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Ren.Nu, a Dietary Program for Individuals with Autosomal-Dominant Polycystic Kidney Disease Implementing a Sustainable, Plant-Focused, Kidney-Safe, Ketogenic Approach with Avoidance of Renal Stressors

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Abstract: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of renal failure and has limited pharmacological treatment options. Disease progression is relentless, and regression is not a known feature of ADPKD even with pharmacological intervention. Recent research has uncovered underlying pathogenic mechanisms that may be amenable to dietary interventions. Cyst cells in ADPKD are thought to depend on glucose for energy and are unable to metabolize fatty acids and ketones. High-carbohydrate diets and lifestyles leading to hyperglycemia appear to worsen progression of ADPKD. Additionally, renal stressors such as oxalate, phosphate and uric acid, that lead to renal tubular micro-crystal burden appear to accelerate disease progression. Based on these research findings, we have created a remote, dietitian-supervised training program to teach individuals with ADPKD the implementation of dietary and lifestyle changes to avoid factors that may worsen disease progression. Using web-based platforms, digital tools, one-on-one remote meetings, and video group meetings, participants learn to implement a plant-focused ketogenic diet that avoids renal stressors, the science behind these changes, how to self-measure health parameters, and track nutrient intake. Dietary changes are supplemented with a medical food containing the ketone beta-hydroxybutyrate and alkaline citrate, and mindfulness exercises. Here, we report the first experience with this program from a beta test with approximately 24 participants. Most participants completed the program and reported improvements in their health and well-being including pain levels, weight loss, hypertension, and eGFR. Adherence to the program was very high and the feasibility of the dietary and lifestyle changes was rated highly. The Ren.Nu program is now publicly available to individuals with ADPKD.

Keywords: polycystic kidney disease; ketogenic diet; ketosis; plant-focused diet; oxalate; lifestyle interventions; prevention; dietary recommendations

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1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a common, life-threatening monogenic disease with a prevalence of at least ~1:1000 [1], thereby affecting millions of individuals worldwide. Hallmarks of the disease are proliferative, bilateral renal cysts, organ growth, fibrosis, and a slow decline in kidney function leading to end-stage renal disease in most affected individuals, typically by their 50s or 60s [2–4].

ADPKD is well established to be relentlessly progressive, and patients can be categorized into the highly predictive Mayo classification scheme based on the determination of total kidney volume (TKV) during a single time point [5,6]. Regression is not a known

feature of this disease with the current standard of care. This includes pharmacological intervention with the sole drug approved for ADPKD, the vasopressin V2-receptor antagonist tolvaptan. Tolvaptan has been shown to slow the growth in TKV and the decline in the estimated glomerular filtration rate (eGFR) [7]. However, tolvaptan does not prevent the progression of the disease. Unfortunately, only a subset of patients qualify for tolvaptan, and its use is further hampered by side effects and toxicities as well as the very high cost that makes it unavailable to most affected individuals worldwide [8–11].

Nutrition guidelines for ADPKD generally follow the same guidelines for chronic kidney disease (CKD), without specific dietary therapy to address mechanisms involved in cystogenesis, cyst growth, fibrosis, inflammation, and disease progression. Therapeutic dietary approaches to ADPKD have become a recent focus of attention [12,13], and there is very high interest among individuals affected with ADPKD in learning how diets and nutrition may beneficially affect their disease [14,15].

Recent research has established that cyst cells in ADPKD have an altered metabolism characterized by defective mitochondrial structure and function, defective fatty acid oxidation, and reliance on glucose and glycolysis [16,17]. These characteristics are similar to the Warburg effect that is well-known in many forms of cancer and thought to lead to a cellular survival and growth advantage [18]. In PKD rodent models, the glucose dependency has been exploited for pharmacological intervention with the glycolysis inhibitor 2-deoxy glucose [19,20].

Exciting recent research suggests that pharmacological intervention may not always be necessary but that dietary interventions affecting metabolism can be highly effective in PKD animal models. We and others initially showed that mild reduction in food intake has a profound effect on PKD progression in PKD mouse models [21,22]. We later showed that the effect involves the metabolic state of ketosis, and several interventions that induce ketosis—time-restricted feeding, acute fasting, and a ketogenic diet—proved highly effective in several PKD animal models including mice, rats, and cats [23]. The beneficial effects of ketosis could largely be replicated by supplementation with the ketone beta-hydroxybutyrate (BHB) [23]. Ketosis is the physiological adaptation to periods of carbohydrate restriction that enables the body to use fat, from both diet and body reserves, for energy. In ketosis, adipose cells release fatty acids which can be further converted by the liver to the ketones acetoacetate and BHB. Fatty acids and ketones then replace glucose as the main energy carrier to sustain the energy needs of most organs, tissues, and cells in the human body. BHB, considered the main ketone, is produced in large quantities by the liver during ketosis, and—besides being used for energy generation—also acts as a signaling molecule with potent cellular effects including anti-inflammatory effects [24–26].

These results suggest that dietary and lifestyle habits that promote persistently high glucose levels may be detrimental to ADPKD progression compared to habits that promote the metabolic state of ketosis. This is consistent with clinical associations. Individuals with ADPKD and type 2 diabetes have significantly larger TKV than those with ADPKD alone [27]. Fasting serum glucose levels in non-diabetic ADPKD patients were found to positively associate with the rate of ADPKD progression as measured by the average annual TKV change [23]. Furthermore, overweight or obesity associate with faster progression in early-stage ADPKD [28].

Efforts have been underway to translate these research findings into the clinic. In a recent retrospective case series study, we studied 131 individuals with ADPKD who had utilized ketogenic dietary interventions for an average duration of 6 months [15]. The results suggested that ketogenic dietary interventions appear to be safe in ADPKD, were considered feasible by patients, and—remarkably—were reported to have led to substantial improvements in pain and other typical ADPKD-related symptoms, as well as improvements in hypertension and eGFR [15]. A randomized clinical trial is currently ongoing comparing ketogenic diet vs. intermittent fasting vs. control in ADPKD (NCT04680780). Results from a pilot trial were recently published in which overweight and obese individuals with ADPKD employed daily caloric restriction (DCR) or intermittent fasting (IMF)

for weight reduction [29]. Results suggested that slowed kidney growth correlated with loss of body fat weight suggesting that the observed effects may involve periods of ketosis. Altogether, biological plausibility, animal model experimentation, and clinical data strongly suggest that the high carbohydrate diets and lifestyles leading to hyperglycemia and avoidance of ketosis that are most common in industrialized societies are not beneficial in ADPKD and likely lead to faster disease progression.

Another line of basic science experimentation has recently led to the realization that renal stressors that are largely controlled by dietary intake may have strongly detrimental effects on ADPKD progression. Dietary intake of oxalate or inorganic phosphate can lead to calcium oxalate and calcium phosphate micro-crystals, respectively, that form in renal tubules and can strongly accelerate PKD disease progression in animal models [30]. Citrate is the kidney's natural defense against calcium crystal precipitation but hypocitraturia is very common in individuals with ADPKD due to excessive urine acidification [31–33] which is associated with an increased risk of kidney stone disease in ADPKD compared to the general population [34–36]. We reported that urinary citrate levels inversely correlate with disease progression in individuals with ADPKD [30]. It was recently shown that genetic conditions that lead to persistent calcium nephrolithiasis are also associated with cyst formation in the kidneys [37,38]. Similarly, hyperuricemia is associated with faster ADPKD progression [39,40] and is known to lead to the risk of uric acid precipitation in renal tubules and renal injury [41]. The low urine pH commonly observed in individuals with ADPKD would increase the risk of uric acid precipitation. Indeed, gout and hyperuricemia are more prevalent in individuals with ADPKD than in the general population [33,42–44]. Uric acid levels are, in part, controlled by diet due to the metabolization of purines (primarily from animal meat sources) into uric acid which needs to be excreted via the kidneys. Altogether, these results suggest that diets that lead to an increased load of oxalate, inorganic phosphate, and purines/uric acid may lead to faster ADPKD progression. Conversely, diets that promote a more neutral urine pH and normal urine citrate levels are expected to be beneficial. Indeed, supplementation of PKD animal models with alkaline citrate was shown to antagonize renal calcium crystal precipitation [30] and to strongly ameliorate disease progression [45–47].

Based on these recent scientific insights, we have developed a dietary intervention program that is aimed at avoiding diet and lifestyle habits that can reasonably be expected to worsen ADPKD progression. This program, termed Ren.Nu (for Renal Nutrition; pronounced "renew"), utilizes a plant-focused ketogenic diet (PFKD) that avoids the renal stressors oxalate, inorganic phosphate, and purines/uric acid, and incorporates a medical food specifically developed for the dietary management of ADPKD. The rationale for the plant-focused feature is that animal protein worsens urine acidification, and consequent hypocitraturia, due to its high content in cysteine and methionine. In contrast, plant-focused diets are known to be more alkaline. Furthermore, meat consumption leads to a higher uric acid burden. Plant-focused diets are already recognized as being renoprotective in chronic kidney disease [48]. Dietary sources that contain a substantial oxalate load, primarily from plants such as spinach, almonds, etc., are avoided. Inorganic phosphates are common food additives in highly processed foods and are avoided. The medical food, KetoCitra® (Santa Barbara Nutrients, Inc, Santa Barbara, CA 93106, USA) contains BHB together with citrate in a formulation with potassium, calcium, and magnesium and delivers ~51 mEq alkaline base. KetoCitra® is taken with meals and includes calcium and magnesium to bind dietary oxalate and inorganic phosphate to suppress their absorption.

An important component of the Ren.Nu program is the strong educational guidance that is provided. After 4 weeks of onboarding, patients complete a 12-week remote learning program, supervised by an experienced renal dietitian, during which they learn the dietary concepts and the reasons behind them. They learn how to track nutrients, select foods, and self-measure relevant health parameters. The program is facilitated by mobile phone apps, an online platform, easy-to-implement recipes, weekly group meetings for peer exchange, an online community platform, and supported by mindfulness exercises.

