KIDNEY RESEARCH INSTITUTE
A collaboration between Northwest Kidney Centers and UW Medicine

Division of Nephrology
University of Washington

KIDNEY DISEASE AND FUNCTIONAL DECLINE IN OLDER ADULTS

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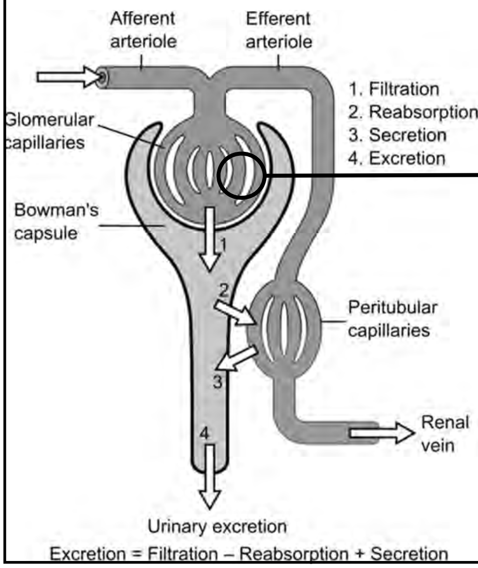
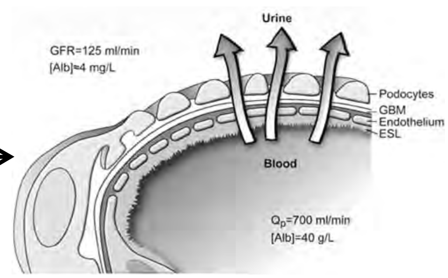
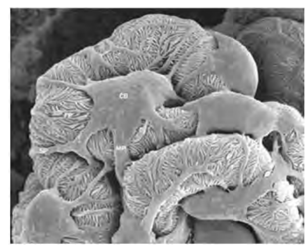
Outline

- Measurement of kidney function
- Definition of CKD
- Management issues for older adults with CKD (Adult vs Older Adults)
- Functional decline in kidney disease
- Dialysis versus conservative management in CKD
- Summary

Measurement of Kidney Function
Secretion vs Filtration

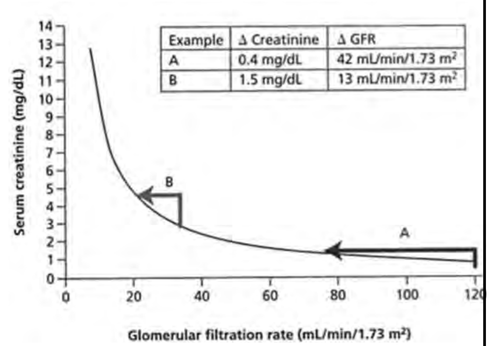






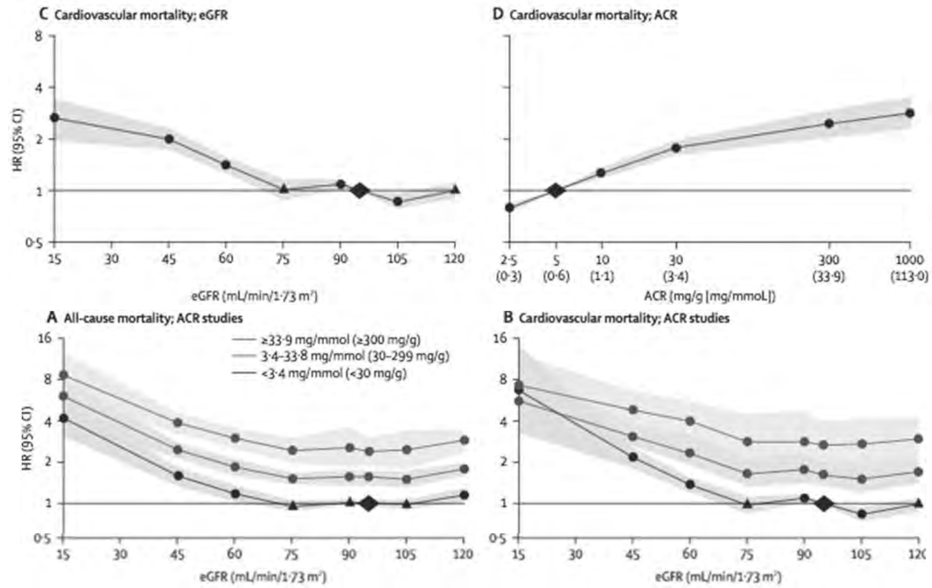
Clinical evaluation of kidney function:
Estimated Glomerular Filtration Rate (GFR)

- Relationship between GFR and Serum Creatinine not linear
- Problems with Creatinine
  - **Confounded by muscle mass (malnutrition, amputation, cirrhosis)**
  - Also secreted by tubules (impaired by trimethoprim, cimetidine, cobicistat, pyrimethamine)



Example	Δ Creatinine	Δ GFR
A	0.4 mg/dL	42 mL/min/1.73 m²
B	1.5 mg/dL	13 mL/min/1.73 m²

Association of kidney function with mortality

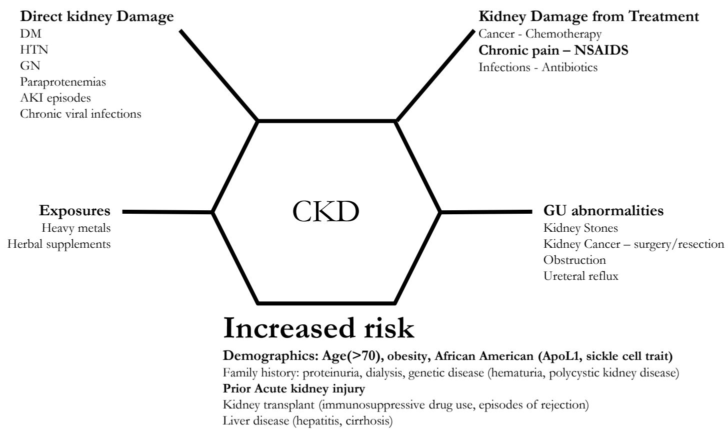


Matsushita K et al. Lancet. 2010; 375:2073-2081

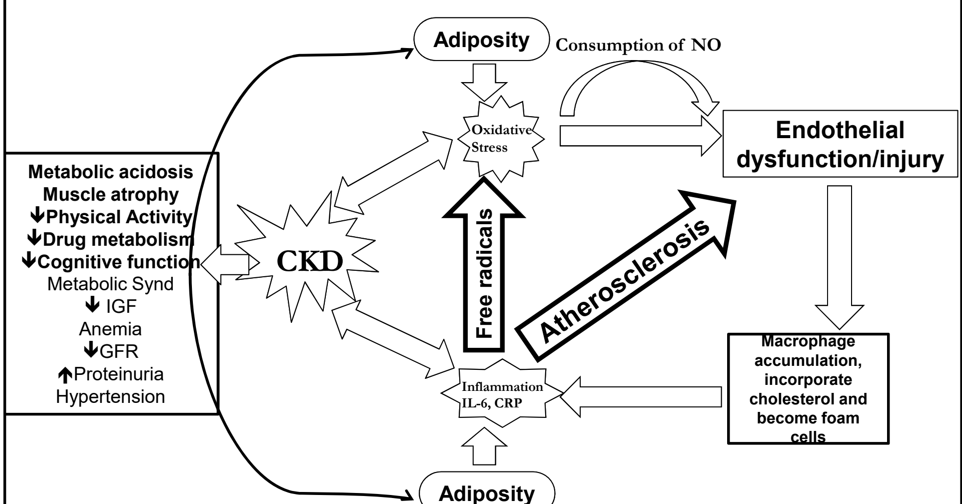
Definition of CKD

Criteria for CKD (either of the following present for >3 months)	
Markers of kidney damage	Albuminuria (AER 30mg/24hr; ACR 30mg/g) Urine sediment abnormalities Structural abnormalities detected by imaging History of kidney transplant
Decreased GFR	GFR<60ml/min/1.73m^2

Possible causes of CKD



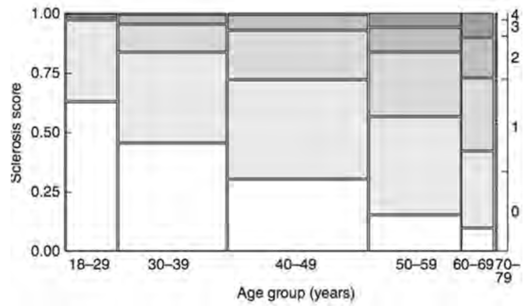
Malnutrition-Inflammation Complex Syndrome in CKD



Adapted from Moinuddin I, Leehey DJ. Adv Chron Kidney Dis. 2008. 15(1):83-96.

