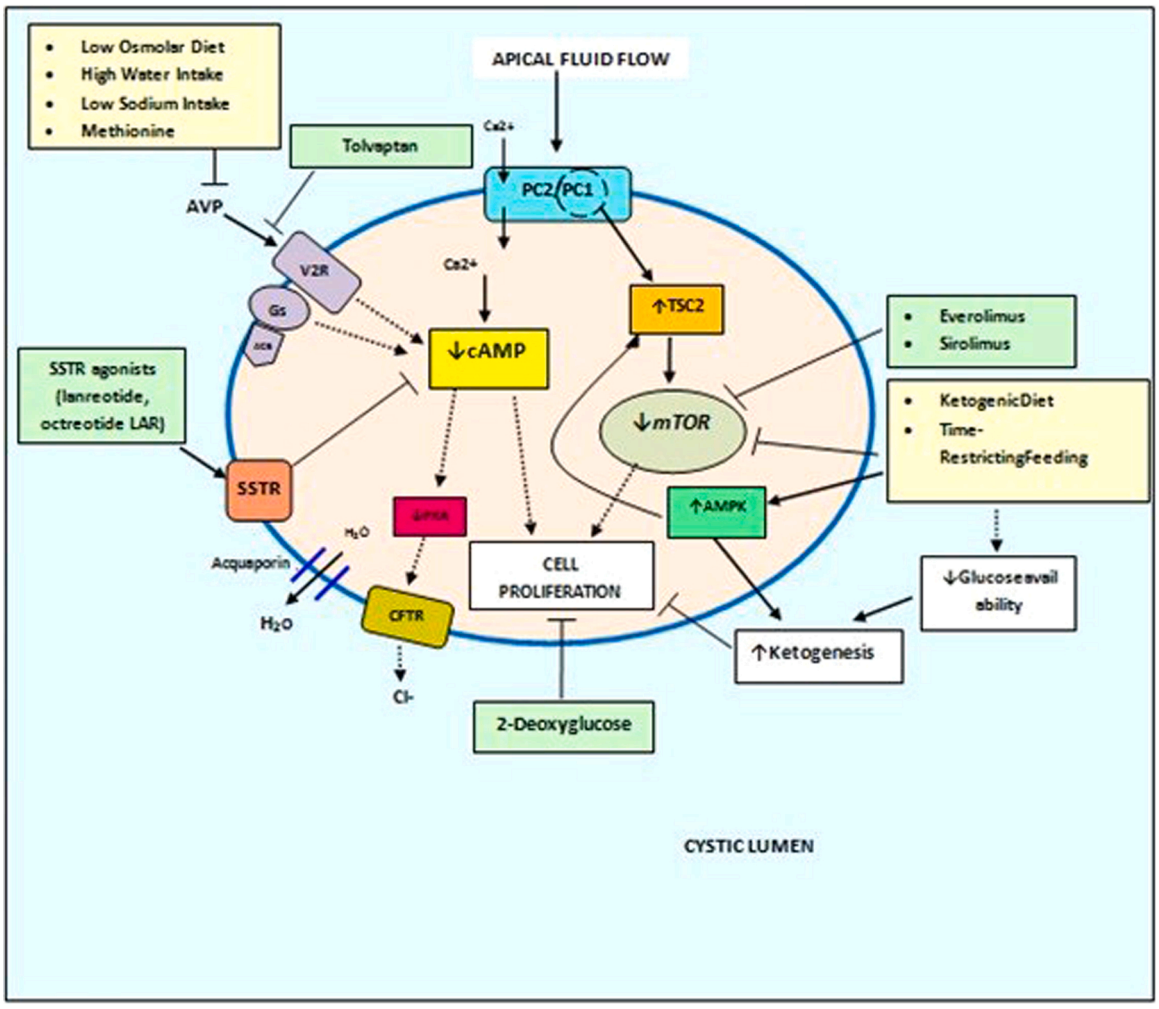

Fig. 1. Converging effects of pharmacological and nutritional interventions in ADPKD. Dotted arrows indicate pathways that are negatively regulated by the action of pharmanutrition interventions.

these kinase inhibitors.