Here, we describe the features of the Ren.Nu program and the first experience with a beta test group of approximately two dozen individuals with ADPKD. The beta test was not a clinical trial but primarily for the purpose of testing the curriculum and gathering feedback for future refinement of the program. Beta testers completed questionnaires and surveys. Clinical biomarker endpoints were evaluated in an exploratory fashion.

Our long-term goal is to develop a safe and feasible nutritional program for ADPKD that may have the potential to ameliorate ADPKD-related symptoms, lead to improved health and well-being as well as slow cyst progression and preserve renal function. The program is designed to be scalable, culturally adaptable, and suitable as the training phase for clinical trials to assess outcomes. To our knowledge, there is no previous dietary intervention program for ADPKD available, let alone one that incorporates recent scientific results addressing the role of metabolic abnormalities and renal stressors in ADPKD.

2. Materials and Methods

2.1. Tools and Materials Used

The professional version of the Cronometer smartphone app (Cronometer, Revelstoke, BC, VOE 250, Canada) was used by participants to track their daily macronutrient and micronutrient intake and to acquire or enter health data. All uploaded Crono-meter data were regularly reviewed by the program dietitian. The Keto-Mojo GK+ Blood Glucose and Ketone Meter (Keto-Mojo, Napa, CA 94559, USA) was used by participants to monitor their blood glucose and blood BHB levels. The meter interfaces with the Cronometer app to upload data for review by the program dietitian. Participants used various consumer-grade electronic scales and blood pressure monitors to keep track of body weight and blood pressure, respectively. Participants used pH test paper with a range of pH 4.5–8.5 (Santa Barbara Nutrients, Inc, Santa Barbara, CA 93106, USA) to self-measure urine pH. Practice Better (Practice Better, Toronto, ON M5C 2L7, Canada), a HIPAA compliant platform was used for the distribution of materials, recipes, recorded videos, guides, and for direct communication between the program dietitian and participants. The Zoom video meeting platform (Zoom Video Communications, San Jose, CA 95113, USA) was used to hold weekly class meetings, led by the dietitian, to provide education on different topics, Q&A, and peer support. A private social media group (Facebook, Menlo Park, CA 94025, USA) was provided to facilitate communication between the study team and the participants as well as for peer-to-peer discussions. The medical food KetoCitra® was provided to participants. KetoCitra® is a ready-to-mix powder to be dissolved in 8–16 oz of water and taken twice per day with meals. Per day, two servings of KetoCitra® provide 5.3 g of beta-hydroxybutyrate (BHB), 3.5 g citrate, 600 mg potassium, 300 mg calcium, 250 mg magnesium, and 51 mEq alkaline base.

2.2. Design and Features of the Ren.Nu Program

Ren.Nu is a dietitian-led and supervised, remote training program in a class setting of approximately 20 participants per class. The program is facilitated by digital technology to enable teaching, communication, as well as tracking and monitoring of nutrient and health data. The program includes weekly, live educational classes and group discussions. Participants met one-on-one, virtually with a registered dietitian three times during the program: an initial assessment prior to starting the program, a mid-point session 6 weeks into the program, and a final exit session 12 weeks into the program and post-lab blood draw. Participants were actively monitored by Ren.Nu's team of registered dietitians for the entire program. Written informed consent was obtained prior to enrollment. The Ren.Nu program is structured into four phases as outlined in Figure 1.

While the diet is plant-focused, it is not a vegan or vegetarian diet. Moderate intake of fish, eggs, and full-fat dairy are incorporated to avoid nutrient deficiencies, while maintaining a normalized protein intake of $\leq$0.8 gm/kg. A whole-food approach is encouraged, eliminating heavily processed food, added inorganic phosphates, and added sugar. Starchy vegetables are limited due to their high carbohydrate content. Pre-specified

lower-carbohydrate fruits are permitted in limited quantity to manage overall sugar and fructose intake. Sodium intake is controlled based on individual needs.

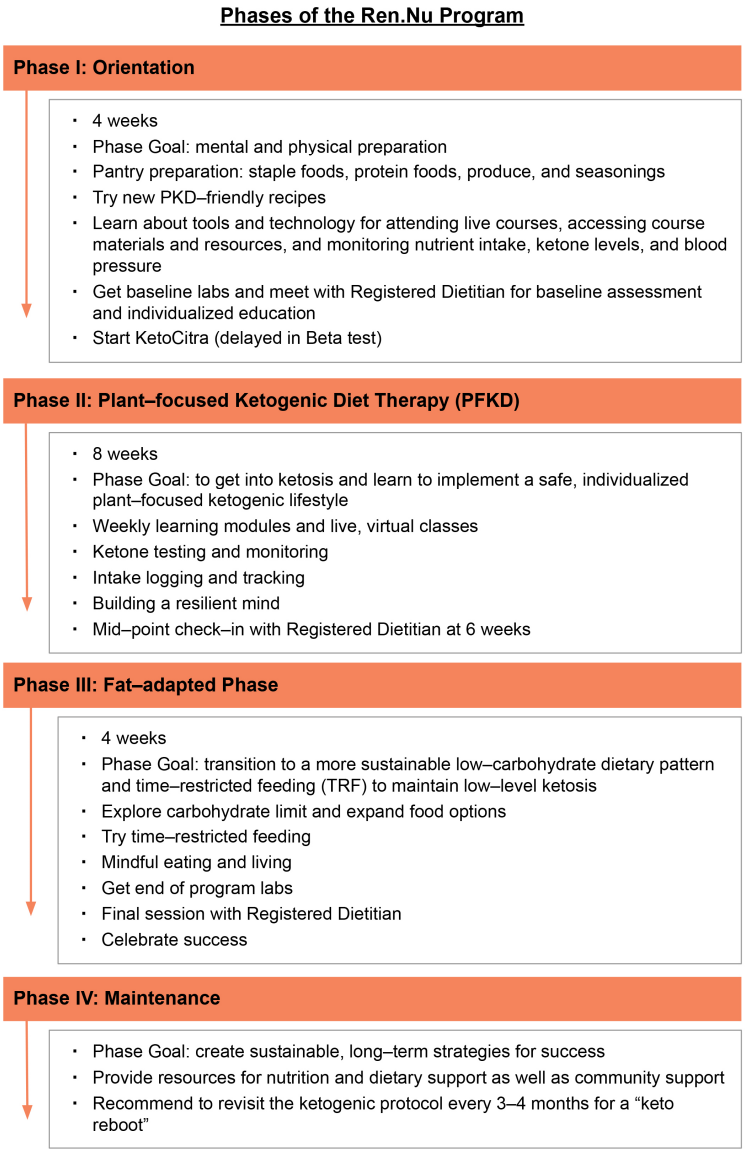

Figure 1. Four phases of the Ren.Nu program—implementation of the Ren.Nu program involves four phases including the orientation phase, plant-focused ketogenic diet (PFKD) phase, fat-adapted phase, and maintenance phase.

In addition, health, lifestyle, and food literacy are increased by education on the underlying pathophysiology of metabolism of different nutrients and metabolic abnormalities in ADPKD. Shopping lists, menus, and recipes as well as numerous educational materials are provided. The program also includes activities for teaching mindfulness, managing stress, tackling obstacles, and implementing a focus on health instead of disease. Participants are provided 12 weeks of intensive guidance by a support team including registered dietitians. The core founding principles for Ren.Nu are summarized in Box 1.

Box 1. Core principles of the Ren.Nu program. The 10 guiding principles upon which the Ren.Nu program is developed to deliver a dietary-, lifestyle-, and mindset-focused program based on a kidney-friendly, plant-focused ketogenic diet for individuals with polycystic kidney disease.

Core Principles of the Ren.Nu Program
1. Ketogenic intervention with low-carb/high fat diet and time-restricted eating to raise ketones and lower blood glucose/insulin.
2. Plant-focused, alkaline diet with incorporation of some dairy, eggs, and fish.
3. Limiting renal stressors oxalate, inorganic phosphate, and purines/uric acid to avoid renal injury by microcrystals.
4. Nutrient-dense, whole foods and minimally processed foods.
5. Remote participation for increased accessibility and scalability.
6. Digital and online tools to facilitate participation, supervision, and sense of community.
7. Education on scientific background and hands-on skills for implementation of diet and lifestyle changes.
8. Tracking of nutrient intake and self-monitoring of health parameters to stay on track.
9. Supervised and monitored by registered dietitian.
10. Individualization, education, and practice allows long-term sustainability of diet and lifestyle changes.

Phase 1: Orientation (4 weeks): Orientation began with a live virtual meeting and included introductions, a review of the course curriculum, a highlight of the entire program's flow, and tasks were presented to complete over the next 4 weeks. During the 4-week orientation phase, participants are guided to stock their pantry with necessary items, perform baseline lab tests, consult with their nephrologists/PCPs, try several plant-focused ketogenic recipes, complete online platform training, and meet one-on-one with the program's registered dietitian for a baseline assessment. Participants completed a structured intake questionnaire to facilitate the baseline assessment. During their initial session with the registered dietitian, participants were educated on and given individualized macronutrient breakdowns. Individual goals included total daily calories, protein, net carbohydrates, and fat. The diet therapy goals were individualized for each participant based on their dietary intake, weight goals, biometric markers, and any comorbidities. Vitamins and supplements were recommended based on current nutritional status, lab results, and to correct any micronutrient deficiencies.

Phase 2: Induction of ketosis (6–8 weeks): Weekly learning modules began during this phase. Participants became immersed in Ren.Nu's ketogenic diet therapy. The primary goals were to start and maintain a level of therapeutic ketosis (blood BHB level between 1.5 and 3.0 mmol/L), to manage oxalate and inorganic phosphate intake, to practice appropriate protein intake, and to ensure the proper balance of fluid and electrolytes. During Phase 2, participants started tracking their nutrient intake and health parameters. The recommended testing patterns were as follows:

- Serum ketone testing in the AM—prior to eating, 30–60 min after waking.
- Serum ketone testing in the PM—prior to eating dinner, ideally 2–3 h after the last food intake.
- Urine pH—measuring several times throughout the day using provided test paper.
- Body weight, blood pressure, and blood glucose were self-measured at the participant's discretion.

