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Role of Obesity and Diet in Polycystic Kidney Disease (PKD) progression

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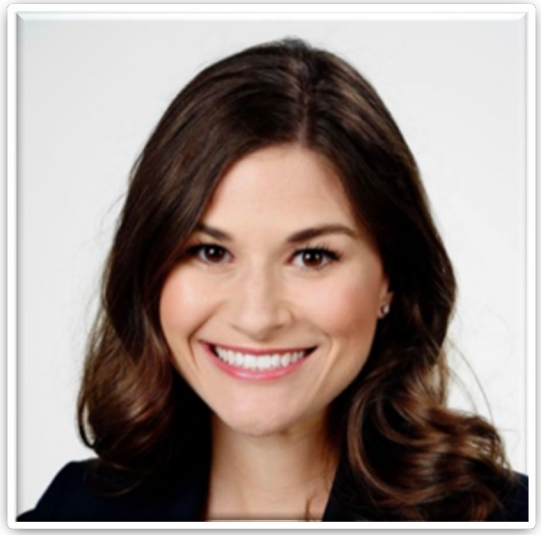
Panel

Kristen Nowak, PhD, MPH

Expert Speaker



Hannah N. Lambert, PharmD

Co-Moderator

Sachin Hajarnis, PhD

Co-Moderator

Objectives

- Overview of ADPKD
- Overweight and Obesity in ADPKD
- Dysregulated metabolism in ADPKD
- Dietary Studies in Humans
- Future Studies
- Key takeaways

What is PKD?

Polycystic kidney disease (PKD) is a group of monogenic disorders characterized by the propensity to develop numerous renal cysts[1]

- **Syndromic forms[1,2]** → **Rare, recessively inherited**
- **Autosomal dominant (ADPKD)[3,4]**
  - ***PKD1/PKD2*** **(~91%)**
  - ***NMD**** **(~9%)**
- **Autosomal recessive (ARPKD)[1]** → ***PKHD1***

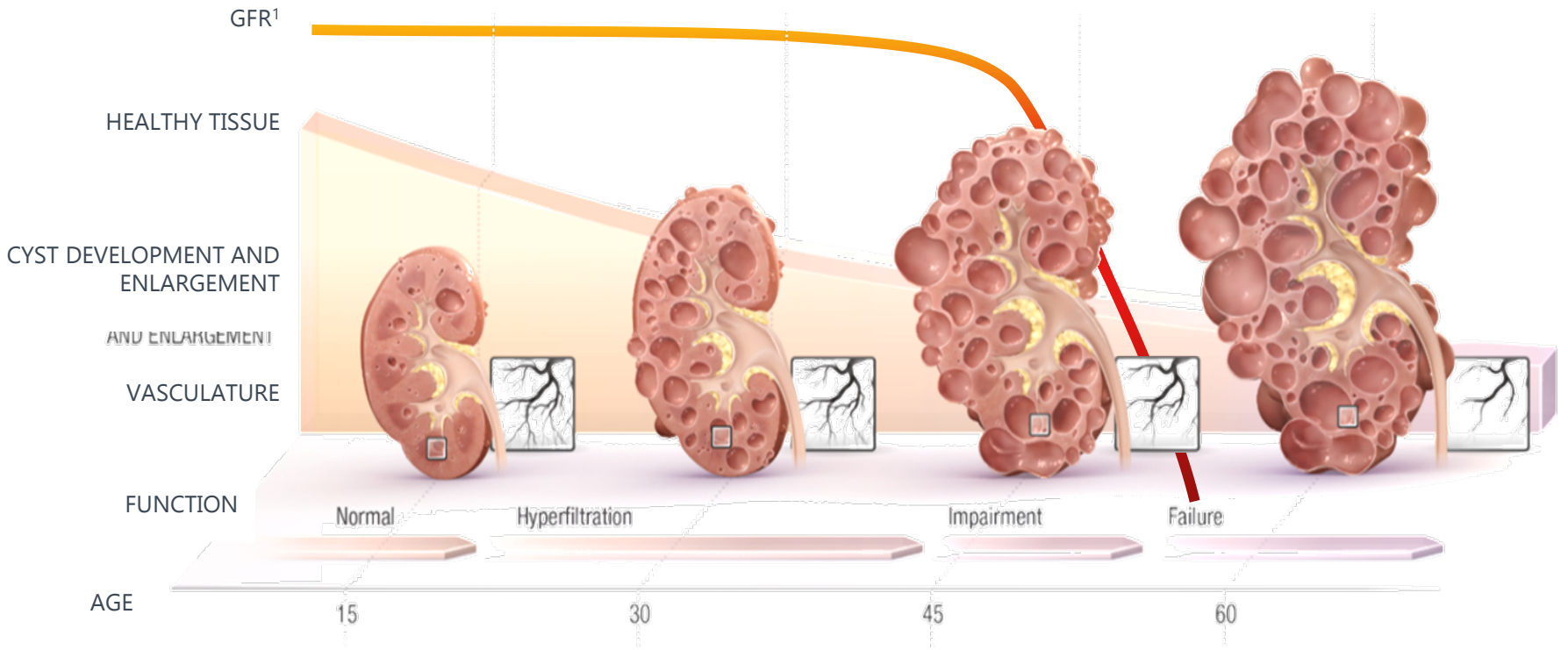
***The "no mutation detected" (NMD) group may contain those patients with mutations in other genes impacting cystic development, such as GANAB.[5]**

ADPKD=autosomal dominant PKD; ARPKD=autosomal recessive PKD; GANAB=gene encoding glucosidase II subunit-α; NMD=no mutation detected; PKD=polycystic kidney disease; *PKHD1*=polycystic kidney and hepatic disease 1.

