PROTEIN ENERGY WASTING IN CHRONIC KIDNEY DISEASE

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INTRODUCTION

Protein Energy Wasting

- **simultaneous loss of systematic body protein and energy stores**
- **leading ultimately to loss of muscle, fat mass and cachexia**

2007 International Society of Renal Nutrition and Metabolism (ISRNM)

INTRODUCTION

2007 ISRNM

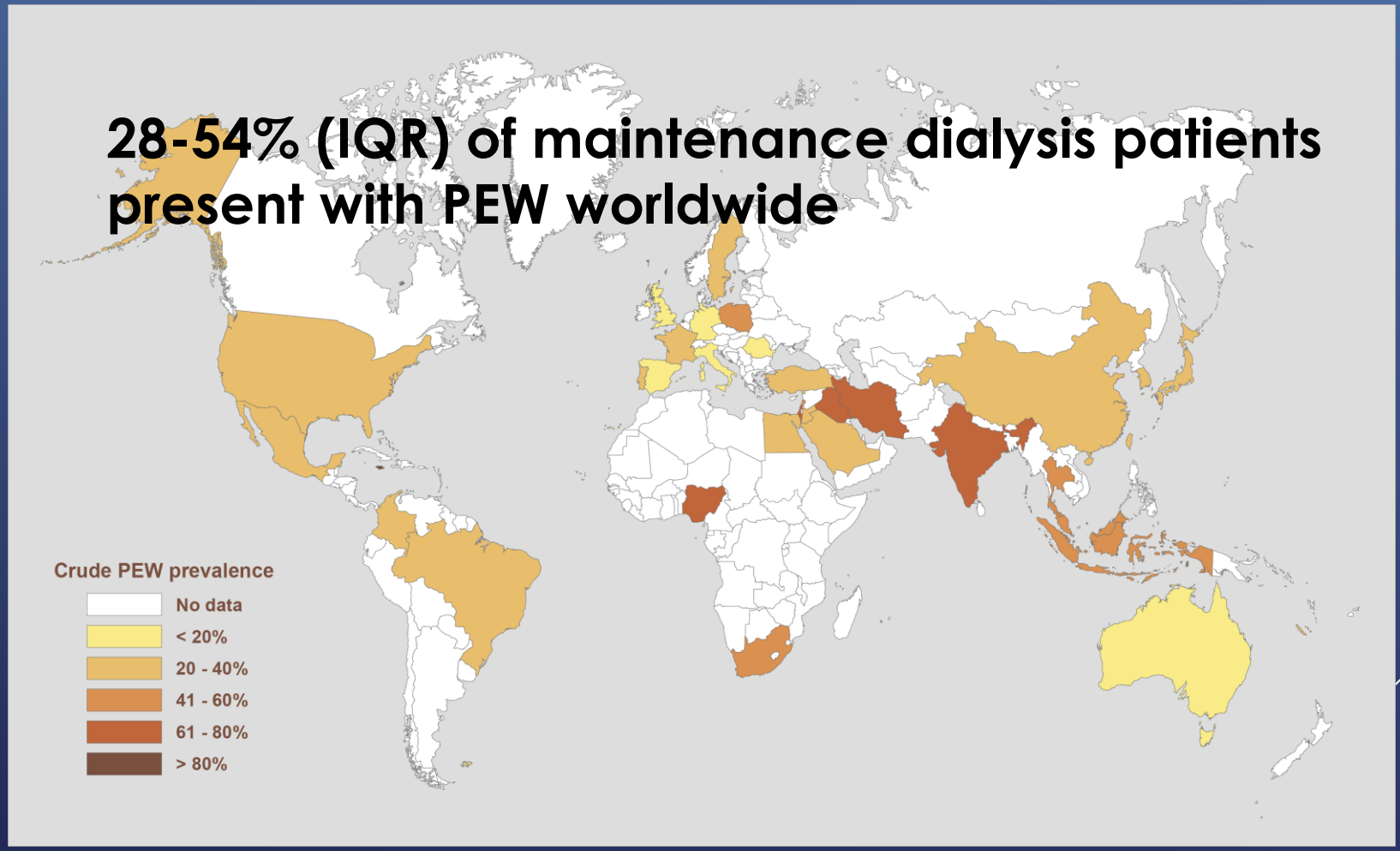
Criteria for clinical diagnosis in CKD	
Lab	Albumin < 3.8 g/dl Prealbumin < 30 mg/dl (maintenance RRT pt only) Cholesterol < 100 mg/dl
BMI	BMI (edema-free) < 23 kg/m2 Unintentional weight loss ≥ 5% over 3 months, or ≥ 10% over 6 months Total body fat percentage < 10%