Week one of this phase was initiated, if possible, with a 1-day modified fast that consisted of 500–600 kcal and moderate protein and carbohydrates. Following the modified fast, participants followed a provided guided menu providing an average of 30–40 g net carbohydrates (i.e., total carbohydrates minus fiber) for the remainder of the week to expedite the induction of ketosis. Ren.Nu's dietary protocol includes meals that are fat-rich, lower in oxalate, phosphorus, and purines, and primarily uses plant-based ingredients. Eggs, fish, and full-fat dairy are incorporated to provide beneficial sources of calcium, dietary fat, omega-3 fatty acids, essential amino acids, fat-soluble vitamins,

and other micronutrients that are difficult to obtain from plant-based sources including carnitine, choline, and iron. The percent-caloric breakdown of macronutrient ranges used were approximately 10–15% net carbohydrates, 10–15% protein, and 70–75% dietary fat. Individual percentages were based on, but not limited to, kidney function, biometric data, daily energy needs, comorbidities, and activity level. The specific micronutrients, related to positive outcomes with ADPKD, and overall kidney health that were monitored and managed include calcium, magnesium, omega-3 fatty acids, oxalates, potassium, sodium, zinc, vitamin D, and inorganic phosphates. In addition, the overall PRAL (potential renal acid load) was monitored. The medical food KetoCitra® was started during this phase to help facilitate metabolic adaptation into ketosis by providing exogenous BHB, replenish electrolytes to ameliorate "keto flu" symptoms, and to counter urine acidification that can occur during the body's transition into ketosis. Since the initiation of ketosis can also temporarily raise uric acid levels, keeping urine pH close to the neutral range is important to avoid uric acid precipitation.

Phase 3: Fat-adaptation (4–6 weeks): Participants transitioned into a fat-adapted state that continued for the second half of the program. The primary goal was to maintain low-level, baseline ketosis (blood BHB level between 0.5 and 1.0 mmol/L) while exploring the addition of lower glycemic index foods or an overall increase in net carbohydrates. This dietary lifestyle transition was to foster a sustainable, and nutrient-diverse, low-carbohydrate dietary pattern. During Phase 3, participants were guided to start a time-restricted feeding (TRF) practice. The TRF goal was a 16:8 regime of fasting to eating (i.e., a daily eating window of 8 h). New recipes were introduced to provide variety and seasonally focused options. The medical food KetoCitra® was continued throughout the remainder of the Ren.Nu program to support levels of BHB as more carbohydrates are re-introduced, to help keep urine pH and urine citrate levels in the normal range, and to continue to suppress the dietary absorption of oxalate and inorganic phosphates. The curriculum included meal and recipe guidance, weekly lessons on meaningful food lifestyle changes, a resilient mindset, and clinical monitoring by a registered dietitian.

Phase 4: Maintenance (1–2 weeks): During the final weeks of the Ren.Nu program, the education and discussion center on long-term strategies for success and resources for community and nutrition support. Exit questionnaires included a request for feedback from the participants on their wants and needs for continued support for successful maintenance.

3. Results

3.1. Design of the Ren.Nu Program

The Ren.Nu program was specifically created to translate the latest diet-related research findings into a comprehensive and practical program that lay individuals with ADPKD can follow with the goal of enabling long-lasting, sustainable changes in dietary and lifestyle habits. The primary nutritional goals are to facilitate a sustainable lifestyle change to a kidney-safe, plant-focused ketogenic diet that avoids renal stressors and provides a complete and healthful profile of macro- and micronutrients. Dietary changes are supported by a medical food that provides exogenous BHB, citrate, a blend of minerals, and 51 mEq of alkaline base. The dietary changes are intended to:

- Reduce net carbohydrate intake to lower blood glucose and insulin levels.
- Raise blood ketone levels.
- Avoid excessive consumption of the renal stressors oxalate, inorganic phosphate, and dietary protein acid precursors.
- Avoid the acidifying effect on urine pH and lowering of serum bicarbonate levels associated with heavy consumption of animal protein.
- Avoid heavy consumption of purine-rich meat to lower the burden of uric acid filtration and excretion by the kidneys.
- Support a nutrient-dense and diverse dietary intake with a focus on whole foods and minimally processed foods.

3.2. Beta Test of the Ren.Nu Program

The complete Ren.Nu program was beta tested with a group of approximately 24 participants with ADPKD between March and June 2021 to test the curriculum, digital platforms, and tools, and to gather feedback from participants to aid in the refinement of the program. The objective was to better understand the experiences of participants, including a qualitative assessment of their views while following a PFKD. The primary outcomes were tolerability, feasibility, and adherence to a PFKD using a structured group program. Secondary outcomes, including clinical biomarkers, were evaluated in an exploratory fashion.

Based on experiences with the beta test, the Ren.Nu program was launched in January 2022 and is now available to individuals with ADPKD (ren-nu.org). The Ren.Nu program is administered by the non-profit company RenAlign (Titusville, FL 32780, USA).

Inclusion criteria for the beta test were ADPKD diagnosis, age 18 years or older, an estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min/1.73 m^2. Active treatment with tolvaptan did not preclude enrollment. Exclusion criteria included type 1 diabetes, active eating disorder, kidney transplant, hyperkalemia, metabolic instability, malabsorption issues, pregnancy, and an estimated glomerular filtration rate (eGFR) < 30. Participants provided informed written consent before enrollment.

Pre- and post-program surveys were collected using online questionnaires adapted from previous studies and programs [15,49–51]. Health parameters, collected at baseline and program completion, were obtained by the participant's nephrologist or PCP. All participants were encouraged to keep in regular contact with the program dietitian, each other, and the support team, and to engage in a provided, private online community platform. Monitoring and logging of dietary intake, ketone levels, blood pressure, weight, urinary pH, and blood sugar were encouraged. Tracking was voluntary, the request for a minimum of 3 days per week was made to enable review and feedback from the registered dietitian.

3.3. Primary Outcomes of the Beta Test

In total, 24 participants were initially enrolled including individuals who applied in response to social media posts or from personal invitations. Of those enrolled, two dropped out for unknown reasons. Two additional participants were excluded from the exploration of clinical biomarkers because they did not complete their last session with the dietitian or provide exit labs (90-day labs). A total of 20 participants completed the beta test. Because not all participants completed all questionnaires, the total numbers of respondents are indicated for each question in context below. Baseline characteristics of the program enrollees are summarized in Table 1.

Table 1. Baseline characteristics of Ren.Nu Beta participants who completed the program (n = 20) after exclusion of two participants that dropped out and two participants that did not complete the exit labs.

Demographics	
Age, mean (SD [1]) (years)	48.3 (7.4)
Male participants (%)	40
Female participants (%)	60
Caucasian/White (%)	85
BMI, mean (SD [1])	25.6 (3.9)
Hypertension (%)	85
Active treatment with tolvaptan (%)	55
Active treatment with ACE inhibitor (%)	30
Active treatment with Angiotensin II receptor blocker (%)	55

Table 1. *Cont.*

CKD Stage	
CKD 1 (GFR = 90 or higher) (%)	0
CKD 2 (GFR = 60–89) (%)	30
CKD 3 (GFR = 30–59) (%)	65
CKD 4 (GFR = 15–29) (%)	5

[1] SD: standard deviation.

3.3.1. Serious Adverse Events

One UTI, one gout flare, and one passed kidney stone were reported during the program. Given that these conditions are common among individuals with ADPKD, and that participants had histories of UTIs, gout, and kidney stones, it could not be definitively determined whether the occurrence during the program was related to the diet changes. All the affected participants continued in the program without further adverse events.

3.3.2. Qualitative Findings

Trends and feedback were assessed regarding tolerability, feasibility, and adherence to the program. When analyzing participant feedback, survey responses, and input from one-on-one sessions with the dietitian, several themes emerged. The themes below highlight the trends we observed and identified.

Satisfaction, Tolerability, and Effects on Health and Well-Being

- Health and Physical Wellness (n = 18 Unless Otherwise Noted). When asked about any changes with recurrent health issues experienced prior to starting the Ren.Nu program, respondents reported the biggest changes and improvements were regarding flank pain and fatigue (Table 2). In total, 50% (n = 9) of respondents "strongly agreed", and 39% (n = 7) "somewhat agreed" that the Ren.Nu program improved their PKD symptoms. No participant disagreed (scale: 1 = strongly disagree, 5 = strongly agree) (Table 2). The most common new symptoms reported during the first 2 weeks of starting a PFKD were fatigue and brain fog. A total of 72% (n = 13) of respondents reported experiencing fatigue while 56% (n = 10) reported brain fog. After the initial 2 weeks, and a transition into ketosis, 85% (n = 11) of newly reported fatigue resolved and 100% (n = 10) of brain fog resolved. A total of 83% (n = 15) of respondents believed that the Ren.Nu program improved their overall health. The average level of belief was 4.8 on the agreement scale (1 = disagree, 5 = agree) (Table 2). There was also a high level of belief that the Ren.Nu program improved their "overall kidney health" with 83% (n = 15) of respondents agreeing at the highest level of 5. The average level of belief was 4.8 on the agreement scale (1 = disagree, 5 = agree) (Table 2).
- Dietary Satisfaction (n = 17 Unless Otherwise Noted). Overall satisfaction with the way they were eating while following a PFKD was rated high with participants. In total, 59% (n = 10) rated their diet satisfaction as a 4 and 36% (n = 6) liked their diet "very much", the highest rating (scale: 1 = dislike extremely, 5 = like very much) (Table 2). Compared to how they ate prior to Ren.Nu vs. following a PFKD, 35% (n = 6) of respondents enjoyed their new pattern of eating better, and 29% (n = 5) enjoyed it "much better" (scale: 1 = I liked my previous eating pattern much better, 5 = I like my present eating pattern much better). Satisfaction with the amount of food eaten also ranked high. In total, 41% (n = 4) of respondents ranked satisfaction as a 4 and 35% (n = 6) ranked satisfaction as a 5 "very satisfied" (scale: 1 = not satisfied, 5 = very satisfied). When asked how their food tasted while following a PFKD, 41% (n = 7) of respondents ranked their satisfaction as "very satisfied", and 41% (n = 7) ranked it at 4 on the satisfaction scale (scale: 1 = not satisfied, 5 = very satisfied).
- Curriculum and Ren.Nu Experience (n = 18 Unless Otherwise Noted). In total, 83% (n = 15) of respondents agreed that the nutrition curriculum content in the Ren.Nu

program was easy to understand. The overall average was 4.8 on the agreement scale (1 = disagree, 5 = agree) (Table 2). Participants strongly agreed, with an average agreement response of 4.8, that the nutrition curriculum helped them make necessary dietary changes to preserve kidney function. A total of 94% (n = 17) of respondents agreed at the highest level of 5 (scale: 1 = disagree, 5 = agree) (Table 2).