1. Harris PC and Torres VE. (2009). *Annu Rev Med*. 60:321-337. 2. Jauregui AR et al. (2005). *Exp Cell Res*. 305(2):333-342. 3. Heyer CM et al. (2016). *J Am Soc Nephrol*. 27(9):2872-2884.
4. Irazabal MV et al. (2017). *Nephrol Dial Transplant*. 32(11):1857-1865. 5. Lanktree MB, Chapman AB. (2017). *Nat Rev Nephrol*. 13(12):750-768.

Total Kidney Volume by MRI Indicates Disease Severity Prior to Kidney Function Decline

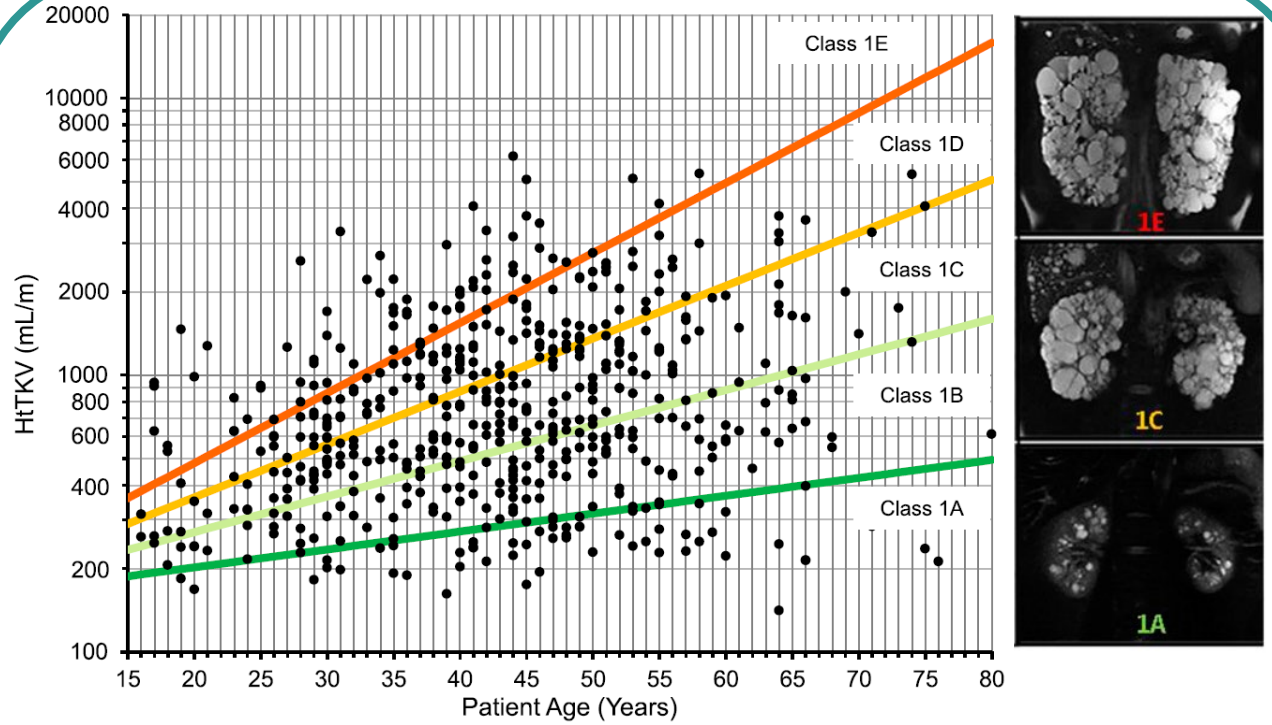
Kidney Disease Progression in ADPKD



ADPKD=autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate.

1. Grantham JJ et al. (2011). *Nat Rev Nephrol*. 7(10):556-566.

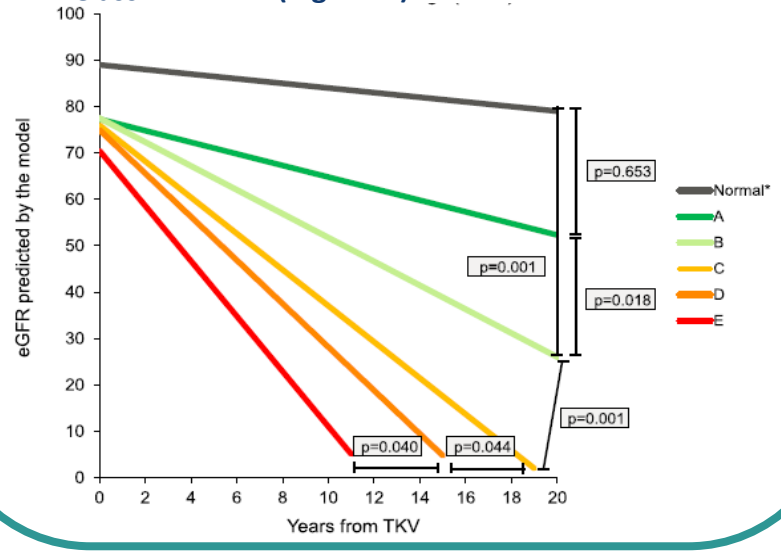
Baseline htTKV predicts risk of kidney function decline