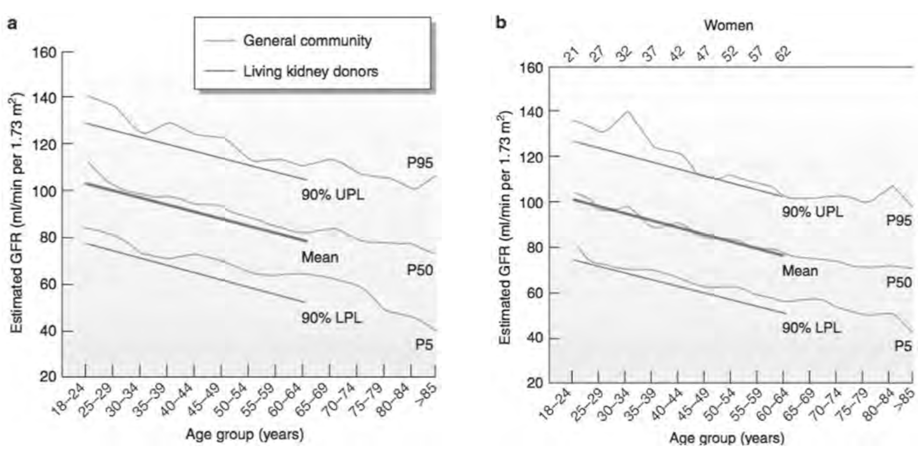
Age-related changes in kidney

- Glomerulosclerosis
- Tubular atrophy
- Interstitial Fibrosis
- Arteriosclerosis
- Increased volume of glomeruli and decreased glomerular density with age



Glassock RJ, Rule AD. Kidney Int. 2012. 82:270-277

Aging and the kidney



Rule AD, Semret MH et al. Mayo Clinic Proc 2011; 86: 282-290

Prognosis of CKD by GFR and Albuminuria – KDIGO 2012

CKD prognosis determined by GFR and Albuminuria categories				**Persistent albuminuria categories**			**Evaluation & Plan**
				A1	A2	A3	
				Nl-mild increase	Moderate	Severe	
				<30mg/g	30-300mg/g	>300mg/g	
GFR categories (ml/min/1.73m^2)	1	Nl/high	≥90				Evaluate chronicity and cause.
	2	Mild	60-89				
	3a	Mild-moderate	45-59				
	3b	Moderate-severe	30-44				Check PTH, Ca, Phos, Vit D and treat.
	4	Severe	15-29				Prepare for dialysis, Anemia W/U, Dietary couseling (K, Phos, protein)
	5	Failure	<15				Consider dialysis or Transplant

Management Issues

- Prevent progression or adverse outcomes
  - Hypertension
  - Glycemic control
  - Metabolic acidosis
  - CKD-Mineral Bone Disorder

Case 1

70 y/o male with T2DM found to have microalbuminuria. He has DM for the last 15 years. Hgb A1c 8%. BP is 146/88. The rest of his exam is normal except for mild background diabetic retinopathy. Serum labs: Cr 1.8 (GFR37 ml/min per 1.73m^2). Urinalysis shows +1 protein and Urine Albumin/Cr ratio of 150mg/gm.

Questions

- How may chronic kidney disease impact treatment of diabetes in older adults?
- What are the recommendations for blood pressure control in older adults?
- What are the pitfalls of applying clinical trial results to the care of older adults patients in the outpatient setting?
- What can be done to mitigate progression of his kidney disease?
- What is the risk of progression to dialysis vs. death in the older adult population?

Management challenges in older adults with CKD

- Glycemic control
- Blood pressure targets
- Progression to dialysis

Glycemic Control in CKD

• Control of blood glucose paramount to prevent cardiovascular disease.

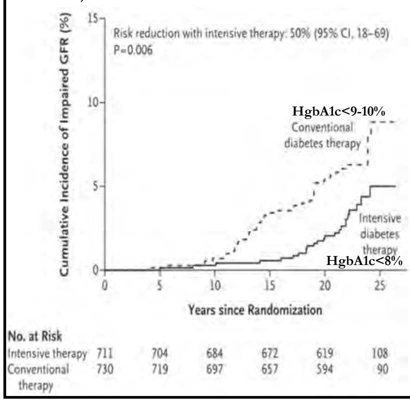
• General Population: In UKPDS of type 2 DM, 1 % reduction in A1C was associated with a 35% reduction in microvascular endpoints, an 18% reduction in myocardial infarction, and a 17% reduction in all-cause mortality.

•Challenge of hypoglycemia in older adults

Tight glycemic control in T1DM vs T2DM – Experience from Randomized Trials

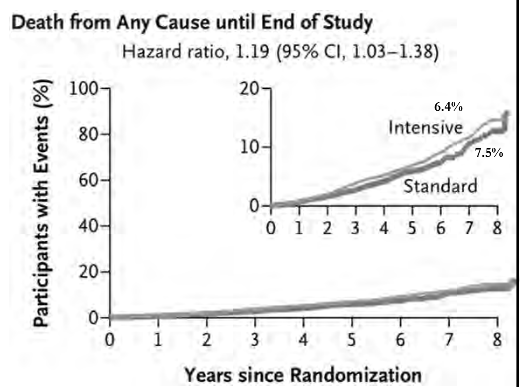
Incident T1DM
DCCT/EDIC trial

Tight glycemic control delays:
(1) onset of albuminuria and over proteinuria
(2) Risk of developing reduced renal function (GFR<60 and ESRD)



Prevalent T2DM
ACCORD

Tight glycemic among those with CVD or risk factors for CVD:
(1) Greater risk of all-cause mortality
(2) Greater risk of death from cardiovascular causes

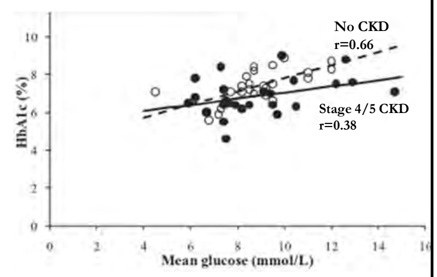


Glycemic control in T2DM

- KDOQI – Target in CKD
  - Target hemoglobin A1c (HbA1c) of ~□ 7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD

Accuracy of Hgb A1c in CKD

- Stage 3 and Stage 4 CKD: glucose levels higher than expected for level of Hgb A1c
- Iron supplementation or EPO administration leads to modest fall in Hgb A1c of 0.5-0.7% along with rise in total Hgb



Hypoglycemia more common in older adults with CKD

Hodge M, McArthur E, et al. AJKD 2017

- Population based cohort study of older adults (mean age 75) in Ontario Canada from April 2002 through March 2013
- Exposure: eGFR stage, Albuminuria and use of antihyperglycemic medications
- Outcome: 3 year incidence of hospital encounter with hypoglycemia (emergency room or inpatient encounter) (ICD-10 code)

Higher risk category by eGFR and Albuminuria associated with greater risk of hypoglycemia in older adults

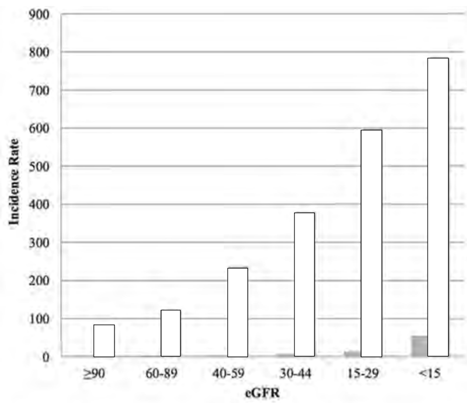


Figure 1. The 3-year incidence rate of hypoglycemia per 10,000 person-years stratified by estimated glomerular filtration rate (eGFR) stage (mL/min/1.73 m^2) and use of antihyperglycemic medications. Dark bars represent antihyperglycemic medication users. Light bars represent antihyperglycemic medication nonusers.

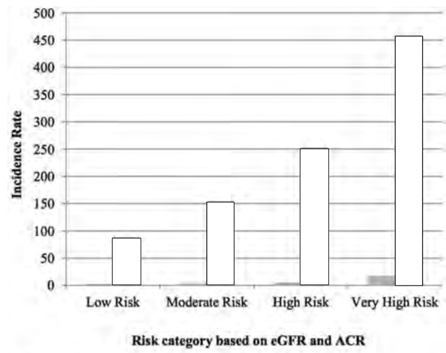
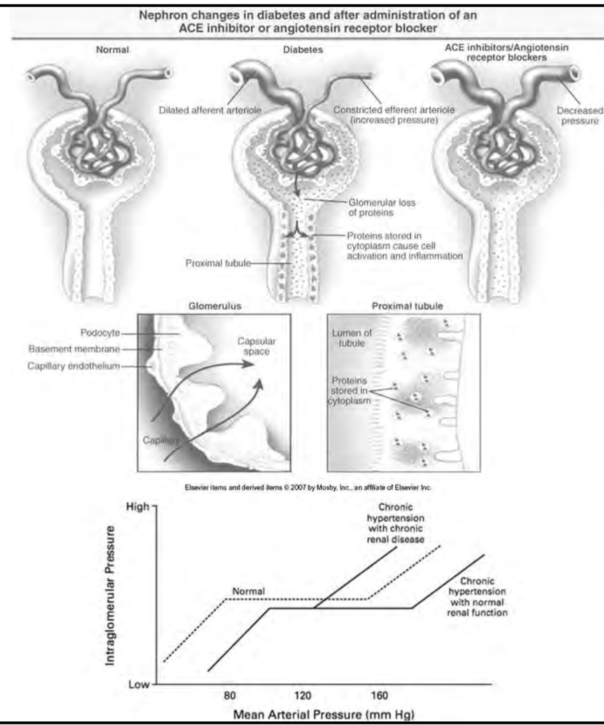


Figure 2. The 3-year incidence rate of hypoglycemia per 10,000 person-years stratified by estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) risk category (eGFR in mL/min/1.73 m^2; ACR in mg/mmol) and antihyperglycemic medication use. Dark bars represent antihyperglycemic medication users. Light bars represent antihyperglycemic medication nonusers.