- A Resilient Mindset and Overall Satisfaction. Mindfulness exercises were an integral part of the Ren.Nu program and received positive comments. See Figure 2 for details on key curriculum survey findings (scale: 1 = disagree, 5 = agree) (Table 2).

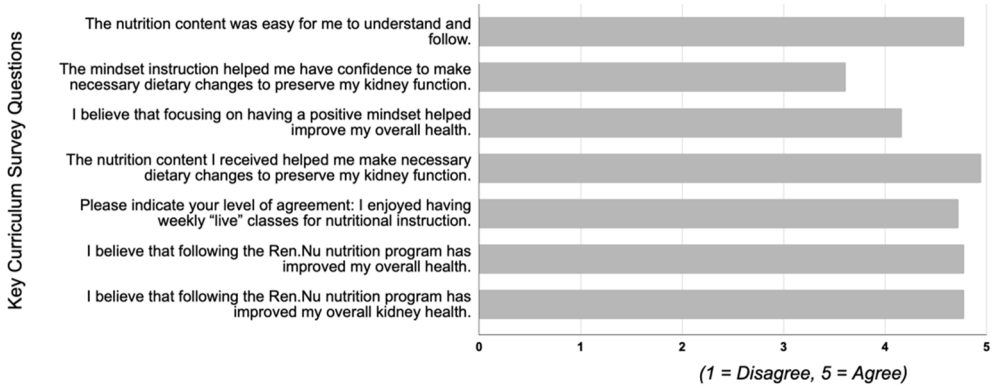

Figure 2. Key curriculum survey findings regarding satisfaction, tolerability, and health effects of the Ren.Nu program (scale: 1 = disagree, 5 = agree).

Table 2. Examples of comments provided by participants that illustrate experiences.

Health and Physical Wellness
"Before joining the program, I was encountering daily flank pain, and fatigue. Now I have a new outlook on life, I feel empowered that the food I consume is going to help heal my body." (Participant M7)
"The kidney pain I experienced on a weekly, if not daily basis, has been reduced dramatically. I even sleep better because of it." (Participant F11)
"The Ren.Nu program has been beneficial to my kidneys and overall health because of the weekly PKD modules. I loved learning how certain foods hurt your kidneys and liked it even more when I learned about foods that are beneficial to kidney" (Participant F2)
"Eating a plant-based keto diet that is lower protein has left me feeling better, emphasized the importance of diet and mindset in improving my health and given me hope that I am doing everything in my control to tackle my PKD." (Participant F8)
"I have learned more about how to best care for my kidney health in the past 12 weeks than I have learned in the past decade!" (Participant F11)
"I feel like I have the tools and mindset to choose better foods from now on, knowing that my choices will help my kidneys continue to function longer." (Participant F1)
Dietary Satisfaction
"The great meal suggestions and gradual transitions have made me feel very satisfied with my new diet and I finally feel like I can keep going with this plan." (Participant F5)
Curriculum and Ren.Nu Experience
"I believe the instruction, support, and attention to detail that has been given throughout this program is unsurpassed." (Participant F11)
"The beta program made it very easy to switch to a new diet and set me up for success in the long run. I found the science-driven information in the program to be very educational and empowering." (Participant F10)
"The Ren.Nu program helped me to put the entire puzzle together. I needed more knowledge how to plan and make nutritional and healthy meals, and keto-friendly menu. I was lost on my own." (Participant M5)

Table 2. *Cont.*

Resilient Mindset and Overall Satisfaction
"It taught me to think consciously about my meals. It gave me the confidence to ask restaurants what ingredients are in the menus." (Participant M7) *"I could follow recommendations more easily because I had tools to let go of stress and visualize creating healthier kidneys."* (Participant F1) *"With the discussions and training, it felt like we had direction, insight, training, enthusiasm, and a place we could ask a lot of questions. The food chart and meal plans were amazing, and I am not sure I could have done it without those tools. Each week we have learned valuable new tools and information."* (Participant M6) *"The Ren.Nu program breaks down the diet and health changes into manageable steps while giving us all the information and science behind their recommendations." (Participant F8)* *I found the science-driven information in the program to be very educational and empowering."* (Participant F10)
Feasibility
"I am so incredibly grateful to the entire team who have put this research together in a way that I can actually put it into practice." (Participant M6) *"I am really glad that I started this program. I feel like even if I do half of the things I've learned about, I will improve my kidney health. This change was shockingly easier than expected."* (Participant F13) *"This program goes far beyond just a ketogenic approach, has changed my eating habits and made these lifestyle changes feel sustainable long term."* (Participant F8)
Overall Impact on Time and Routine
"I go shopping every few days it seems (more often than I used to), and I probably spend 1–2 h a day with meal cooking (dinner is usually the most time-consuming). When I'm on it and think of a few meals ahead of time it is much smoother." (Participant F8) *"I have prepared a menu with my favorite meals that give my wife a really good idea of what to shop for and what we can make. This has been very helpful."* (Participant M6)
Impact of Nutrient and Data Tracking
Tracking was very time-consuming but I don't know how to improve that. I understand that that level of data is needed." (Participant M8)
Biggest Barrier
"Protein intake lowering and source of protein, this was difficult to do." (Participant M10) *"It was so much easier to eat meat to get protein than to figure out how to get enough in plant protein. However, I liked eating much less meat than I did before. It would have been much more difficult if I had never tried eating Keto before."* (Participant F1) *"Eating too much protein"* (Participant F13) *"The low protein was and is honestly the hardest part for me—I try now if I go over on my protein level to make it all plant-based. I had no idea how much protein I was eating before and I think most Americans don't and those who eat meat at every meal are well over 100 gms/day!"* (Participant F8)
Renal Function Measures
"I have rigorously done this diet for two months now and my labs showed a steady improvement of my eGFR and my creatinine levels, making me the first family member with PKD to improve his kidney function ever, something unheard of." (Participant F9) *"I saw my first downward trend in creatinine (and improvement in GFR) in 5 years and I feel so much more excited for the future!"* (Participant F8)

Table 2. *Cont.*

Overall Participant Experience and Continued Support
"The classes I was able to attend—feeling like I was part of a group and connecting to other PKD people, the one-on-one sessions, and the recipes/menus" (Participant F8)
"Before this program, I hadn't ever talked to anyone with PKD personally (besides for patients in the hospital) so it was great to see other "real" people who are facing the same issue I am." (Participant F8)
"The online classes and hearing the questions of classmates. I forgot that we all had PKD because I was so focused on the diet journey we were on! I loved being part of this community." (Participant F1)
"Hearing about other people's experiences." (Participant F12)
"I loved hearing others ask the same questions I have each week and knowing I am not alone in this journey." (Participant M6)
"I also appreciated the community of PKD warriors that they are building that makes you feel less alone on this journey." (Participant 10)
"Some kind of personal or group check-in with one or all of you." (Participant F9)
"I would love to be able to stay in touch with the dietitians and people in this group in some way. I hope we can continue the smaller FB group and that the next ren.nu program group gets added. I also love the idea of monthly emails or the occasional recipe sent out and maybe organize a group check-in bi-annually to see how people are doing!" (Participant F8)
"1 on 1 dietitian time, group facilitated discussions with other PKD beta testers so we can stay connected and learn from each other." (Participant M10)
"Keep supporting me with a quarterly/semi-annual follow-up." (Participant M7)

Feasibility

With regard to the overall feasibility of a plant-based, low oxalate, ketogenic diet in daily life, the vast majority (88%, n = 15) of respondents gave a rating of 4 or 5 (scale: 1–5). In total, 47% (n = 8) rated the feasibility as "5: no problem at all, I am following the diet daily" and 41% (n = 7) rated the feasibility as "4: no real problem, but sometimes I skip it several times a month". When asked if they felt the Ren.Nu program was "easy" for people with PKD, 39% (n = 7) strongly agreed (rating 5) and 39% (n = 7) gave a rating of 4. The average ease of the program was 4.1 (scale: 1 = strongly disagree; 5 = strongly agree) (Table 2).

- Overall Impact on Time and Routine How eating a PFKD and tracking for the program affected participant's time and routine and the financial impact were the two major themes represented in participant responses for feasibility. Participants reported that their eating habits did not interfere very much with their life activities on the feedback questionnaires (scale: 1 = very much, 5 = not at all). In total, 41% (n = 7) ranked their eating habits as a 4, having little impact. A fair number of respondents were neutral on the impact at 29.4% (n = 5). When asked about the average amount of time spent on planning, shopping, and prepping meals, 60% of respondents (n = 3) reported an additional hour, on average, was needed daily. This was interesting as one of the concerns frequently expressed pre-enrollment was about the amount of time that was going to be required to eat with more whole-food patterns (Table 2). Based on observations and feedback given to the dietitian, the amount of time needed decreased over the course of the program. During the first 4–6 weeks of the program, it was expressed that planning, shopping, and cooking did affect normal patterns and routine and took a considerable amount of time. There was a learning curve, for many participants, regarding incorporating PFKD into daily life and getting into a feasible routine that supported success.
- Feasibility of Self-Measurement of Health Parameters (n = 17) A total of 41% (n = 7) of respondents ranked the difficulty of taking ketone and blood sugar measurements as "not at all" and 35% (n = 6) ranked the difficulty level at 4 (scale: 1 = very difficult, 5 = not at all). The task of measuring ketones and blood sugar, once participants understood how and when to measure, did not appear to impact daily routine. The task of measuring urine pH did not appear to impact daily routines with 29% (n = 5) of

respondents ranking impact at 4. The average ranking was 3.4 (scale: 1 = very difficult, 5 = not at all).