Magnetic resonance images correspond to three 41-year-old patients with various kidney sizes. Top image corresponds to Class 1E, middle image corresponds to Class 1C, and the bottom image corresponds to Class 1A.[1]

Expected Annual Kidney Growth & Risk Stratification

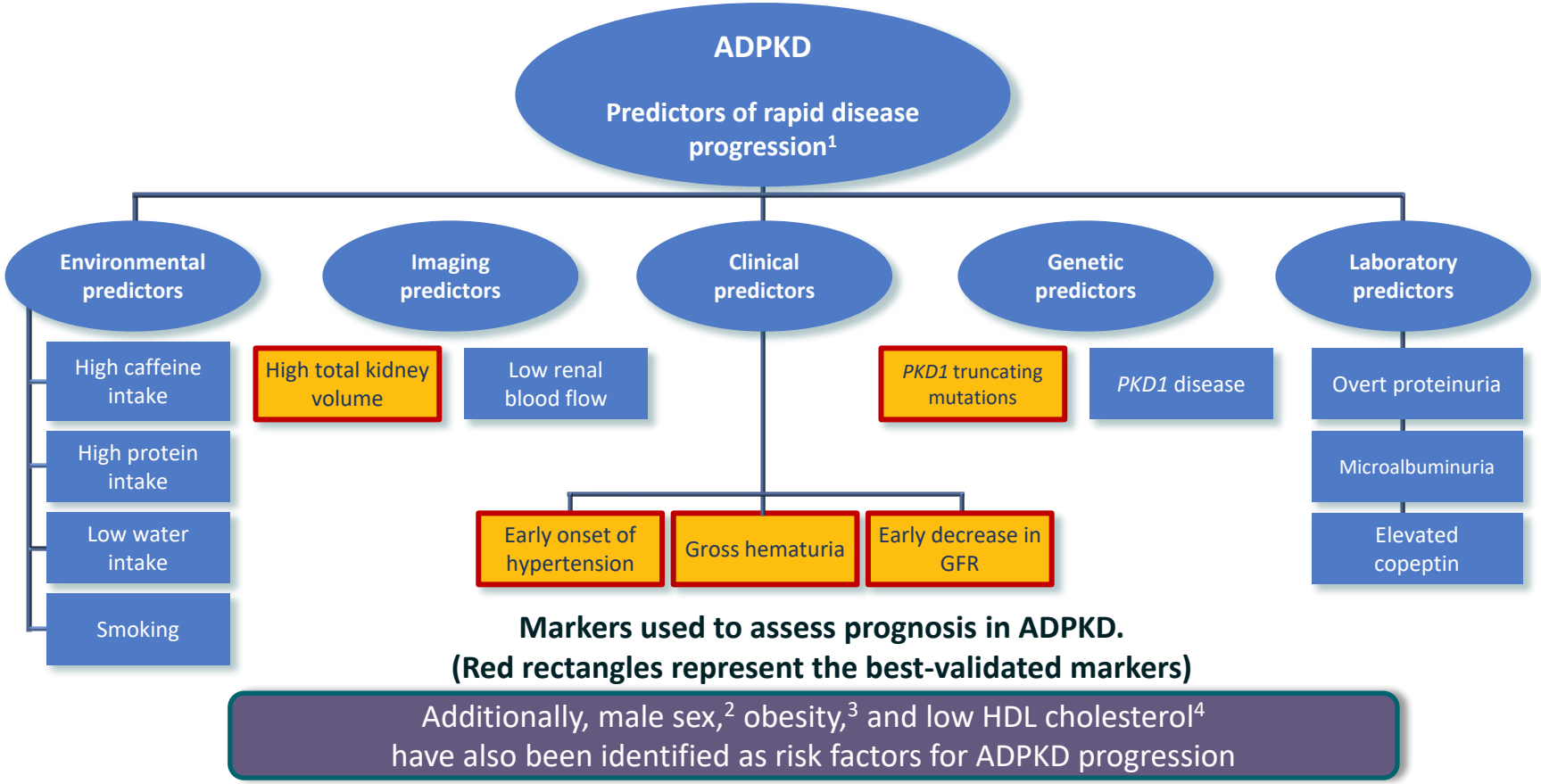
- **Class 1A: 1.5% (low risk)**
- **Class 1B: 1.5-3.0% (intermediate risk)**
- **Class 1C: 3-4.5% (high risk)**
- **Class 1D: 4.5-6% (high risk)**
- **Class 1E: >6% (high risk)**



eGFR=estimated glomerular filtration rate; htTKV=height-adjusted total kidney volume.

1. Irazabal MV et al. *J Am Soc Nephrol*. 2015; 26(1): 160–72

Predictors of Rapid Disease Progression in ADPKD



ADPKD=autosomal dominant polycystic kidney disease; GFR=glomerular filtration rate; HDL=high-density lipoprotein; *PKD1*=polycystic kidney disease gene 1.

1. Figure adapted from Gansevoort RT et al. (2016). *Nephrol Dial Transplant.* 31(3):337-348. 2. Schrier RW et al. (2014). *J Am Soc Nephrol*. 25(11):2399-2418. 3. Nowak KL, et al. (2018). *J Am Soc Nephrol*. 29(2):571-578. 4. Torres VE, et al. (2011). *Clin J Am Soc Nephrol*. 6(3):640-647.