INTRODUCTION

2007 ISRNM

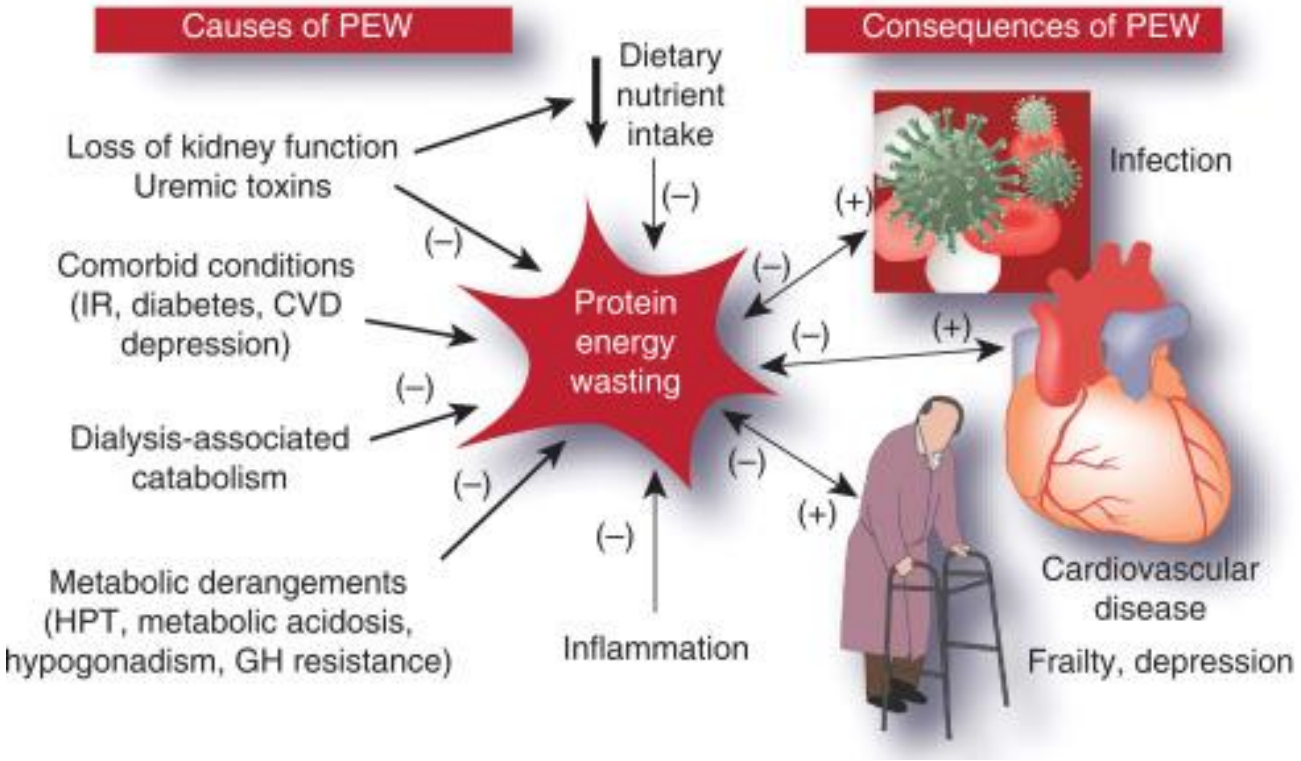
Criteria for clinical diagnosis in CKD	
Muscle mass	Reduced muscle mass ≥ 5% over 3 months or ≥ 10% over 6 months Reduced mid-arm circumference area ≥ 10% in relation to 50th percentile of reference
Dietary intake	Unintentional low dietary protein intake < 0.8 g/kg/day for at least 2 months for dialysis pt < 0.6 g/kg/day for CKD stage 2-5 pt Unintentional low dietary energy intake < 25 kcal/kg/day for at least 2 months