- Impact of Nutrient and Data Tracking (n = 17) The tracking and inputting of ketone levels, blood sugar, and other data seemed to be the biggest struggle for participants and most disruptive to their daily routine. When asked if entering food intake and biometrics into the Cronometer app impacted daily routine, 35% (n = 6) of participants reported it did "very much". The average was 2.4 (scale: 1 = very much, 5 = not at all). The difficulty of data tracking should be considered when planning future clinical trials (Table 2).
- Financial Impact Since beginning the Ren.Nu program, 53% (n = 9) of respondents reported spending "more" out of pocket on food, whereas 41% (n = 7) reported they "spend about the same". In total, 36% (n = 4) of respondents who spent "more" indicated increased spending of USD 25–50 more per week. Equal to that, 36% (n = 4) indicated increased spending over USD 50 more per week.

Adherence

The program completion rate was 92% (22 out of 24 participants completed the program). Themes that emerged about beliefs, health, and diet likely contributed to the high level of adherence. When asked how likely they are to continue with a PFKD lifestyle and dietary pattern, 72% (n = 13) of respondents selected "very likely" (scale: 1 = very unlikely, 5 = very likely).

- Confidence In total, 94% (n = 16) of respondents indicated they "very much" believed that what they eat affects their health (scale: 1 = does not affect, 5 = very much). A total of 88% (n = 15) of respondents also strongly believed that making changes in their diet "very much" improves how they feel (scale: 1 = does not help at all, 5 = very much). Between enrollment and program completion, there was an increase in confidence with knowing how to cook and prepare foods that preserve kidney health. At enrollment, the average confidence was 6.2 on a 10-point confident scale. The average confidence level increased to 8.4 after program completion (scale: 1 = not confident, 10 = very confident). Confidence in understanding what to eat and what to avoid to help preserve kidney function also showed a similar increase. Respondents' confidence averaged 6.2 at enrollment and increased to an average of 8.4 during the Ren.Nu program (scale: 1 = not confident, 10 = very confident).
- Most Difficult, Struggles Consistently, the most difficult aspect reported when following a PFKD lifestyle was eating out, either in restaurants or other homes. Eating at someone else's house, while maintaining a PFKD, was reported as being difficult. In total, 47% (n = 8) of respondents ranked the level of difficulty as a 2 on a 5-point difficulty scale (scale: 1 = very much, 5 = not at all). Eating at restaurants also ranked high for the level of difficulty. Additionally, 35% (n = 6) of respondents reported that eating at restaurants was "very much" difficult and 24% rated the level of difficulty as a 2 for eating out (scale: 1 = very much, 5 = not at all).
- Biggest Barrier Lowering protein intake, specifically animal protein, to a moderate amount was consistently expressed as the biggest barrier participants came up against with following a PFKD (Table 2). This is the opposite of previously published qualitative findings [52] that reported that reducing dietary protein intake was one of the easiest parts of an ADPKD dietary intervention which implemented a diet "to lower intake of sodium, protein, and acid precursors". Of note, the dietary intervention lasted for 4 weeks compared to the 12-week Ren.Nu program.
- Ease of Change Switching to a PFKD eating pattern, food shopping, and preparing meals were areas reported to be relatively easy. A total of 59% (n = 10) of respondents reported that switching from how they previously ate to a PFKD "took some time, but it was manageable". In total, 35% (n = 5) of respondents found shopping for food was "not at all" difficult, and 29% (n = 5) ranked this at a score of 4. Planning and preparing

meals was not perceived as difficult either. Finally, 47% (n = 8) of respondents ranked the difficulty as a 4 (scale: 1 = very difficult, 5 = not at all).

3.4. Secondary Outcomes of the Beta Test

Several health parameters were collected either from the participant's physicians (metabolic panels before and after the program) or self-measured/reported. Since not all participants provided all health parameters, the respective numbers of respondents are indicated in context below.

Weight and BMI. In total, 89% (n = 16 out of 18) of respondents reported weight loss during participation in the program (Figure 3). The average self-reported weight change (n = 16) was a loss of 8.9 pounds (range 0–35 lbs lost) corresponding to an average weight decrease of 5.6% compared to the baseline at the start of the program. Correspondingly, participants' BMI (n = 17) was reduced from a baseline range of 20.0–32.3 to an end range of 18.0–31.7, representing an average reduction in BMI by 1.33 points. Note that weight-loss goals were individualized to participants, and that only participants in the overweight/obese range were prescribed weight-loss goals. The Ren.Nu diet can be adapted for weight loss or weight gain depending on individual goals.

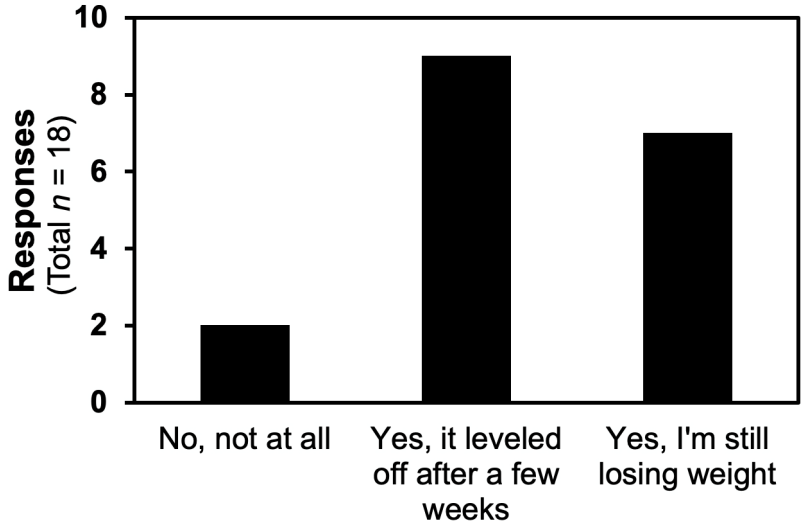

Figure 3. Did you experience any weight loss after starting a plant-focused ketogenic diet?

Blood glucose and ketones. Participants provided results from basic or comprehensive metabolic blood panels that were conducted by their physicians prior to starting the beta test and at the conclusion of the beta test. Fasting blood glucose levels decreased by an average of 16.5% (−19 mg/dL) leading to a change from the baseline average of 115.5 mg/dL (range 79–139 mg/dL) to the end average of 96.5 mg/dL (range 65–104 mg/dL). Blood ketones (BHB) were self-measured during the course of the program. BHB levels were variable from day to day and during the course of the day. All participants reached a level of ketosis as defined by BHB $\geq$ 0.5 mM within a few days of starting the program. The average self-reported BHB levels were 1.3 mM during the first 6 weeks and 1.1 mM during the final 6 weeks of the program, respectively. Therefore, all participants reached the metabolic state of ketosis and were able to maintain it for most of the time during the program.

Blood pressure. A total of 83% (n = 15) of participants reported that their blood pressure "improved," and 11% (n = 2) reported that it "improved a lot" during the program (scale: 1 = worsened a lot, 5 = improved a lot) (Figure 4). Blood pressure did not worsen for any participant. Several participants reduced their blood pressure medication during the course of the program.

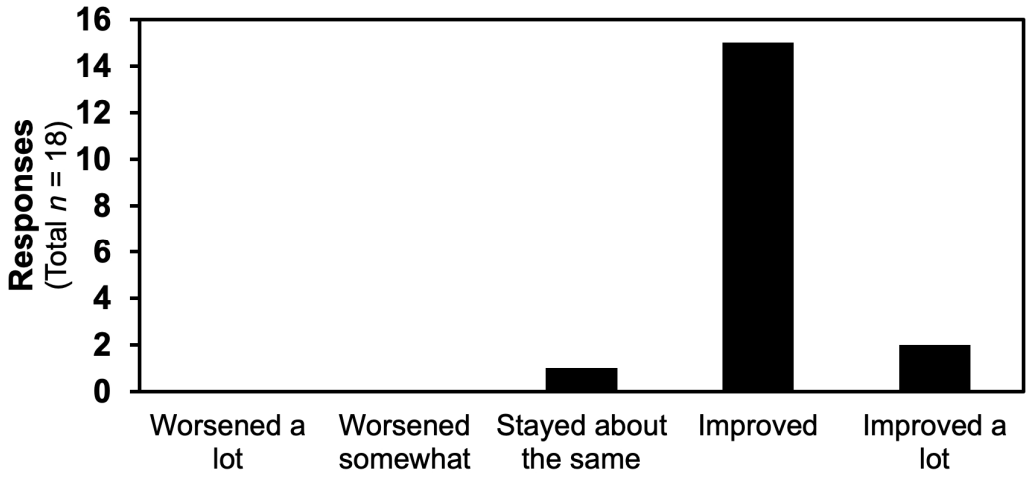

Figure 4. Define the changes in blood pressure you measured over the course of the Ren.Nu program.

Renal function measures. Renal function parameters among participants were highly variable reflecting the diversity of levels of kidney function. The average serum creatinine level (n = 19) at baseline was 1.53 mg/dL (range 0.70–3.63 mg/dL) and trended downwards by 0.1 mg/dL (5.8% decrease) by the end of the program to an average of 1.44 mg/dL (range 0.70–2.85 mg/dL). Correspondingly, the estimated glomerular filtration rate (eGFR; n = 19) trended up by an average increase of 8.6% (4.4 mL/min/1.73 m^2) from the baseline average of 52.2 mL/min/1.73 m^2 (range of 24–94 mL/min/1.73 m^2) to the end average of 56.5 mL/min/1.73 m^2 (range 26–99 mL/min/1.73 m^2). Blood urea nitrogen (BUN; n = 20) trended downwards by a change of −3 mg/dL (10.1% decrease) from the baseline average of 21.8 mg/dL (range 11–49 mg/dL) to the end average of 18.9 mg/dL (range 8–39 mg/dL) (Table 2).