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Overweight and Obesity in ADPKD

Overweight and Obesity in ADPKD

- Prevalence of overweight/obesity in ADPKD is increasing, similar to the general population
- Overweight and obesity are predictors of progression in early ADPKD
- In the HALT PKD Study A (n = 441)
  - Annual percent change in total kidney volume (TKV) was greater with Increasing Body Mass Index (BMI) category.
  - Associations (OR [95%] CI) of BMI categories with annual %Δ in TKV (≥7% vs. <5%)
    - Normal weight : Ref
    - Overweight : 2.02 [1.15, 3.56]
    - Obese : 3.76.[1][1.81, 7.80]
  - Associations (Beta-estimates [95%] CI) of BMI categories with eGFR slope (kidney function)
    - Normal weight : Ref
    - Overweight : -0.20 [-0.08, 0.03]
    - Obese : -0.08.[1][-0.15, -0.02]

1. Nowak KL, et al. (2018). *J Am Soc Nephrol*. 29(2):571-578.

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Dysregulated Metabolic Pathways in Obesity and ADPKD

ADPKD and Nutrient Metabolism Have Converging Pathways

- Central cellular processes that are known to be impaired in ADPKD pathology and are characteristic of metabolic reprogramming include autophagic flux, glycolysis, fatty acid oxidation, and mitochondrial function.
- Central signaling nodes that overlap between ADPKD and metabolic response include mammalian target of rapamycin(mTOR), AMP-activated kinase (AMPK), sirtuin-1 (SIRT-1), IGF-I, and peroxisome proliferator–activated receptor-alpha/gamma (PPARα/γ).
- Alterations in diet intake or composition can affect many of these overlapping processes/pathways. Similarly, multiple pharmacologic approaches that are known to alter metabolic reprogramming target these central processes/signaling hubs.
- Collectively, this suggests that such interventions have high potential in alleviating ADPKD in humans.

1. Nowak, KL and Hopp, K. (2020*) CJASN* 15(4):p 577-584.

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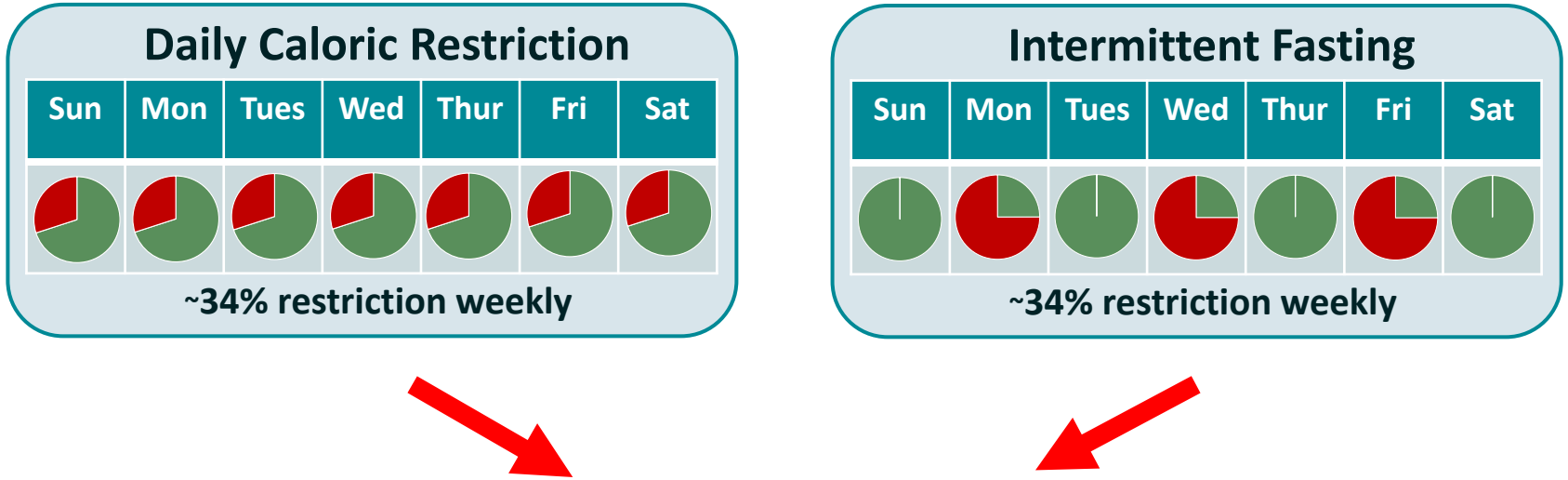
Dietary Studies in Humans:

Pilot Studies on Daily Caloric Restriction and Intermittent Fasting

Pilot Study: Weight Loss via Daily Caloric Restriction (DCR) or Intermittent Fasting (IMF)