An issue that deserves attention when considering ketogenic diets for ADPKD treatment is how much proteins are given with the diet [103]. In patients with chronic renal failure,a high protein intake may worsen renal damage and accelerate its progression. It induces, in fact, intraglomerular hyperfiltration by enhancing the release of vasopressin and glucagon, which impact on urea handling and on electrolyte concentration at the *macula densa* ultimately altering the tubuloglomerular feedback [104]. As a matter of fact, a low protein intake, which should not exceed 0.55–0.60 g dietary protein/kg ideal body weight/day in stage 3–5 CKD, is recommended by the KDOQI Clinical practice guideline for nutrition in CKD [105]. Even though high protein diets worsen the progression of renal disease in animal models of ADPKD [106] also increasing cytokine release and tissue fibrosis [107], a formal demonstration that a reduced protein intake slows the disease in humans is still lacking. Nonetheless, current guidelines on ADPKD recommend reducing protein intake(down to 0.75–1.0 g/kg/day according to the KHA-CARI guidelines) [108,109]. Therefore, even though there is no specific limitation in the Atkins diet, protein intake should be reduced when this ketogenic diet is given to ADPKD patients [103]. Alternatively, the classical ketogenic diet should be preferred since it requires that about 70–80% of the 2000 daily calories should come from fat, 5–10% from carbohydrate, and 10–20% from proteins corresponding to 1.0–1.2 g protein/kg ideal body weight/day.

Whilst a reduction of protein content might be beneficial in ADPKD for the same reason it is in other forms of CKD, additional and more specific mechanisms could also be involved. For instance, it has been demonstrated that, in ADPKD mice models, the selective restriction of the amino acid methionine reduces cyst growth, which is, instead, increased upon dietary methionine or S-adenosyl-mehionine supplementation [110]. The mechanism proposed to explain these effects involvesthe methylating enzyme Mettl3 which operates an S-adenosyl-methionine-dependent methylation of mRNAs in position N6 of their adenosine residues. This process is highly dependent on methionine availability since this amino acid is requires for SAM synthesis. N6 adenosine methylation is an *epitranscriptomic* mechanism which regulates RNA transcription and, therefore, can be implicated in the modulation of physiologically relevant processes. Specifically, in cyst-lining cells, in which methionine and SAM concentration are higher than normal, Mettl3-dependent N6-adenosine methylation increase the translation of the mRNAs encoding for the oncogene c-myc, which promotes cell proliferation, and for Avpr2, the type 2 AVP receptor, which induces cAMP increase and aquaporin translocation to plasma-membrane. Therefore, methionine restricted diets, not differently from tolvaptan, are expected to decrease AVP-dependent cAMP generation in cystic cells and these two strategies could theoretically synergize. This could represent another example beside ketogenic diet and mTORC1, of how a nutritional intervention does impinge on the same transduction mechanism affected by a drug effective in ADPKD. Interestingly, beneficial effects have been obtained in animal models of ADPKD in response to overhydration through water ingestion, another non-pharmacological strategy capable to decrease AVP-dependent renal

cAMP generation by suppressing vasopressin release [111]. The feasibility of this approach has also been demonstrated in pilot studies in human patients [112,113]. Table 2 summarizes the clinical trials on nutritional interventions in ADPKD that have been completed or are still ongoing.

4. Concluding remarks

In the present narrative review, we went through the recent literature on ADPKD to illustrate how pharmacological therapies and nutritional interventions target the same molecular pathways responsible for this disease (as summarized in Fig. 1). This is due to the specific pathogenetic mechanism of ADPKD, which affects key molecular switches of cell energy metabolism. Despite the considerable progress in the understanding of ADPKD pathophysiology, tolvaptan still remains the only approved therapy for this disease but it raises some safety concern. Other targeted therapies such as mTOR inhibitors showed a limited efficacy probably because they cannot be given at the effective dosage without inducing toxicity.

The evidence that nutritional interventions could be effective in this disease could be valuable to overcome these limitations of current therapy either by offering a safer alternative to drugs or, even more importantly, since they could be used in combination with drugs that could, therefore, be used at lower dosages. In this context, designing and performing RCTs aiming to compare conventional drug therapy with pharmanutrition combinations appears a priority for the future.

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Declaration of Competing Interest

None.

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