Potential reasons for increased frequency of hypoglycemia in CKD in older adults

- Anti-hyperglycemic medications metabolized by the kidney accumulate in advanced disease
- Polypharmacy and comorbidity (cognitive dysfunction)
  - **Beta blockers mask hypoglycemic symptoms**
- Malnourished (lower glycogen stores)
- Impaired glucose counter-regulation and reduced kidney gluconeogenesis

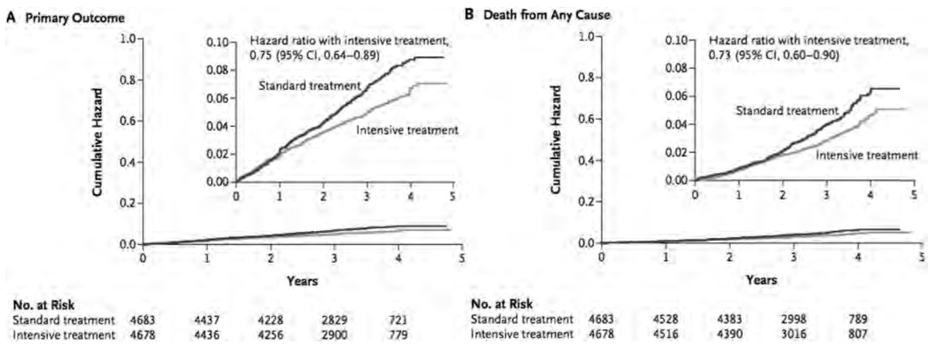


Systolic Blood Pressure Intervention Trial (SPRINT)

NEJM. 2015. 373(22):2103-2116

- RCT of intensive BP control (<120) vs usual control (<140).
- 9361 non-diabetic adults at high risk of CVD
  - 2636 older adults (75 years and older) with high risk of cardiovascular disease and without diabetes.
  - Excluded eGFR<20 or proteinuria>1g/day

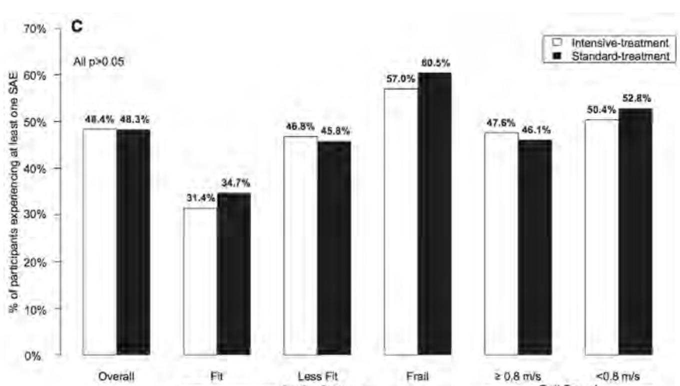
Intensive control associated with lower risk of cardiovascular events and CVD death



Applying Systolic Blood Pressure Intervention Trial (SPRINT) Results to Older Adults.

Supiano MA, Williamson JD. JAGS. 2016. 65:16-21, 2017

- No difference in percent of older adults experiencing at least 1 serious adverse event



Efficacy vs Effectiveness

- **Inherent difference in monitoring/followup in clinical trials vs. real world (usual care)**

Table 1. Comparison Between Usual Care and Randomized Clinical Trial Hypertension Management

Care Component	Usual Care	Randomized Clinical Trial
BP measurement	Manual aneroid or digital sphygmomanometer Single reading	Automated office BP device Standard protocol with 5 minute rest period Three serial readings
Orthostatic BP readings	Only symptom driven	Routinely assessed
BP monitoring visits	Physician directed No set frequency Target often not clearly established	Team approach Protocol directed: monthly × 3, then every 3 months Standardized protocol to meet defined target
Medication management	Drug costs borne by patients Adherence not always monitored	Free medications Strict adherence checks
Medication titration	Ad lib	Standardized protocol
Adverse events	Not routinely assessed	Close monitoring

Expert BP recommendations

- ACE-I/ARB dose adjustment Q4-8wks
- Safe to continue if GFR decreases <30% over 4 months and serum K is <5.5mEq/L.
- **"Go-slow" treatment approach for older adults**

Table 1. Summary of national and international recommendations for target BP

Guideline	Younger Target (mmHg)	Older Target (mmHg)	Diabetes Target (mmHg)	CKD Target (mmHg)
2014 Evidence-Based Guidelines for the Management of High Blood Pressure[1]	<140/90	>60 years of age: <150/90	<140/90	<140/90
2013 Canadian Hypertension Education Program[6]	<140/90	SBP=150	<130/80	<140/90
2013 ESH/ESC Guidelines[13]	<140/90	<80 years of age: 140–150; consider <140 if tolerated; >80 years of age: 140–150	<140/85	<140/90
American Society of Hypertension and the International Society of Hypertension[10]	<140/90	>80 years of age: <150/90	<140/90	<140/90; consider <130/80 if albuminuria
American Diabetes Association[17]			<140/80	
KDIGO Blood Pressure Work Group[11]				ACR<30: 140/90; ACR>30: 130/80

ACR, albumin/creatinine ratio.

Reisen E, Harris RC, Rahman M. JASN 25:2419-2424. 2014

Acidosis and progression of kidney disease

- Health ABC study: 3075 older adults age 70-79 without functional limitation
  - Exposure: Serum bicarbonate
  - Outcome: Change in kidney function (GFR from combined cystatin C and Creatinine equation) over 7 years

- Metabolic acidosis was associated with faster decline in kidney function.

Serum Bicarbonate Concentrations and Kidney Disease Progression in Community-Living Elders: Health ABC Study

Goldenstein L, Driver TH et al. Am J Kidney Dis. 2014; 64 (4): 542-549

Table 2. Association of Baseline Bicarbonate Category With Annual Change in eGFR

	<23.0 mmol/L	23.0-28.0 mmol/L	>28.0 mmol/L
No. of participants (%)	85 (8%)	887 (83%)	101 (9%)
Annual change in eGFR			
Unadjusted	−0.436 (−0.870 to −0.003); 0.05	(referent group)	−0.337 (−0.735 to −0.067); 0.1
Model 1[a]	−0.552 (−0.974 to −0.131); 0.01	(referent group)	−0.270 (−0.658 to 0.118); 0.2
Model 2[b]	−0.543 (−0.965 to −0.121); 0.01	(referent group)	−0.245 (−0.640 to 0.150); 0.2

Note: Annual change in eGFR is expressed as mL/min/1.73 m^2 per year. Unless otherwise indicated, values are given as Δ (95% confidence interval); *P* value.

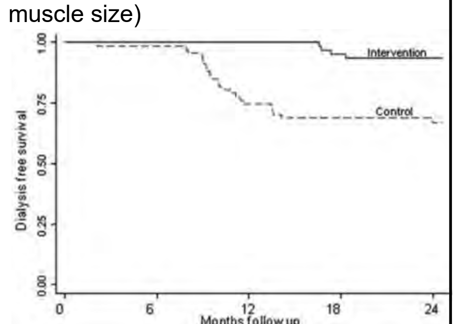
Abbreviation: eGFR, estimated glomerular filtration rate.

[a]Adjusted for age, race, sex, clinical site, baseline eGFR, and urine albumin-creatinine ratio.

[b]Adjusted for model 1 variables plus diabetes, systolic blood pressure, obstructive lung disease, smoking, renin-angiotensin-aldosterone system inhibitor use, and diuretic use.

Acidosis and progression

- Randomized trial of oral sodium bicarbonate among advanced CKD (CrCl 15-30ml/min) with metabolic acidosis (serum bicarbonate 16-20mmol/L)
- Bicarbonate supplementation in stage 4-5 CKD associated with lower risk of progression to dialysis
  - Slower progression to ESRD.
  - Improved nutritional parameters (albumin, muscle size)
  - Better control of potassium



De Brito-Ashurst et al. JASN. 20:2075-2084, 2009.

Lower physical activity is associated with more rapid progression of kidney disease

Robinson-Cohen C, Katz R, et al. Arch Intern Med. 2009; 169 (22): 2116-2123

- 4011 ambulatory participants in the Cardiovascular Health Study 65 years and older. Mean age of 76 years
- Exposure: physical activity score combining self-reported leisure-time physical activity (kcal/wk) and walking pace.
- Outcome: Change in kidney function measured over 7 years
  - Rapid kidney function decline: GFRcysc loss of more than 3ml/min/1.73m^2 per year.