Aim 1) Feasibility: enrollment, retention, weight loss

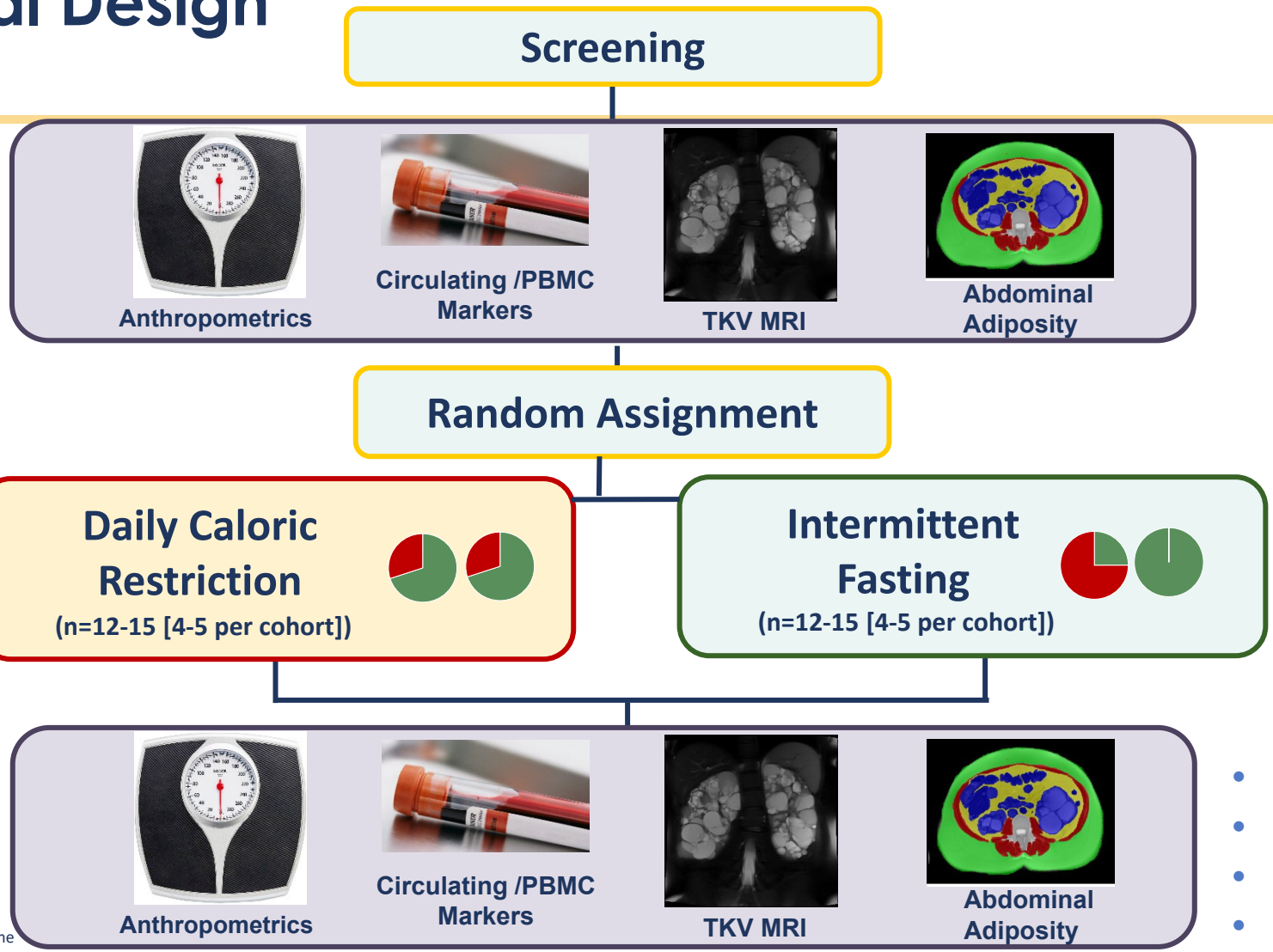
Aim 2) Safety, acceptability, tolerability

Aim 3) Circulating/PBMC markers, MRI

1. Hopp K, et al. (2021). iScience. 25(1):103697.

PBMC = Peripheral blood mononuclear cells

Experimental Design



- Feasibility
- Safety
- Acceptability
- Tolerability

1. Hopp K, et al. (2021). iScience. 25(1):103697.

PBMC = Peripheral blood mononuclear cells, TKV = Total Kidney volume

Baseline Characteristics

Variable	Daily Caloric Restriction (n=15)	Intermittent Fasting (n=13)	All (n=28)
Age, yrs	47±12	46±6	46±9
Sex, n (%) male	6 (40%)	6 (46%)	12 (43%)
Race/Ethnicity, n (%) Non-Hispanic White	13 (87%)	11 (85%)	24 (86%)
Weight, kg	103.3±15.7	97.7±10.7	100.7±13.7
BMI, kg/m^2	34.6±5.1	34.8±5.1	34.7±5.0
CKD-EPI eGFR, $ml/min/1.73m^2$	64±26	75±16	69±22
htTKV, ml/m	994 (589, 1180)	835 (476, 1363)	916 (476, 1363)
SBP, mmHg	116±12	125±12	120±13
DBP, mmHg	76±8	84±9	80±9

1. Hopp K, et al. (2021). iScience. 25(1):103697.

Results: Effects of DCR vs IMF on Weight Loss

- Both groups achieved clinically significant weight loss at 3 months

  DCR: -7.1+4.2%

  IMF: -5.5+3.3%

- At 12 months, participants in the DCR group had lost additional weight, while weight loss in the IMF group plateaued

  DCR: -9.1+6.0%

  IMF: -4.9+5.6%

1. Hopp K, et al. (2021). iScience. 25(1):103697.

Results: Effect of DCR and IMF on Adipose tissue, htTKV and eGFR

Adipose tissue

MRI quantification of data pooled across both groups showed that the following were significantly reduced at 12 months -