Other health parameters. Electrolytes from pre- and post-program metabolic blood panels (n = 19) were all within normal ranges except for one participant who exhibited low sodium (129 mM) in their post-program panel but showed no signs or symptoms of hyponatremia. It should be noted that individuals with ADPKD are generally advised to lower their sodium intake. Low sodium intake in the Ren.Nu program is facilitated by the avoidance of highly processed foods. Furthermore, ketogenic diets are known to lead to sodium loss. Therefore, Ren.Nu participants should be monitored for sodium levels and may be advised to increase sodium intake at a personalized level. Lipid profiles (n = 16) generally trended towards improvement during the Ren.Nu program including triglycerides (pre-program average 117 mg/dL to post-program average 94 mg/dL) and HDL cholesterol (pre-program average 56 mg/dL to post-program average 60 mg/dL). Averages of total cholesterol, LDL cholesterol, and albumin levels remained unchanged.

3.5. Overall Participant Experience and Continued Support

The level of support, the knowledge of the Ren.Nu team regarding diet and PKD, and sharing a common experience were highlighted in the feedback of participants as most valuable to them. Many participants reported that their favorite part of the program was the group setting and the connection they felt to the program team and their peer community. Participants liked hearing and learning from questions that other participants had, knowing they were not alone with experiences. Feeling safe to express difficulties, struggles, and successes regarding their health and disease were mentioned frequently in conversation and feedback (Table 2).

When asked about their preferences for continued support, respondents had three main suggestions: (1) one-on-one check-in with a registered dietitian, (2) continued peer-support with the participants for connection and check-ins, and (3) support with recipes, emails, and continued contact with the Ren.Nu team.

4. Discussion

Here, we describe the first real-life experience with a dietary intervention program specifically designed for individuals with ADPKD that implements dietary changes based on recent research results. Participants were overall highly satisfied with the experience in the program, and the vast majority of participants felt that their participation led to tangible improvements in their health and well-being.

Improvement in body weight and pain levels were frequently reported. This is consistent with reported improvements in body weight, pain levels, abdominal fullness, and acid reflux in our retrospective case series study of ADPKD patients who had switched to ketogenic diets [15] and with a recent post-hoc study reporting that obesity is associated with greater back and radicular pain in ADPKD [53]. Based on these findings and common sense, it seems clear that individuals with ADPKD—who are burdened by abdominal organ enlargement—can benefit from reducing visceral fat deposits. Ketogenic dietary approaches are highly effective in reducing visceral fat [54,55].

Whether ketogenic dietary approaches can also slow—or even reverse—renal cystic disease progression in patients remains to be rigorously tested. Despite the common belief that ADPKD progression is relentless, and that reversal is impossible, previous animal experiments have demonstrated that disease regression is indeed possible. We showed that treatment of an orthologous PKD mouse model with the mTOR inhibitor rapamycin leads to regression of existing renal cystic disease [56]. Similarly, we demonstrated that a ketogenic diet leads to reversal of renal cystic disease in a rat model [23]. Recent genetic reconstitution experiments in mice also demonstrated reversal of cystic disease in a PKD mouse model [57]. The long-held belief that individuals with ADPKD will inevitably progress and that no interventions can halt, let alone reverse, the progression may have to be revised.

Our results suggest that markers of renal function may improve with the dietary interventions of the Ren.Nu program. Caution is warranted with the interpretation of these results because our study lacks (1) statistical power and (2) information on longer-term effects, and because (3) serum creatinine and BUN levels could be influenced by dietary changes independent of changes in renal function. In particular, a change to a plant-focused diet may lead to a reduction in the metabolic burden of creatinine and urea. We note, however, that reduction in serum creatinine, and the corresponding increase in calculated eGFR, was also documented in our recent retrospective case series study of 131 individuals with ADPKD who had switched to ketogenic dietary interventions for an average duration of 6 months [15]. The individuals in that study were not necessarily utilizing plant-focused diets and were more likely to have used meat-heavy ketogenic diets which should have unfavorable effects on serum creatinine levels and calculated eGFR values. Our experience is consistent with a recent study of low-carbohydrate intervention in patients with type 2 diabetes which was found to be safe and led to improvement in all parameters of renal function [58]. Our experience is also consistent with a recent pilot study that suggested that weight loss due to daily caloric restriction or intermittent fasting in obese and overweight individuals with ADPKD correlated with slowed kidney growth [29]. While the level of ketosis was not investigated in that study, loss of fat weight involves a certain level of ketosis, and it seems likely that the individuals in that study experienced at least mild ketosis some of the time. While longer-term effects of ketogenic dietary interventions on renal function will have to await additional studies, all information known to date shows that these diets are not detrimental to kidney function.

In contrast to low-carbohydrate diets, it is clear that diets and lifestyles that promote hyperglycemia and hyperinsulinemia are detrimental to renal function. Diabetes is the leading cause of chronic kidney disease in most industrialized societies. Similarly, individuals with ADPKD and type 2 diabetes have significantly increased renal disease compared to those with ADPKD alone [27]. Even in non-diabetic individuals with ADPKD, we previously demonstrated that the fasting serum glucose level is a strong predictor of greater total kidney volume increase over time [23]. Consistent with this, overweight

and obesity have been shown to correlate with faster progression of ADPKD [59], and overweight and obesity are most commonly caused by high carbohydrate diets that lead to relentless triglyceride deposition in adipose tissue due to persistently high glucose and insulin levels. Animal experimentation also showed that hyperglycemia accelerates disease progression in a PKD mouse model [60]. These results are consistent with recent research showing that cyst cells in PKD have metabolic abnormalities that lead them to become highly glycolytic and—at the same time—unable to properly conduct mitochondrial fatty acid oxidation [16,17].

Based on the sum of clinical findings, animal experimentation, information about signaling mechanisms and metabolic abnormalities, and biological plausibility, we strongly suggest that high carbohydrate diets and lifestyles that lead to avoidance of ketosis should not be recommended to individuals with ADPKD. For the last few decades, the US government-sponsored Dietary Guidelines for Americans have promoted "low fat" diets which are, in turn, "high carbohydrate" diets. Even though these dietary recommendations are only intended for healthy individuals, they have become standard advice by most clinicians for individuals with ADPKD. However, to our knowledge, no clinical studies have ever been conducted to test whether high carbohydrate (as known as low fat) diets are beneficial in ADPKD. There is no compelling justification to recommend high carbohydrate diets for ADPKD.

Another important aspect of the Ren.Nu program is that it aims to antagonize metabolic abnormalities in ADPKD that lead to metabolic acidosis, excessive urine acidification, hypocitraturia, and a higher risk of forming kidney stones. Metabolic acidosis, as measured by low serum bicarbonate levels, has been shown to be associated with worse ADPKD progression [61]. Metabolic acidosis leads to urine acidification which, in turn, leads to hypocitraturia, and the combination of these factors promotes the precipitation of microcrystals in tubule lumens during urine concentration. Our recent research has shown that microcrystals (e.g., calcium oxalate) in renal tubules act as a trigger to accelerate disease progression in PKD animal models [30]. The most common types of kidney stones in humans are composed of calcium oxalate, uric acid or calcium phosphate, and all of these are influenced by dietary intake. Low urine pH leads to hypocitraturia; thereby promoting the precipitation of calcium crystals. Low urine pH also directly promotes the precipitation of uric acid crystals. The Ren.Nu program reduces acidifying animal protein, and instead focuses on alkalizing plant foods. Urine pH and urine citrate levels are further normalized by utilizing the medical food KetoCitra® which provides 51 mEq of alkaline base in combination with citrate.

There are many "internet versions" of ketogenic diets available that utilize a high intake of meat and animal protein. We argue that meat-predominant ketogenic diets may be less beneficial in ADPKD due to the burden they place on the kidneys. In contrast, plant-focused, alkalizing diets have generally been shown to be beneficial in chronic kidney disease [48].

There are several limitations of our study. This study was not conducted as a clinical trial but rather as a beta test of a program curriculum. As such, there was no control group, data were not rigorously collected, and we depended on self-measuring and self-reporting of health data which led to incomplete data that precluded statistical analysis. The dietary intervention occurred during 12 weeks and longer-term studies are needed to evaluate whether any perceived benefits persist over a longer period of time. Several clinical trials are currently ongoing to study ketogenic diets or caloric restriction diets in ADPKD that may lead to insights into long-term effects. Finally, the group of participants in this beta test consisted of individuals who were highly motivated to implement dietary changes. The participants were also generally well-educated on their disease. It is likely that this selection bias contributed to the observed very high level of adherence to the program and the reported high scores on questions concerning the feasibility of the dietary interventions. It is likely that adherence and judgment of feasibility would be lower with other populations of participants. However, one should not underestimate the level of

motivation of individuals with ADPKD who have been found to have a very high level of interest in learning about dietary information that may benefit their health and well-being [14,15].

In conclusion, our initial experience with the Ren.Nu dietary program has been highly positive. Participants were able to adhere to the program well and generally reported improvements in their health and well-being.

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Institutional Review Board Statement: Not applicable. The work describes a beta-test primarily aimed at evaluating user experience (including program tools and materials), satisfaction, adherence, and feasibility of a specific training program and curriculum among a targeted audience, and not to generate generalizable knowledge for PKD patients.

Informed Consent Statement: Informed consent was obtained from all participants prior to enrollment in the Ren.Nu program.

Data Availability Statement: Not applicable.