Lower physical activity is associated with more rapid progression of kidney disease

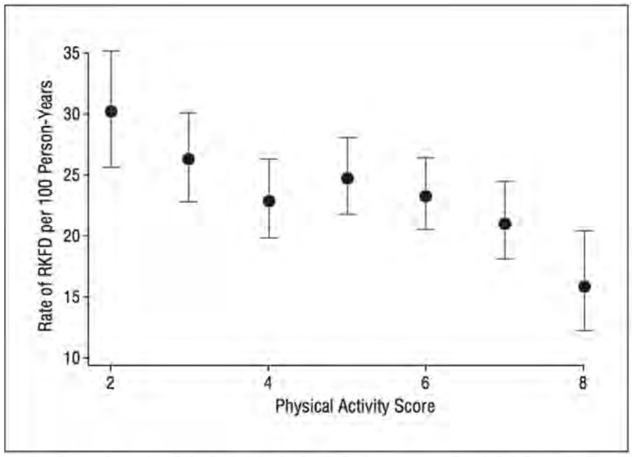
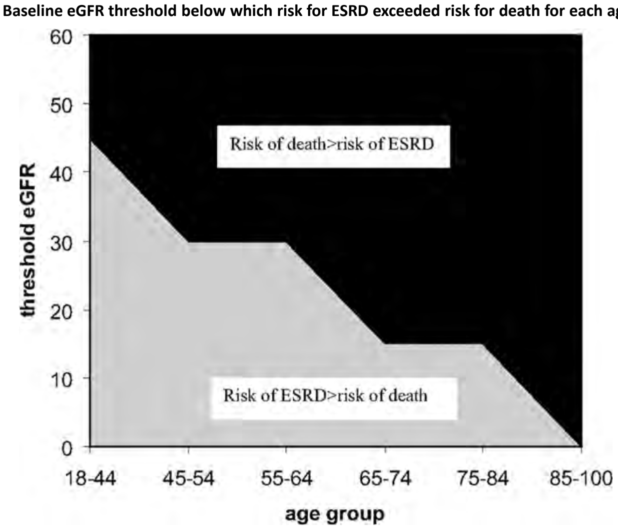


Figure. Rate of rapid kidney function decline (RKFD) by physical activity score. Data points represent risk estimates; error bars, 95% confidence intervals.

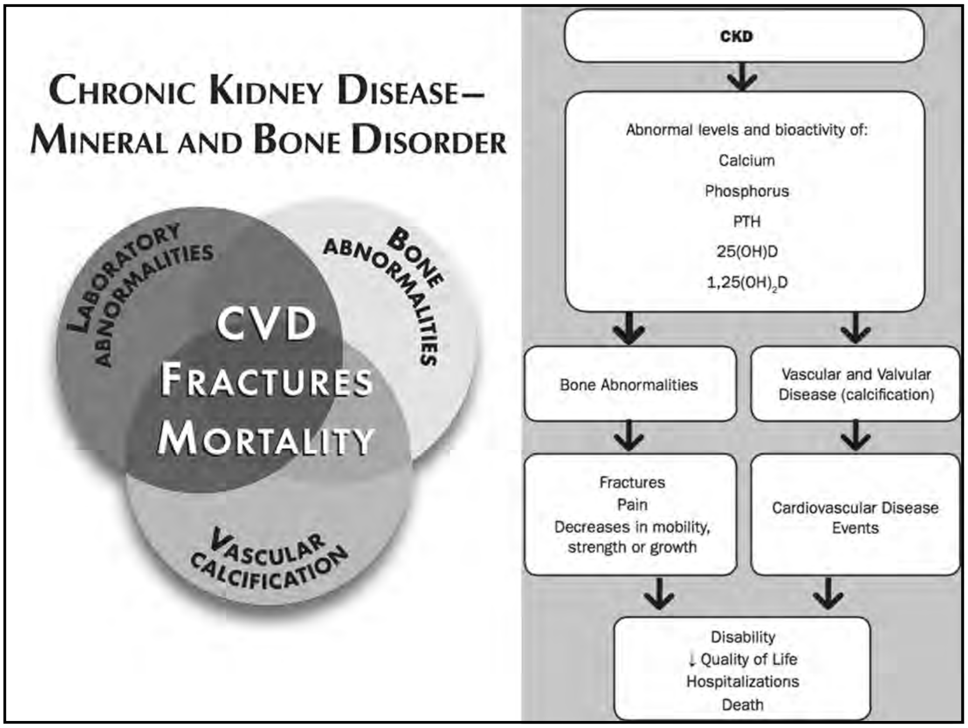
Progression to ESRD Depends on Age

Baseline eGFR threshold below which risk for ESRD exceeded risk for death for each age group

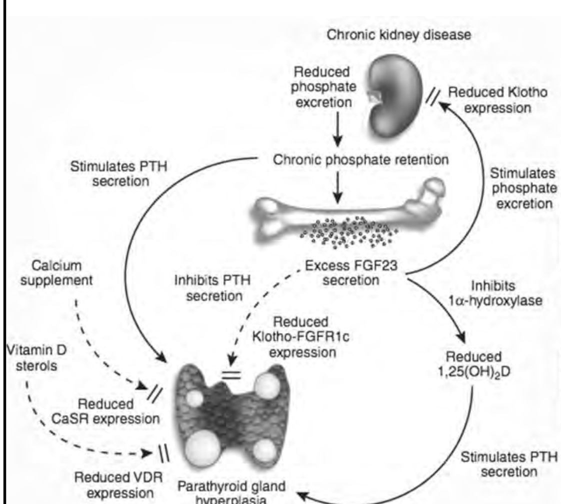


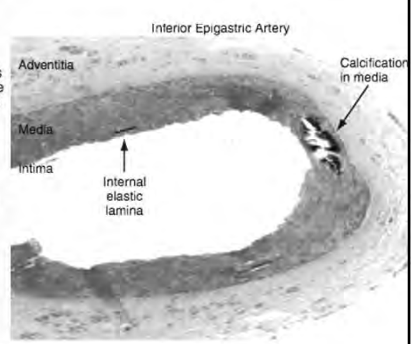
O'Hare, A. M. et al. J Am Soc Nephrol 2007;18:2758-2765

JASN



Vascular calcifications and CKD

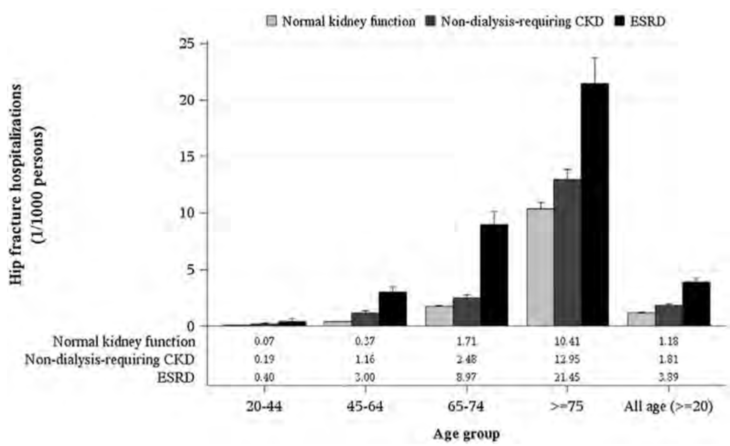




http://uwmsk.org/residentprojects/hpth.html

Kidney function and hip fracture

- **2010 data from nationwide inpatient sample (NIS) with 278,000 eligible participants**
- **Non-dialysis CKD (& ESRD) associated with higher age-standardized rates of hip fracture, post-hip fracture mortality and higher resource utilization**



Kim SM, Chertow GM, et al. Journal Bone and Min Research. 2016. Vol 31(10): 1803-1809

Summary

- Measurement of kidney function (GFR) using serum creatinine confounded by muscle mass, nutritional status and medication use
- Lower kidney function associated with increased risk of cardiovascular disease and mortality
- Caution should be taken in treatment of diabetes and hypertension in older adults with kidney disease
- Among the very old (85 and older) risk of death exceeds risk of progression to dialysis
- Lower kidney function is associated with higher hip fracture rates among older adults

"Matthews ... we're getting another one of those strange 'aw blah es span yol' sounds."

Outline

- Measurement of kidney function
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- **Functional decline in kidney disease**
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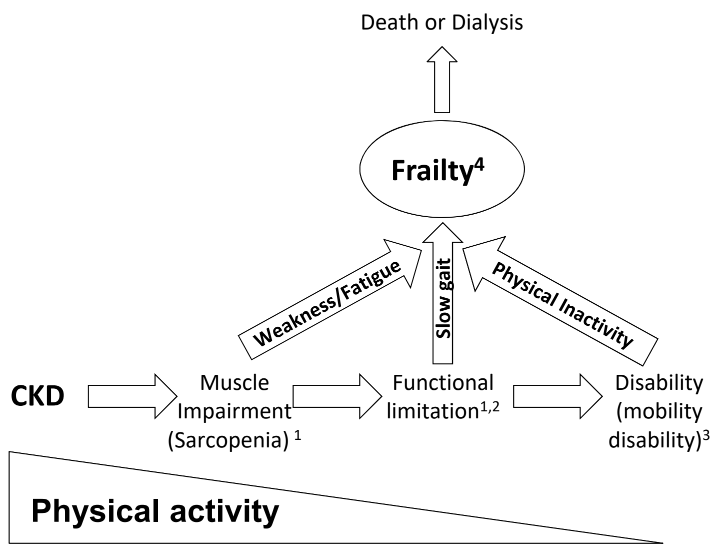
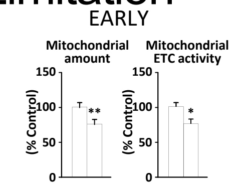
CKD and the Disablement Process

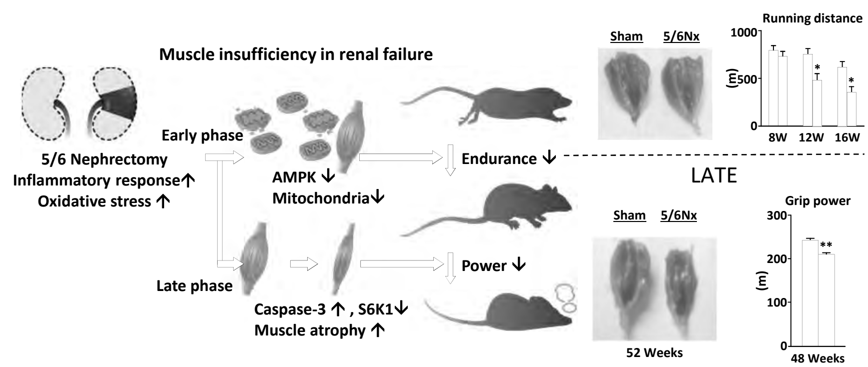


1. Roshanravan B, et al. *Am J Kid Dis*. 2015;65(5):737-747. 2. Roshanravan B, et al. *J Am Soc Neph.* 2013;24(5):822-30. 3. Roshanravan B, et al. *J Gerontol: Med Sci.* 2016 (in press). 4. Roshanravan B, et al. *Am J Kid Dis.* 2012:60(6):912-21.