- Abdominal subcutaneous adipose tissue (SAT),
- visceral adipose tissue (VAT)
- total adipose tissue (TAT)

htTKV

Although htTKV was an exploratory endpoint (small sample size and short follow-up of 1 year), htTKV was not significantly different between groups, but qualitatively low in comparison to historical data, despite comparable clinical characteristics

eGFR

Neither group demonstrated a change in eGFR, although %Δ in weight was inversely correlated with ΔeGFR in the DCR group (r=-0.63, p=0.04)

1. Hopp K, et al. (2021). iScience. 25(1):103697.

Results: Associations of TKV with Weight Loss and Abdominal Adiposity Loss

- At 12 months, annual %Δ in htTKV was highly correlated with:
  - %Δ in weight,
  - Change in Body Mass Index (BMI),
  - Change in Visceral adipose Tissue (VAT),
  - Change in Total Adipose Tissue (TAT),
  - No correlation with change in Abdominal Subcutaneous Adipose Tissue (SAT)

- When participants were divided into losing clinically significant weight (>5%):
  - Kidney growth was significantly slower in those that did lose weight.

1. Hopp K, et al. (2021). iScience. 25(1):103697.

Results: Safety and Tolerability

Treatment-Emergent Adverse Events	Daily Caloric Restriction	Intermittent Fasting
Hunger	5 (33%)	11 (85%) *
Gastrointestinal distress	4 (27%)	8 (62%)
Fatigue	1 (7%)	8 (62%) *
Lightheadedness/dizziness	3 (20%)	5 (39%)
Cold Intolerance	1 (7%)	7 (54%) *
Change in mood	2 (14%)	4 (31%)
Irritability	1 (7%)	6 (46%) *
Insomnia	2 (13%)	7 (54%) *
Headache	2 (13%)	4 (31%)
Impaired concentration / cognitive difficulties	0 (0%)	3 (23%)
Tremor	0 (0%)	1 (8%)

1. Hopp K, et al. (2021). iScience. 25(1):103697.

Limitations of the study

- Since the human study was designed as a pilot and feasibility study:
  - The sample size is small
  - htTKV data while an *a priori* endpoint were exploratory
  - A control group was not included

- Statistical testing was not adjusted for multiple comparisons given the exploratory nature of many outcomes in the human study; thus, significant *p* values may be spurious.

1. Hopp K, et al. (2021). iScience. 25(1):103697.

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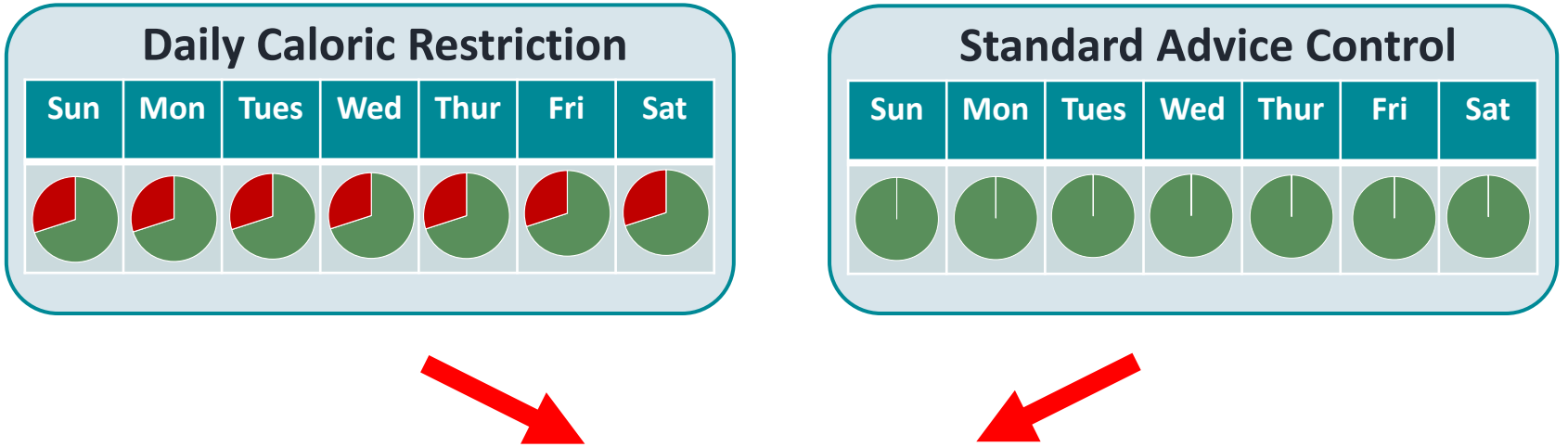
Future Studies

Future Studies :
New Phase II - R01-Funded Study - Weight Loss via Daily Caloric Restriction