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References

1. Lanktree, M.B.; Haghighi, A.; Guiard, E.; Iliuta, I.-A.; Song, X.; Harris, P.C.; Paterson, A.D.; Pei, Y. Prevalence Estimates of Polycystic Kidney and Liver Disease by Population Sequencing. *J. Am. Soc. Nephrol.* **2018**, *29*, 2593–2600. [CrossRef] [PubMed]
2. Cornec-Le Gall, E.; Alam, A.; Perrone, R.D. Autosomal Dominant Polycystic Kidney Disease. *Lancet* **2019**, *393*, 919–935. [CrossRef]
3. Muller, R.U.; Benzing, T. Management of Autosomal-Dominant Polycystic Kidney Disease-State-of-the-Art. *Clin. Kidney J.* **2018**, *11*, i2–i13. [CrossRef] [PubMed]
4. Bergmann, C.; Guay-Woodford, L.M.; Harris, P.C.; Horie, S.; Peters, D.J.M.; Torres, V.E. Polycystic Kidney Disease. *Nat. Rev. Dis. Primers* **2018**, *4*, 50. [CrossRef]
5. Irazabal, M.V.; Rangel, L.J.; Bergstralh, E.J.; Osborn, S.L.; Harmon, A.J.; Sundsbak, J.L.; Bae, K.T.; Chapman, A.B.; Grantham, J.J.; Mrug, M.; et al. Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials. *J. Am. Soc. Nephrol.* **2015**, *26*, 160–172. [CrossRef]
6. Yu, A.S.L.; Shen, C.; Landsittel, D.P.; Grantham, J.J.; Cook, L.T.; Torres, V.E.; Chapman, A.B.; Bae, K.T.; Mrug, M.; Harris, P.C.; et al. Long-Term Trajectory of Kidney Function in Autosomal-Dominant Polycystic Kidney Disease. *Kidney Int.* **2019**, *95*, 1253–1261. [CrossRef]

7. Torres, V.E.; Chapman, A.B.; Devuyst, O.; Gansevoort, R.T.; Perrone, R.D.; Koch, G.; Ouyang, J.; McQuade, R.D.; Blais, J.D.; Czerwiec, F.S.; et al. Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. *N. Engl. J. Med.* **2017**, *377*, 1930–1942. [CrossRef]
8. Erickson, K.F.; Chertow, G.M.; Goldhaber-Fiebert, J.D. Cost-Effectiveness of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease. *Ann. Intern. Med.* **2013**, *159*, 382–389. [CrossRef]
9. Müller, R.-U.; Haas, C.S.; Sayer, J.A. Practical Approaches to the Management of Autosomal Dominant Polycystic Kidney Disease Patients in the Era of Tolvaptan. *Clin. Kidney J.* **2018**, *11*, 62–69. [CrossRef]
10. Chebib, F.T.; Perrone, R.D.; Chapman, A.B.; Dahl, N.K.; Harris, P.C.; Mrug, M.; Mustafa, R.A.; Rastogi, A.; Watnick, T.; Yu, A.S.L.; et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. *J. Am. Soc. Nephrol.* **2018**, *29*, 2458–2470. [CrossRef]
11. Mustafa, R.A.; Yu, A.S.L. Burden of Proof for Tolvaptan in ADPKD: Did REPRISE Provide the Answer? *Clin. J. Am. Soc. Nephrol.* **2018**, *13*, 1107–1109. [CrossRef] [PubMed]
12. Pickel, L.; Iliuta, I.-A.; Scholey, J.; Pei, Y.; Sung, H.-K. Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease. *Adv. Nutr.* **2022**, *13*, 652–666. [CrossRef] [PubMed]
13. Carriazo, S.; Perez-Gomez, M.V.; Cordido, A.; García-González, M.A.; Sanz, A.B.; Ortiz, A.; Sanchez-Niño, M.D. Dietary Care for ADPKD Patients: Current Status and Future Directions. *Nutrients* **2019**, *11*, 1576. [CrossRef] [PubMed]
14. Ma, T.; Lambert, K. What Are the Information Needs and Concerns of Individuals with Polycystic Kidney Disease? Results of an Online Survey Using Facebook and Social Listening Analysis. *BMC Nephrol.* **2021**, *22*, 263. [CrossRef] [PubMed]
15. Strubl, S.; Oehm, S.; Torres, J.A.; Grundmann, F.; Haratani, J.; Decker, M.; Vuong, S.; Kaur Bhandal, A.; Methot, N.; Haynie-Cion, R.; et al. Ketogenic Dietary Interventions in Autosomal-Dominant Polycystic Kidney Disease (ADPKD)—A Retrospective Case Series Study: First Insights into Feasibility, Safety and Effects. *Clin. Kidney J.* **2021**. [CrossRef]
16. Nowak, K.L.; Hopp, K. Metabolic Reprogramming in Autosomal Dominant Polycystic Kidney Disease: Evidence and Therapeutic Potential. *Clin. J. Am. Soc. Nephrol.* **2020**, *15*, 577–584. [CrossRef]
17. Podrini, C.; Cassina, L.; Boletta, A. Metabolic Reprogramming and the Role of Mitochondria in Polycystic Kidney Disease. *Cell. Signal.* **2020**, *67*, 109495. [CrossRef]
18. Tidwell, T.R.; Soreide, K.; Hagland, H.R. Aging, Metabolism, and Cancer Development: From Peto's Paradox to the Warburg Effect. *Aging Dis.* **2017**, *8*, 662–676. [CrossRef]
19. Magistroni, R.; Boletta, A. Defective Glycolysis and the Use of 2-Deoxy-D-Glucose in Polycystic Kidney Disease: From Animal Models to Humans. *J. Nephrol.* **2017**, *30*, 511–519. [CrossRef]
20. Riwanto, M.; Kapoor, S.; Rodriguez, D.; Edenhofer, I.; Segerer, S.; Wuthrich, R.P. Inhibition of Aerobic Glycolysis Attenuates Disease Progression in Polycystic Kidney Disease. *PLoS ONE* **2016**, *11*, e0146654. [CrossRef]
21. Kipp, K.R.; Rezaei, M.; Lin, L.; Dewey, E.C.; Weimbs, T. A Mild Reduction of Food Intake Slows Disease Progression in an Orthologous Mouse Model of Polycystic Kidney Disease. *Am. J. Physiol. Ren. Physiol.* **2016**, *310*, F726–F731. [CrossRef] [PubMed]
22. Warner, G.; Hein, K.Z.; Nin, V.; Edwards, M.; Chini, C.C.; Hopp, K.; Harris, P.C.; Torres, V.E.; Chini, E.N. Food Restriction Ameliorates the Development of Polycystic Kidney Disease. *J. Am. Soc. Nephrol.* **2016**, *27*, 1437–1447. [CrossRef] [PubMed]
23. Torres, J.A.; Kruger, S.L.; Broderick, C.; Amarlkhagva, T.; Agrawal, S.; Dodam, J.R.; Mrug, M.; Lyons, L.A.; Weimbs, T. Ketosis Ameliorates Renal Cyst Growth in Polycystic Kidney Disease. *Cell Metab.* **2019**, *30*, 1007–1023.e5. [CrossRef] [PubMed]
24. Veech, R.L.; Bradshaw, P.C.; Clarke, K.; Curtis, W.; Pawlosky, R.; King, M.T. Ketone Bodies Mimic the Life Span Extending Properties of Caloric Restriction. *IUBMB Life* **2017**, *69*, 305–314. [CrossRef]
25. Rojas-Morales, P.; Tapia, E.; Pedraza-Chaverri, J. Beta-Hydroxybutyrate: A Signaling Metabolite in Starvation Response? *Cell. Signal.* **2016**, *28*, 917–923. [CrossRef]
26. Newman, J.C.; Verdin, E. Beta-Hydroxybutyrate: A Signaling Metabolite. *Annu. Rev. Nutr.* **2017**, *37*, 51–76. [CrossRef]
27. Reed, B.; Helal, I.; McFann, K.; Wang, W.; Yan, X.D.; Schrier, R.W. The Impact of Type II Diabetes Mellitus in Patients with Autosomal Dominant Polycystic Kidney Disease. *Nephrol. Dial. Transpl.* **2012**, *27*, 2862–2865. [CrossRef]
28. Nowak, K.L.; Steele, C.; Gitomer, B.; Wang, W.; Ouyang, J.; Chonchol, M.B. Overweight and Obesity and Progression of ADPKD. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 908–915. [CrossRef]
29. Hopp, K.; Catenacci, V.A.; Dwivedi, N.; Kline, T.L.; Wang, W.; You, Z.; Nguyen, D.T.; Bing, K.; Poudyal, B.; Johnson, G.C.; et al. Weight Loss and Cystic Disease Progression in Autosomal Dominant Polycystic Kidney Disease. *iScience* **2022**, *25*, 103697. [CrossRef]
30. Torres, J.A.; Rezaei, M.; Broderick, C.; Lin, L.; Wang, X.; Hoppe, B.; Cowley, B.D.; Savica, V.; Torres, V.E.; Khan, S.; et al. Crystal Deposition Triggers Tubule Dilation That Accelerates Cystogenesis in Polycystic Kidney Disease. *J. Clin. Investig.* **2019**, *129*, 4506–4522. [CrossRef]
31. Lucaya, J.; Enriquez, G.; Nieto, J.; Callis, L.; Garcia Peña, P.; Dominguez, C. Renal Calcifications in Patients with Autosomal Recessive Polycystic Kidney Disease: Prevalence and Cause. *Am. J. Roentgenol.* **1993**, *160*, 359–362. [CrossRef] [PubMed]
32. Grampsas, S.A.; Chandhoke, P.S.; Fan, J.; Glass, M.A.; Townsend, R.; Johnson, A.M.; Gabow, P. Anatomic and Metabolic Risk Factors for Nephrolithiasis in Patients with Autosomal Dominant Polycystic Kidney Disease. *Am. J. Kidney Dis.* **2000**, *36*, 53–57. [CrossRef] [PubMed]
33. Nishiura, J.L.; Neves, R.F.; Eloi, S.R.; Cintra, S.M.; Ajzen, S.A.; Heilberg, I.P. Evaluation of Nephrolithiasis in Autosomal Dominant Polycystic Kidney Disease Patients. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 838–844. [CrossRef]