Muscle Mitochondrial Impairment Precedes Muscle Atrophy and Functional Limitation

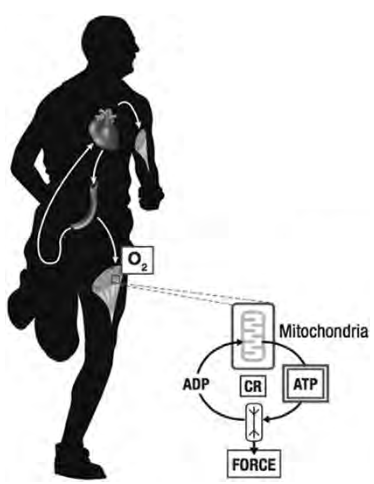
- CKD model: 5/6 nephrectomy of C57Bl/6 mice
- Early changes: Increased oxidative stress, inflammation, decreased endurance, lower mitochondrial function and content without muscle atrophy
- Late changes: muscle atrophy, decreased strength

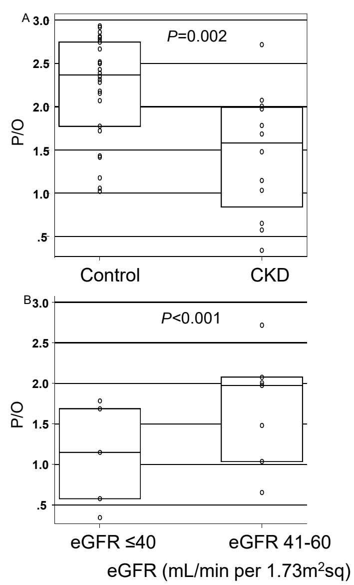




Tamaki M, et al. *Kid Int*. 2014;85:1330-1339.

CKD is Associated With Inefficient Muscle Metabolism





Roshanravan B, et al. *Am J Kidney Dis*. 2016 Oct;68(4):658-9.

P-value adjusted for age, sex, BMI

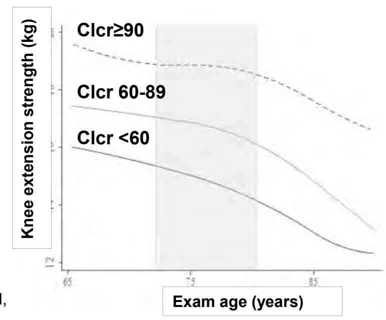
Kidney Disease and Muscle Impairment

CKD ⇨ **Muscle Impairment (Sarcopenia)**

- Population: Community dwelling older adults in InChianti study
  - Average age 74 ± 6.5 years. 56% female, and 12% with diabetes mellitus
  - Mean ClCr 78 ± 23 mL/min/1.73m^2
- Creatinine clearance from 24 hr urine is associated with calf muscle atrophy by CT
- Lower ClCr associated with faster decline in knee extension strength

	Muscle Density (mg/cm^3)		
	No.	Mean (SD)	Adjusted mean difference
ClCr≥90	207	71.7 (3.3)	Reference
ClCr 60-89	410	71.3 (3.4)	-0.10 (-0.62, 0.42)
ClCr<60	179	70 (3.5)	-0.97 (-1.66, -0.28)
Per -10mL/min			-0.15 (-0.26, -0.04)
P value*			0.006
Per 1 yr older age			-0.15 (-0.19, -0.11)

adjusted for age, sex, height, weight, site, smoking, education, DM, CAD, total daily animal protein consumption



Adjusted for age, sex, height, weight, education

Roshanravan B, Patel KV et al. *Am J Kid Dis*. 2015; 65(5):737.

Kidney Disease and Functional Limitation

CKD ⇨ **Muscle Impairment (Sarcopenia)** ⇨ **Functional limitation**

- Lower renal function is associated with objective functional limitation (Gait speed) among referred patients with CKD
  - Seattle Kidney Study: Mean age 57±13, GFR_{cysc} 48±18 ml/min per 1.73m^2
  - Median follow-up of 3 years IQR [2,4]; Mean visits 3.5±1
  - No ADL disability at baseline

	Baseline gait speed (m/s), Mean (SD)	**Adjusted Model Difference in % annual change compared to referent group (95% CI)**
eGFRcysc	1.0 (0.19)	Reference
60 or greater (n=50)	0.98 (0.22)	-3.18 (-5.31, -1.01)
45-59 (n=67)	0.94 (0.20)	-4.4 (-6.85, -1.89)
30-45 (n=64)	0.95 (0.20)	-6.90 (-9.78, -3.94)
<30 (n=32)		<0.001
P for continuous GFRcysc		

Adjusted for age, sex, race, height, weight, education, smoking, DM, Any CVD (CAD, PVD, stroke), logCRP

Kidney Disease and Functional Limitation

CKD → Muscle Impairment (Sarcopenia) → Functional limitation

- Objective physical performance assessment:
  - Captures physiologic changes related to chronic illness, aging, and sedentary lifestyle.
  - Identify non-disabled individuals at risk of disability
  - Evaluate change in functioning and health
  - Clinical “vital sign”
- Poor performance on lower extremity tasks associated with future mobility disability, hospitalization, and death in older adults

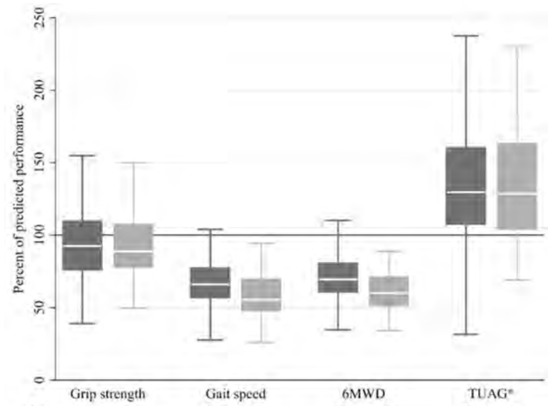
CLINICAL EPIDEMIOLOGY

Association between Physical Performance and All-Cause Mortality in CKD

Baback Roshanravan,* Cassianne Robinson-Cohen,† Kushang V. Patel,‡ Ernest Ayers,* Alyson J. Littman,†§ Ian H. de Boer,* T. Alp Ikizler,| Jonathan Himmelfarb,* Leslie I. Katzel,¶ Bryan Kestenbaum,* and Stephen Seliger** J Am Soc Nephrol **24:** 822–830, 2013

	Overall (N=385)	Fast TUAG (N=240)	Slow TUAG (N=122)
Demographic data			
Age, mean ±SD	61±13	57.7±12	66.4±12
Female, No. (%)	63(16)	33(14)	26(21)
Race, No. (%)			
Non-white	146(38)	91(38)	49(40)
Physical examination data, mean ±SD			
Systolic Blood Pressure (mmHg)	132.9±20.7	131.6±19.8	134.2±21.4
BMI (kg/m^2)	31±6.9	30.2±6.3	32.5±7.7
Laboratory Values			
eGFRcysc(ml/min/1.73m^2)*	47.6±23.3	51.7±24.8	41.1±18.3
eGFR CKD-EPI(ml/min/1.73m^2)	41.3±19.3	43.6±19.9	37.8±17.5
Physical Performance, mean ±SD			
4 meter Walk (m/s)	0.9±0.2	1±0.2	0.7±0.2
TUNG (sec)	11.2±4.5	8.8±2	15.9±4.5
6 Minute walk (meters)	400±100.3	436.8±81.9	308.5±78.9
Grip Strength (kg)	36.15±10.6	38.7±10.2	32.4±9.7
Exercise, No. (%)*			
Never	83(26)	41(21)	31(33)
Prevalent Disease, No. (%)			
Diabetes	213(55)	118(49)	75(61)
Any CAD	99(26)	48(20)	41(34)
Disability, No. (%)			
≥1 ADL task	27(8)	13(6)	10(10)
≥1 IADL task*	112(35)	52(26)	49(50)
≥1 Mobility task*	77(24)	26(13)	37(38)