Aim 1) Kidney growth (TKV by MRI) at 2 years

Aim 2) Abdominal adiposity

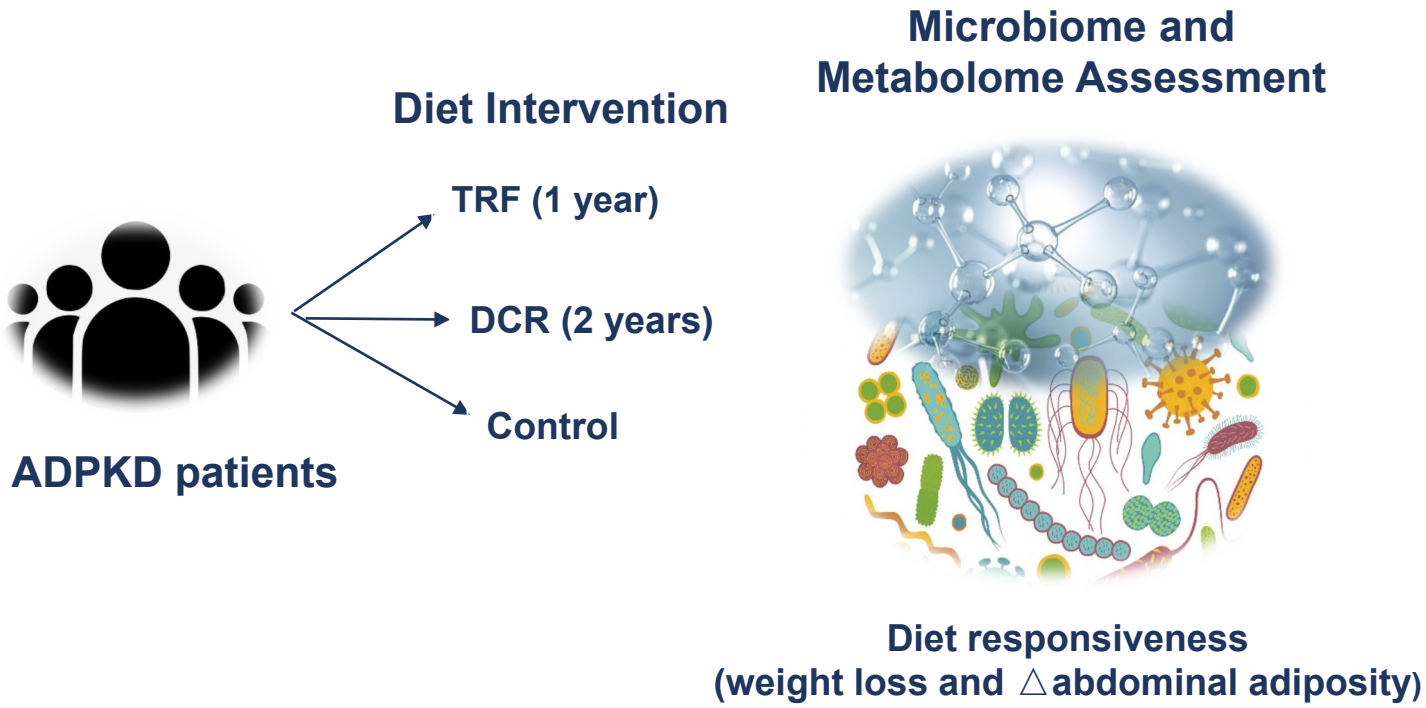
Aim 3) Markers in blood, PBMCs, subcutaneous fat tissue

Aim 4) Further evaluate safety

PBMC = Peripheral blood mononuclear cells, TKV = Total Kidney Volume

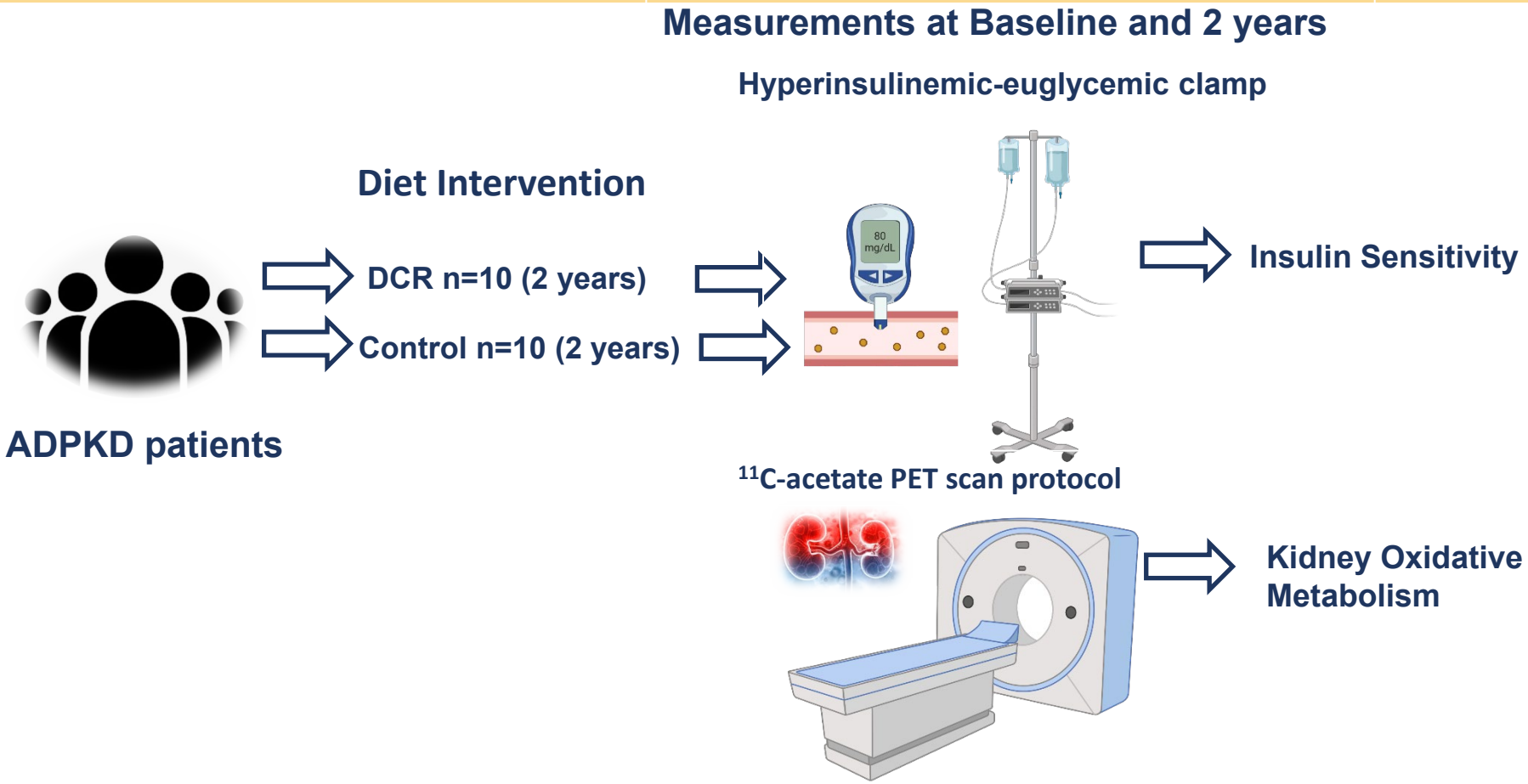
Future Studies :