34. Torres, V.E.; Erickson, S.B.; Smith, L.H.; Wilson, D.M.; Hattery, R.R.; Segura, J.W. The Association of Nephrolithiasis and Autosomal Dominant Polycystic Kidney Disease. *Am. J. Kidney Dis.* **1988**, *11*, 318–325. [CrossRef]
35. Torres, V.E.; Wilson, D.M.; Hattery, R.R.; Segura, J.W. Renal Stone Disease in Autosomal Dominant Polycystic Kidney Disease. *Am. J. Kidney Dis.* **1993**, *22*, 513–519. [CrossRef]
36. Levine, E.; Grantham, J.J. Calcified Renal Stones and Cyst Calcifications in Autosomal Dominant Polycystic Kidney Disease: Clinical and CT Study in 84 Patients. *AJR Am. J. Roentgenol.* **1992**, *159*, 77–81. [CrossRef] [PubMed]
37. Hanna, C.; Potretzke, T.A.; Chedid, M.; Rangel, L.J.; Arroyo, J.; Zubidat, D.; Tebben, P.J.; Cogal, A.G.; Torres, V.E.; Harris, P.C.; et al. Kidney Cysts in Hypophosphatemic Rickets With Hypercalciuria: A Case Series. *Kidney Med.* **2022**, *4*, 100419. [CrossRef]
38. Hanna, C.; Potretzke, T.A.; Cogal, A.G.; Mkhaimer, Y.G.; Tebben, P.J.; Torres, V.E.; Lieske, J.C.; Harris, P.C.; Sas, D.J.; Milliner, D.S.; et al. High Prevalence of Kidney Cysts in Patients with CYP24A1 Deficiency. *Kidney Int. Rep.* **2021**, *6*, 1895–1903. [CrossRef]
39. Panizo, N.; Goicoechea, M.; Garcia de Vinuesa, S.; Arroyo, D.; Yuste, C.; Rincon, A.; Verdalles, U.; Ruiz-Caro, C.; Quiroga, B.; Luno, J. Chronic Kidney Disease Progression in Patients with Autosomal Dominant Polycystic Kidney Disease. *Nefrologia* **2012**, *32*, 197–205. [CrossRef]
40. Helal, I.; McFann, K.; Reed, B.; Yan, X.D.; Schrier, R.W.; Fick-Brosnahan, G.M. Serum Uric Acid, Kidney Volume and Progression in Autosomal-Dominant Polycystic Kidney Disease. *Nephrol. Dial. Transpl.* **2012**, *28*, 380–385. [CrossRef]
41. Ejaz, A.A.; Nakagawa, T.; Kanbay, M.; Kuwabara, M.; Kumar, A.; Garcia Arroyo, F.E.; Roncal-Jimenez, C.; Sasai, F.; Kang, D.-H.; Jensen, T.; et al. Hyperuricemia in Kidney Disease: A Major Risk Factor for Cardiovascular Events, Vascular Calcification, and Renal Damage. *Semin. Nephrol.* **2020**, *40*, 574–585. [CrossRef] [PubMed]
42. Mejias, E.; Navas, J.; Lluberes, R.; Martinez-Maldonado, M. Hyperuricemia, Gout, and Autosomal Dominant Polycystic Kidney Disease. *Am. J. Med. Sci.* **1989**, *297*, 145–148. [CrossRef] [PubMed]
43. Errasti, P.; Manrique, J.; Lavilla, J.; Rossich, E.; Hernandez, A.; Pujante, D.; Ndarabu, A.; Garcia, N.; Purroy, A. Autosomal-Dominant Polycystic Kidney Disease: High Prevalence of Graft Loss for Death-Related Malignancies and Cardiovascular Risk Factors. *Transpl. Proc.* **2003**, *35*, 1717–1719. [CrossRef]
44. Kocyigit, I.; Yilmaz, M.I.; Orscelik, O.; Sipahioglu, M.H.; Unal, A.; Eroglu, E.; Kalay, N.; Tokgoz, B.; Axelsson, J.; Oymak, O. Serum Uric Acid Levels and Endothelial Dysfunction in Patients with Autosomal Dominant Polycystic Kidney Disease. *Nephron Clin. Pract.* **2013**, *123*, 157–164. [CrossRef] [PubMed]
45. Tanner, G.A. Potassium Citrate/Citric Acid Intake Improves Renal Function in Rats with Polycystic Kidney Disease. *J. Am. Soc. Nephrol.* **1998**, *9*, 1242–1248. [CrossRef] [PubMed]
46. Tanner, G.A.; Tanner, J.A. Citrate Therapy for Polycystic Kidney Disease in Rats. *Kidney Int.* **2000**, *58*, 1859–1869. [CrossRef]
47. Tanner, G.A.; Tanner, J.A. Dietary Citrate Treatment of Polycystic Kidney Disease in Rats. *Nephron Physiol.* **2003**, *93*, P14–P20. [CrossRef]
48. Kalantar-Zadeh, K.; Jafar, T.H.; Nitsch, D.; Neuen, B.L.; Perkovic, V. Chronic Kidney Disease. *Lancet* **2021**, *398*, 786–802. [CrossRef]
49. Coyne, T.; Olson, M.; Bradham, K.; Garcon, M.; Gregory, P.; Scherch, L. Dietary Satisfaction Correlated with Adherence in the Modification of Diet in Renal Disease Study. *J. Am. Diet. Assoc.* **1995**, *95*, 1301–1306. [CrossRef]
50. Taylor, J.M.; Hamilton-Reeves, J.M.; Sullivan, D.K.; Gibson, C.A.; Creed, C.; Carlson, S.E.; Wesson, D.E.; Grantham, J.J. Diet and Polycystic Kidney Disease: A Pilot Intervention Study. *Clin. Nutr.* **2017**, *36*, 458–466. [CrossRef]
51. Testa, F.; Marchiò, M.; Belli, M.; Giovanella, S.; Ligabue, G.; Cappelli, G.; Biagini, G.; Magistroni, R. A Pilot Study to Evaluate Tolerability and Safety of a Modified Atkins Diet in ADPKD Patients. *PharmaNutrition* **2019**, *9*, 100154. [CrossRef]
52. Taylor, J.M.; Ptomey, L.; Hamilton-Reeves, J.M.; Sullivan, D.K.; Creed, C.; Carlson, S.E.; Wesson, D.E.; Grantham, J.J.; Gibson, C.A. Experiences and Perspectives of Polycystic Kidney Disease Patients Following a Diet of Reduced Osmoles, Protein, and Acid Precursors Supplemented with Water: A Qualitative Study. *PLoS ONE* **2016**, *11*, e0161043. [CrossRef] [PubMed]
53. Nowak, K.L.; Murray, K.; You, Z.; Gitomer, B.; Brosnahan, G.; Abebe, K.Z.; Braun, W.; Chapman, A.; Harris, P.C.; Miskulin, D.; et al. Pain and Obesity in Autosomal Dominant Polycystic Kidney Disease: A Post Hoc Analysis of the Halt Progression of Polycystic Kidney Disease (HALT-PKD) Studies. *Kidney Med.* **2021**, *3*, 536–545.e1. [CrossRef]
54. Moreno, B.; Crujeiras, A.B.; Bellido, D.; Sajoux, I.; Casanueva, F.F. Obesity Treatment by Very Low-Calorie-Ketogenic Diet at Two Years: Reduction in Visceral Fat and on the Burden of Disease. *Endocrine* **2016**, *54*, 681–690. [CrossRef] [PubMed]
55. Valenzano, A.; Polito, R.; Trimigno, V.; Di Palma, A.; Moscatelli, F.; Corso, G.; Sessa, F.; Salerno, M.; Montana, A.; Di Nunno, N.; et al. Effects of Very Low Calorie Ketogenic Diet on the Orexinergic System, Visceral Adipose Tissue, and ROS Production. *Antioxidants* **2019**, *8*, 643. [CrossRef] [PubMed]
56. Shillingford, J.M.; Piontek, K.B.; Germino, G.G.; Weimbs, T. Rapamycin Ameliorates PKD Resulting from Conditional Inactivation of Pkd1. *J. Am. Soc. Nephrol.* **2010**, *21*, 489–497. [CrossRef] [PubMed]
57. Dong, K.; Zhang, C.; Tian, X.; Coman, D.; Hyder, F.; Ma, M.; Somlo, S. Renal Plasticity Revealed through Reversal of Polycystic Kidney Disease in Mice. *Nat. Genet.* **2021**, *53*, 1649–1663. [CrossRef]
58. Unwin, D.; Unwin, J.; Crocombe, D.; Delon, C.; Guess, N.; Wong, C. Renal Function in Patients Following a Low Carbohydrate Diet for Type 2 Diabetes: A Review of the Literature and Analysis of Routine Clinical Data from a Primary Care Service over 7 Years. *Curr. Opin. Endocrinol. Diabetes Obes.* **2021**, *28*, 469–479. [CrossRef] [PubMed]
59. Nowak, K.L.; You, Z.; Gitomer, B.; Brosnahan, G.; Torres, V.E.; Chapman, A.B.; Perrone, R.D.; Steinman, T.I.; Abebe, K.Z.; Rahbari-Oskoui, F.F.; et al. Overweight and Obesity Are Predictors of Progression in Early Autosomal Dominant Polycystic Kidney Disease. *J. Am. Soc. Nephrol.* **2018**, *29*, 571–578. [CrossRef]

60. Sas, K.M.; Yin, H.; Fitzgibbon, W.R.; Baicu, C.F.; Zile, M.R.; Steele, S.L.; Amria, M.; Saigusa, T.; Funk, J.; Bunni, M.A.; et al. Hyperglycemia in the Absence of Cilia Accelerates Cystogenesis and Induces Renal Damage. *Am. J. Physiol. Ren. Physiol.* **2015**, *309*, F79–F87. [CrossRef]
61. Blijdorp, C.J.; Severs, D.; Musterd-Bhaggoe, U.M.; Gansevoort, R.T.; Zietse, R.; Hoorn, E.J.; DIPAK Consortium. Serum Bicarbonate Is Associated with Kidney Outcomes in Autosomal Dominant Polycystic Kidney Disease. *Nephrol. Dial. Transpl.* **2021**, *36*, 2248–2255. [CrossRef] [PubMed]