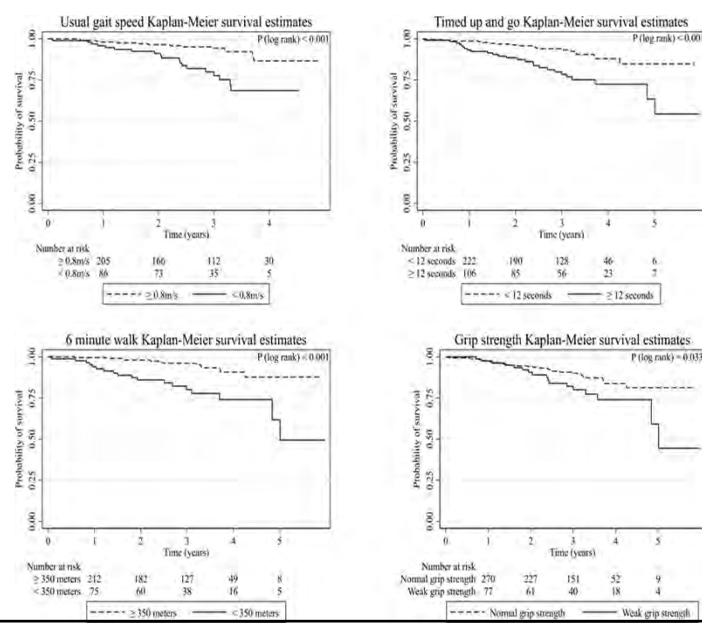
Patients with CKD have impaired physical performance



Sex	M	F	M	F	M	F	M	F
N	319	62	266	36	265	44	303	59
Mean	38.4kg	24.6kg	0.53m/s	0.48m/s	405m	372m	10.9s	12.6s
Mean %	94	93	63	55	70	61	137	145

Figure 1. Percentage of predicted performance for each measure by sex. Numbers under bars represent number of participants in each group and mean performance. Note that gait speeds are normalized to height. *For TUAG, a higher percentage predicted indicates worse and slower performance.

Association of physical performance and survival in CKD

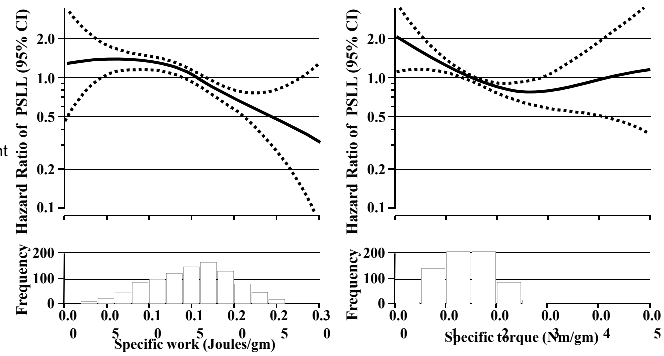


Muscle Impairment and Mobility Disability

CKD → **Muscle Impairment (Sarcopenia)** → **Functional limitation** → **Disability (mobility disability)**

1963 community dwelling older adults in Health ABC

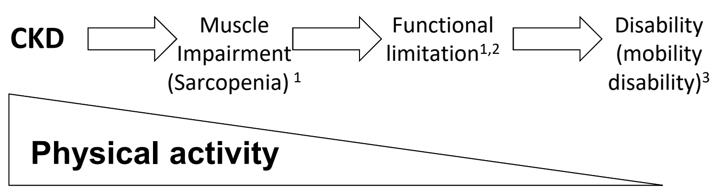
- Mean age 75±2.8 yrs
- Muscle endurance measured by isokinetic fatigue testing. Total work over 30 repetitions
- Isometric strength. Peak torque.
- Outcome: Persistent severe lower extremity limitation (PSLL) – incident severe difficulty or inability to walk ¼ mile on flat surface or ascend 10 steps.



***Adjusted for age, sex, race, site, height, weight, education and eGFRcyse**
***N=1963**

Roshanravan B, Patel KV et al. *J Gerontol: Med Sci*. 2016 (in press).
Roshanravan B, Patel KV et al. *Am Soc Neph*. 2015.

CKD and the Disablement Process



1. **Roshanravan B, et al. *Am J Kid Dis*. 2015;65(5):737-747.**
2. **Roshanravan B, et al. *J Am Soc Neph.* 2013;24(5):822-30.**
3. **Roshanravan B, et al. *J Gerontol: Med Sci.* 2016 (in press).**
4. **Roshanravan B, et al. *Am J Kid Dis.* 2012:60(6):912-21.**

Frailty phenotype and disability

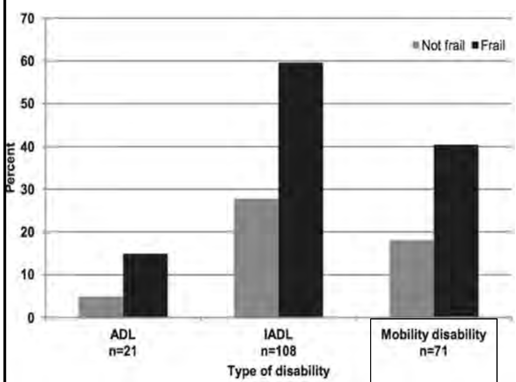
- Frailty is a terminal clinical syndrome of vulnerability characterized by slow gait, low strength, low physical activity, low energy and weight loss.
- Frailty is associated with risk of disability, hospitalization, and death in older adults

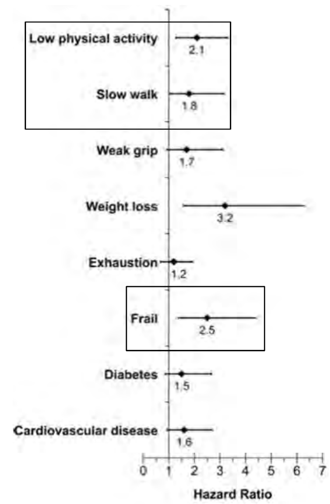
Frailty Phenotype is common in CKD

Cardiovascular Health Study (mean age 76 years, mean BMI 26.9, 36.8% with disability)		**Seattle Kidney Study** (mean age 59 years, mean BMI 31.4, 40% with disability)	
Definition	Prevalence	Definition	Prevalence
Self-reported ≥10 pound unintentional weight loss in past year	6%	Self-reported ≥10 pound unintentional weight loss in past 6 months	10%
Lowest sex and BMI specific 20th percentile grip strength	20%	Same absolute cutoffs as CHS[1,17]	16%
Lowest sex specific 20th percentile kilocalories/week	20%	Self reported exercise less than once per week	35%
Positive response to either exhaustion item on CES-D[1]	17%	Lowest 20th percentile exhaustion score on RAND-36[*]	32%
Slowest sex and height specific quintile walking pace	20%	Same absolute cutoffs as CHS;	26%
Frailty	**7%**		**14%**
Intermediate frailty	**47%**		**52%**

Roshanravan B, Khatri M et al. AJKD 2012; 90(6): 912-921

Frailty is a associated with disability and with risk of death or dialysis in CKD





Roshanravan B, Khatri M et al. AJKD 2012; 90(6): 912-921

Lower kidney function associated with increased prevalence of frailty

Ballew SH, et al. Am J Kidney Dis. 2017; 69(2): 228-36.

- 4987 participants in ARIC study. Mean age 75.6yrs

B

eGFR$_{cys}$ categories (ml/min/1.73 m^2) Description and range			Persistent albuminuria categories (mg/g) Description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30	30-<300	≥300
G1/G2	Normal or high to mildly decreased	≥60	1 (Reference)	1.9* (1.1, 3.2)	2.4 (0.4, 16.4)
G3a	Mildly to moderately decreased	45-<60	2.3*** (1.6, 3.2)	3.7*** (2.4, 5.7)	3.4* (1.1, 10.7)
G3b	Moderately to severely decreased	30-<45	3.2*** (2.2, 4.5)	4.7*** (3.1, 7.1)	5.4*** (2.7, 11.0)
G4/G5	Severely decreased/Kidney failure	<30	5.1*** (3.1, 8.3)	5.7*** (3.5, 9.4)	7.2*** (3.9, 13.1)

Figure 3. Demographically adjusted prevalence ratios (95% confidence intervals [CIs]) of frailty by (A) creatinine-based estimated glomerular filtration rate (eGFR$_{cr}$) or (B) cystatin C–based eGFR (eGFR$_{cys}$) and albuminuria category. *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.

Lower kidney function associated with increased risk of frailty in older adults.
Dalrymple LS, Katz R, et al. CJASN. 2013. 8:2091-2099

- Cardiovascular Health Study: community dwelling older adults (mean age 75 yrs) without baseline frailty
- Exposure: Baseline GFRcysc
- Outcome: incident frailty over 4 years of follow-up

Table 4. Association between kidney function (estimated GFR using cystatin C) and incident frailty

Variable	Total Patients (n)	Patients with Frailty (n)	Unadjusted IRR (95% CI)	IRR Adjusted for Demographic Characteristics[a] (95% CI)	IRR Further Adjusted for Potential Confounders[b] (95% CI)	IRR Further Adjusted for Potential Mediators[c] (95% CI)
Continuous $eGFR_{cys}$ per 10 ml/min per 1.73 m^2 decrease	3459	214	1.18 (1.09 to 1.27)	1.15 (1.06 to 1.24)	1.09 (1.00 to 1.17)[c]	1.09 (1.00 to 1.18)
Category of $eGFR_{cys}$						
≥90 ml/min per 1.73 m^2	622	23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
76–89 ml/min per 1.73 m^2	992	55	1.49 (0.92 to 2.39)	1.58 (0.98 to 2.54)	1.50 (0.92 to 2.45)	1.37 (0.83 to 2.27)
60–75 ml/min per 1.73 m^2	1160	78	1.82 (1.15 to 2.87)	1.90 (1.20 to 3.00)	1.72 (1.07 to 2.75)	1.65 (1.02 to 2.67)
45–59 ml/min per 1.73 m^2	537	41	2.19 (1.33 to 3.59)	2.00 (1.21 to 3.31)	1.53 (0.90 to 2.60)	1.49 (0.87 to 2.57)
15–44 ml/min per 1.73 m^2	148	17	3.69 (2.04 to 6.68)	3.08 (1.67 to 5.68)	2.28 (1.23 to 4.22)	2.08 (1.09 to 3.98)

IRR, incidence rate ratio; $eGFR_{cys}$, estimated glomerular filtration rate using serum cystatin C.
[a]Age, sex, and race
[b]Further adjusted for smoking, body mass index, diabetes mellitus, hypertension, coronary heart disease, and heart failure.
[c]Further adjusted for C-reactive protein, hemoglobin, albumin, LDL cholesterol, and HDL cholesterol.
[c]$P=0.04$.