Metabolome and Microbiome Profiling in Response to Dietary Interventions in Patients with ADPKD



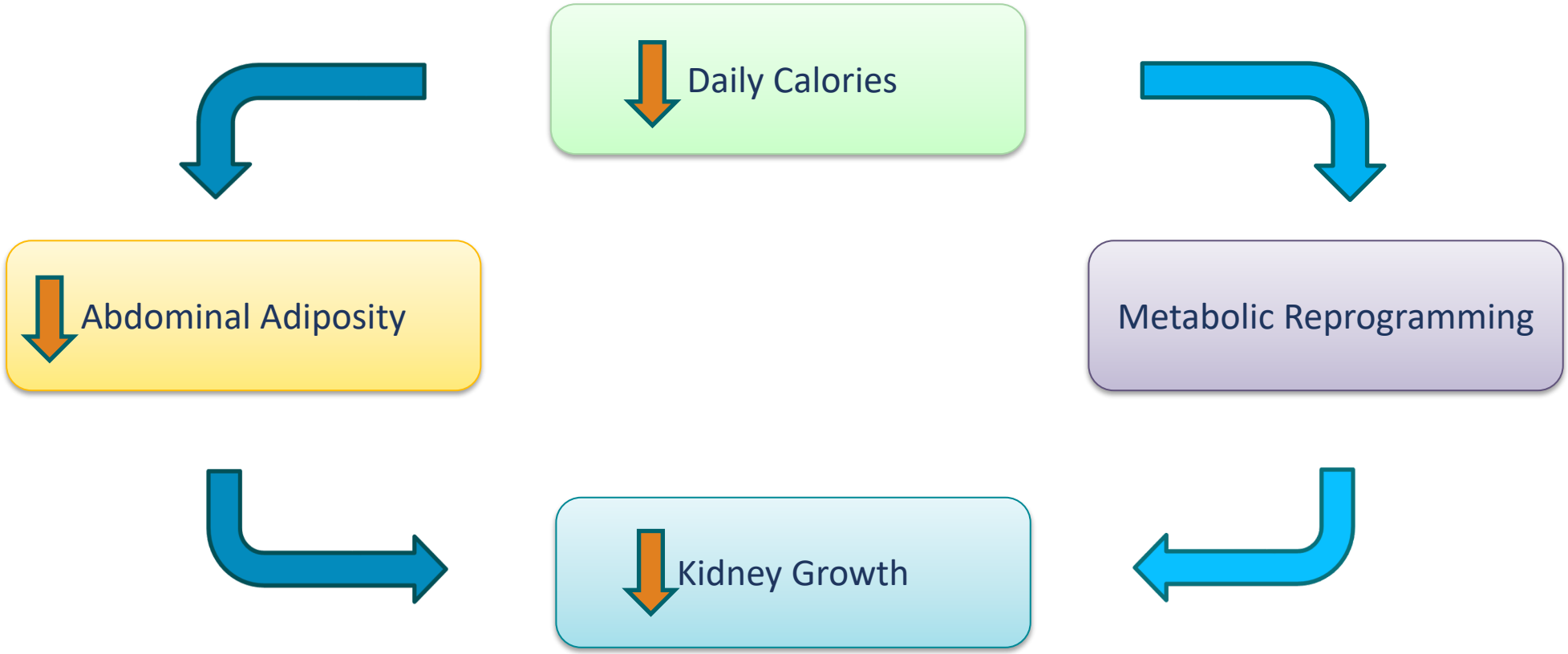
TRF = Time Restricted Feeding, DRC = Daily caloric Restriction

Future Studies : Renal Oxygen Consumption, Insulin Sensitivity, and Daily Caloric Restriction in ADPKD



DRC = Daily caloric Restriction

Working Hypothesis:



Key Takeaways :

- Overweight and Obesity are Predictors of Progression in Early ADPKD
- Clinically significant weight loss in humans occurred with both DCR and IMF. However, weight loss was greater, and adherence and tolerability were better with DCR.
- Slowed kidney growth correlated with body weight and visceral adiposity loss, independent of dietary regimen.
- Weight loss may slow kidney growth in overweight and obese adults with ADPKD independent of the dietary regimen implemented.
- Caloric Restriction is a feasible strategy to induce weight loss and possible slow disease progression in overweight/obese ADPKD patients.

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