Functional status and dialysis initiation

Kurella Tamura M, Covinsky KE et al. NEJM 2009; 361: 1539-47.

- National registry of nursing home residents who started dialysis (n=3702)
- Functional status measured using Minimum Data Set-Activities of Daily Living [MDS=ADL] scale of 0-28 points (higher score = greater functional difficulty)
- Outcome: Change in functional status at 3, 6, 9, and 12 months after initiation of dialysis.

Table 1. Characteristics of the Subjects at the Initiation of Dialysis.*

Characteristic	Subjects†
Age (yr)	73.4±10.9
Estimated glomerular filtration rate (ml/min/1.73 m² of body-surface area)	10.7±4.9
Albumin (g/dl)	2.9±0.6
Female sex (%)	60
Race (%)‡	
White	64
Black	32
Other	4
Coexisting condition (%)	
Diabetes	68
Congestive heart failure	66
Coronary artery disease	44
Peripheral vascular disease	37
Cerebrovascular disease	39
Chronic obstructive pulmonary disease	24
Cancer	12
Dementia	22
Depression	35
Hemodialysis (vs. peritoneal dialysis) (%)	95
Hospitalized at initiation of dialysis (%)	69

Functional status declines after initiation of dialysis

- Initiation of dialysis was associated with a decline in functional status independent of age, sex, race, and trajectory of functional status before initiation of dialysis.

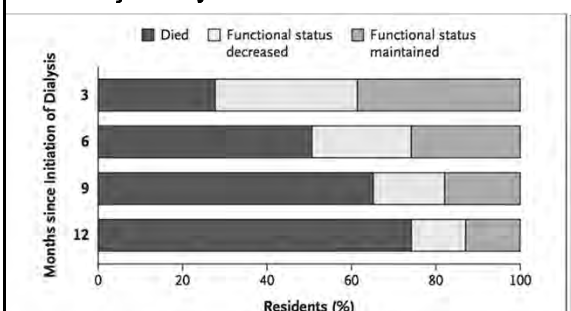


Figure 2. Change in Functional Status after Initiation of Dialysis.
Data were missing for 549 nursing home residents at 3 months, 696 residents at 6 months, 823 residents at 9 months, and 787 residents at 12 months from the full analytic cohort of 3702 residents.

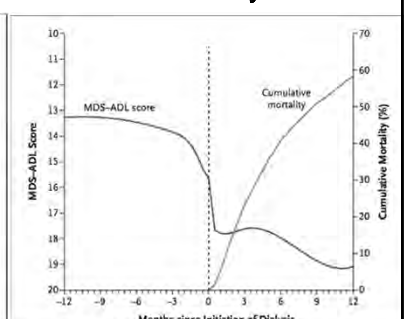


Figure 3. Smoothed Trajectory of Functional Status before and after the Initiation of Dialysis and Cumulative Mortality Rate.
The dashed vertical line indicates the initiation of dialysis in a hypothetical 75-year-old nursing home resident. MDS–ADL denotes Minimum Data Set–Activities of Daily Living. The numbers on the MDS–ADL axis run from highest to lowest.

Exercise in Patients on Dialysis: A Multicenter, Randomized, Clinical Trial

Manfredini F, Mallamaci D'Arrigo et al. JASN. 2016.

- The EXerCise Introduction to Enhance performance in dialysis patient trial (EXCITE)
- 6-month personalized, ***home-based walking exercise program*** to improve walking capacity and muscle strength compared to "usual care"
- Excluded participants with limited mobility or high degree of fitness (6 minute walk distance >550meters), exertional angina, or stage 4 NYHA heart failure

Training customized to level of fitness

- Exercise training on non-dialysis days involved gradual increased intensity of walking cadence.

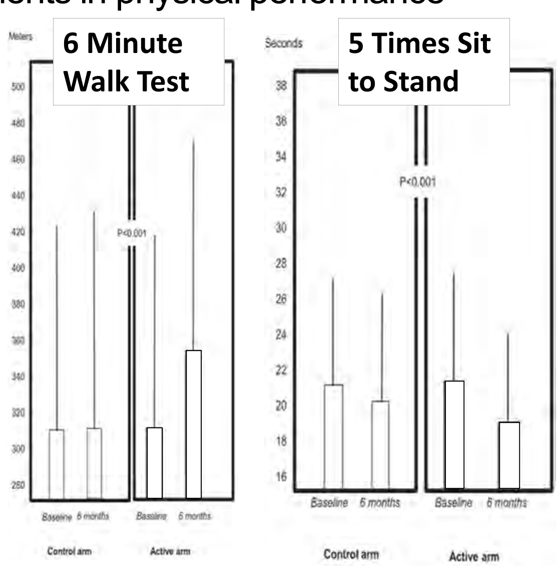
Functioning Capacity Level	Normal	Moderate	Low	Very Low
6 min distance walked at baseline, m	>300 to ≤550	<300 to >200	<200	<200 +severe symptoms
Number of training sessions per d (always on nondialysis days)	2	2	2	2
Duration of training sessions, min	10	10	10	10
Frequency, times per wk	3	3	3	3
Training speed				
Baseline, km/h	2.8	2.0	1.4	1.4
Miles per h	1.7	1.2	0.9	0.9
wk 1–14, steps/min	72–120	66–100	56–80	56–80
wk 15–24, steps/min	90–120	80–100	60–80	60–80
wk 1–14				
Work/rest time, min	5:1	5:1	5:1	2:1
No. of repetitions	2	2	2	5
wk 15–24				
Work/rest time, min	10:0	10:0	10:0	5:1
No. of repetitions	1	1	1	2

Participant Characteristics

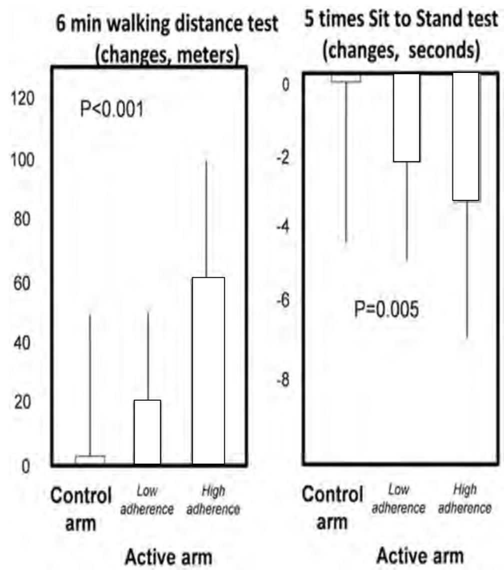
Table 1. Demographic, clinical, and biochemical data of patients that completed the study

	Active Arm (*n*=104)	Control Arm (*n*=123)	P Value
Age, yr	63±13	64±14	0.60
Men, %	64	68	0.54
Hemodialysis/CAPD, *n*	90/14	102/21	0.45
BMI, kg/m^2	26±4	27±6	0.32
Smoking, % (0=no; 1=yes)	18	19	0.93
Diabetes, % (0=no; 1=yes)	18	18	0.88
Systolic BP, mmHg	132±18	127±18	0.06
Diastolic BP, mmHg	72±10	71±12	0.43
HR, beats/min	75±9	74±8	0.51
Total cholesterol, mg/dl	164±39	166±39	0.67
Triglycerides, mg/dl	166±116	160±86	0.68
Hemoglobin, g/dl	11±1	11±2	0.22
Albumin, g/dl	3.9±0.4	3.8±0.5	0.44
Calcium, mg/dl	8.8±0.7	8.9±0.7	0.42
Phosphate, mg/dl	4.9±1.5	4.8±1.4	0.35
PTH, pg/ml	280 (179–456)	283 (156–396)	0.55
Creatinine, md/dl	10.5±2.7	9.8±2.6	0.41
Glycemia, mg/dl	111±64	102±36	0.23
Urea, mg/dl	153±42	148±40	0.33
CRP, mg/L	5.0 (3.1–9.0)	4.6 (3.0–8.0)	0.60
Kt/V hemodialysis	1.42±0.25	1.43±0.30	0.68
Kt/V CAPD	1.96±0.29	1.80±0.60	0.36
Myocardial infarction, %	15	17	0.73
Stroke/transient ischemic attack, %	8	14	0.14
Anginal episodes, %	11	13	0.74
Arrhythmia, %	12	7	0.19
Heart failure, %	17	24	0.24
Peripheral vascular disease, %	7	12	0.16
History of neoplasia, %	22	18	0.52
Antihypertensive therapy, %	77	70	0.27
NYHA class, %			
I	38	34	0.46
II	14	16	
III–IV	4	10	
Mobility, %			
Assisted	4	3	0.56
Independent	96	97	

Exercise is associated with meaningful and significant improvements in physical performance



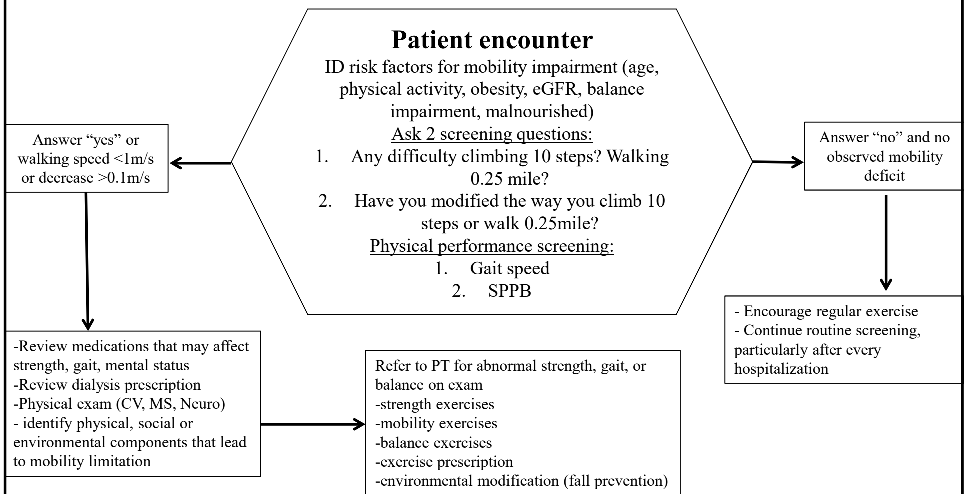
Dose dependent association of exercise with improvement in physical performance



Challenges to exercise

- High prevalence of physical frailty in the kidney disease population may preclude participation in structured physical activity.
- Waning of adherence over time
- **An understanding of a patient's functional status and use of an interdisciplinary approach involving rehabilitative therapies to address functional limitations is vital to providing a feasible, safe, and individualized exercise prescription**

Algorithm for identifying high risk patients for rehabilitative therapies prior to exercise



Roshanravan B, Gamboa J, et al. AJKD (in press)

Summary

- CKD is associated with skeletal muscle impairment
- Impaired physical performance is common in patients with CKD and strongly associated with mortality and mobility disability
- Older adults with lower kidney function are at increased risk of frailty strongly associated with death or dialysis initiation.
- Among older nursing home residents dialysis initiation is associated with decline in functional status
- Early evidence suggests ambulatory exercise may improve physical performance and muscle strength in dialysis patients

Outline

- Measurement of kidney function
- Definition of CKD
- Management issues for older adults with CKD (Adult vs Older Adults)
- Functional decline in kidney disease
- **Dialysis versus conservative management in CKD**
- Summary

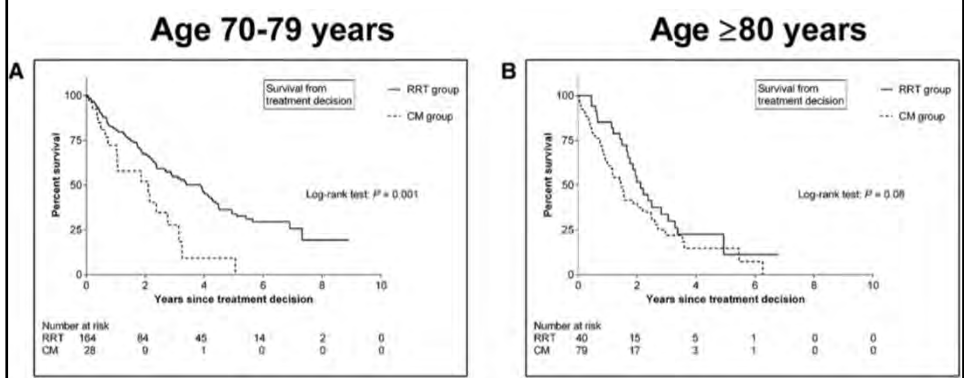
Dialysis vs. Conservative Management

Verbene WR, Tom Greers ABM, et al. CJASN. 2016. 11: 633-640

- Retrospective Survival Analysis of a single center-cohort in the Netherlands from 2004-2014
  - Excluded acute on chronic renal failure
- Comparative survival analysis of 107 patients who underwent conservative management and 204 who chose renal replacement therapy

Dialysis vs. Conservative Management

- **No statistically significant survival advantage among patients aged ≥80 years.**



Renal supportive care without dialysis and Quality of Life

Brown MA, Collett GK et al. CJASN 2015. 10:260-268

- Renal supportive care nondialysis (RSC-NFD) (n=122, mean age 82) vs Pre-dialysis (n=273, mean age 67).
- Predialysis clinic: usual care in addition to attending education clinic. 34% initiated dialysis
- RSC clinics
  - Staffed by a palliative care specialist
  - Senior renal/palliative care nurse
  - Dietician
- Decision to recommend dialysis or nondialysis. Shared decision making between nephrologist with patient and his or her family

Table 1. Baseline characteristics at the first clinic visit in patients planned for dialysis (predialysis) and patients in the RSC-NFD group

Variable	RSC-NFD (n=122)		Predialysis (n=273)		P Value
	Mean (SD) or Proportion	n	Mean (SD) or Proportion	n	
Age (yr)	82 (9)	122	67 (14)	273	<0.001
eGFR (ml/min per 1.73 m^2)	16 (9)	122	16 (7)	273	0.92
Weight (lb)	160 (34)	112	182 (44)	256	<0.001
Height (cm)	162 (10)	108	167 (9)	249	<0.001
BMI	27.7 (5.5)	108	29.1 (6.2)	249	0.06
Creatinine (mg/dl)	3.9 (1.7)	122	3.7 (1.5)	273	0.37
Hemoglobin (g/dl)	10 (1.6)	122	11.3 (1.8)	270	0.04
Albumin (g/dl)	3.4 (0.6)	119	3.5 (0.7)	253	0.10
Corrected Ca (mg/dl)	9.2 (0.07)	117	9.2 (0.07)	267	0.62
PO_4 (mg/dl)	4.7 (1.2)	118	4.7 (1.2)	266	0.95
PTH (pg/ml)	200 (145)	62	218 (218)	150	0.47
Women	45	55	33	90	0.2
CKD group (stage)					0.32
4	57	69	57	155	
5	43	53	43	118	
Diabetes	53	64	52	141	0.88
Clinical dementia	11.5	14	0.4	1	<0.001
Comorbidities (n)					
≥1	89	109	70	190	<0.001
≥2	57	70	40	108	0.001
≥3	38	46	18	48	<0.001
Current or former smoker	25	34	41	112	0.03

- Improved survival among pre-dialysis group (median 46 month) vs RSC-NFD (median 16 month)
- In RSC-NFD group 32% survived >12 months.
- Worse symptom burden at first visit among RSC
- **No difference in change in QOL status over 12 months**

Table 3. Symptoms and QOL at the initial clinic visit and change in symptoms and QOL over time in the RSC-NFD and predialysis groups

	Predialysis	RSC-NFD	P Value
QOL			
Physical composite (SF-36)	137	63	
Score at first visit; mean (SD)	38 (11)	29 (8)	<0.001
Mental composite (SF-36)			
Score at first visit; mean (SD)	50 (10)	46 (12)	0.06
QOL status	49	19	
Change of physical composite score over 12 mo			0.12
Stable	2 (4%)	3 (16%)	
Improved	20 (41%)	4 (21%)	
Worse	27 (55%)	12 (63%)	
Change of mental composite score over 12 mo			0.78
Stable	1 (2%)	1 (5%)	
Improved	26 (53.1%)	10 (53%)	
Worse	22 (44.9%)	8 (42%)	

Summary

- Impact of dialysis to improve survival among older adults >80 yrs old with multimorbidity is questionable
- Supportive care integrated palliative and nephrology approach among older adults with multimorbidity may improve symptom burden despite reductions in survival
- Shared decision making between nephrologist, patient and patient’s family

Take home points 1

- Lower kidney function measured by estimated glomerular filtration or albuminuria is associated with increased risk of Cardiovascular disease
- Lower kidney function among older age complicates treatment of diabetes and hypertension
- Among the oldest-old (>85 years) the risk of death from cardiovascular disease exceeds the risk to progression toward dialysis

Take home points 2

- Lower kidney function is associated with sarcopenia, functional imitation and frailty
- Dialysis initiation among nursing home dwelling older adults is associated with decline in functional status
- Integrative palliative care and rehabilitative therapies are important consideration among patients with advanced kidney disease.

KIDNEY RESEARCH INSTITUTE
A collaboration between Northwest Kidney Centers and UW Medicine

Division of Nephrology
University of Washington

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  - Kushang V. Patel PhD MPH, Department of Anesthesiology and Pain Medicine

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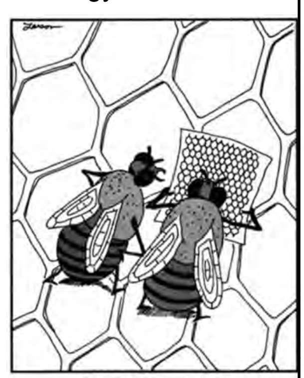

"Face it, Fred—you're lost!"