PREVALENCE

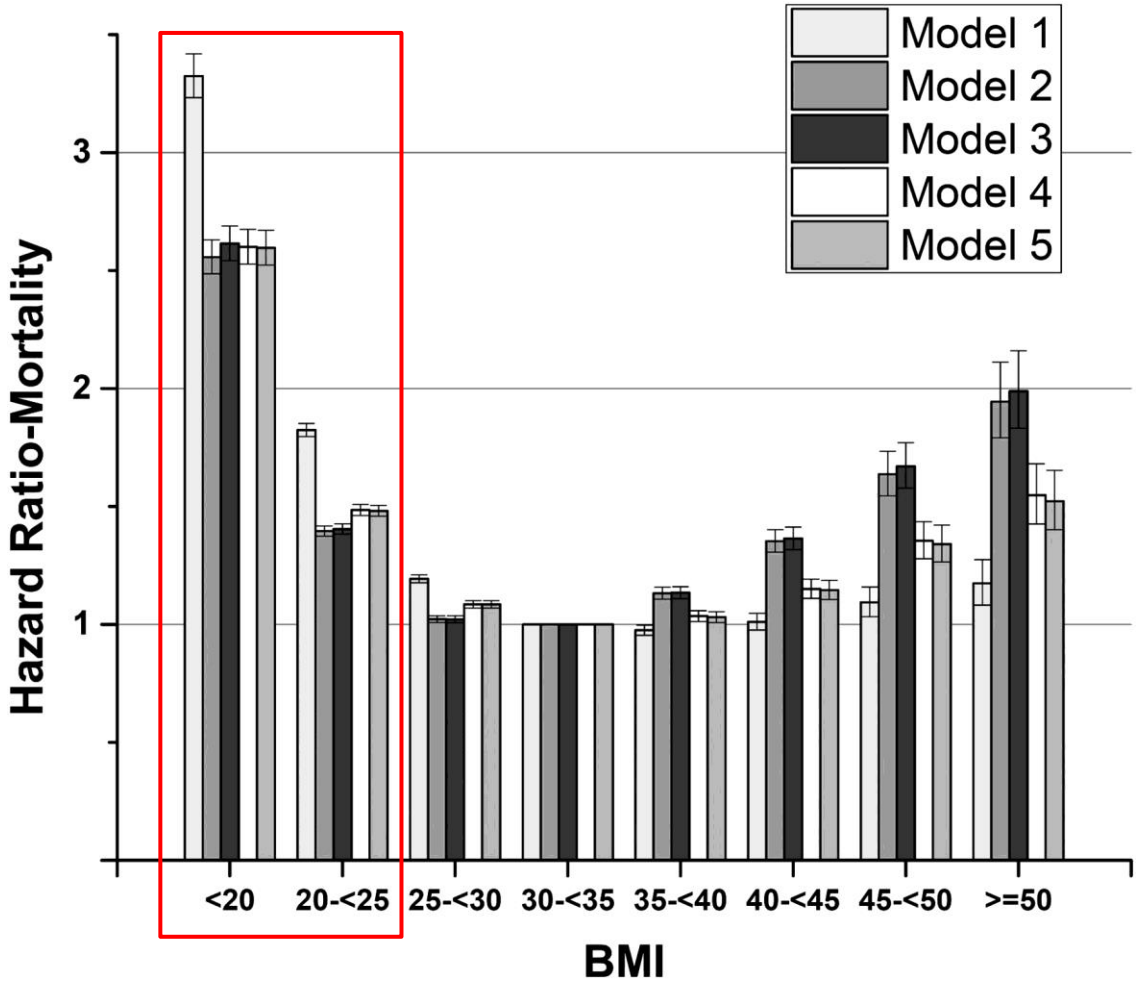

28-54% (IQR) of maintenance dialysis patients present with PEW worldwide
Crude PEW prevalence
No data
< 20%
20 - 40%
41 - 60%
61 - 80%
> 80%

POSSIBLE ETIOLOGY

The conceptual model for etiology and consequences of PEW in CKD



IMPACT ON OUTCOME

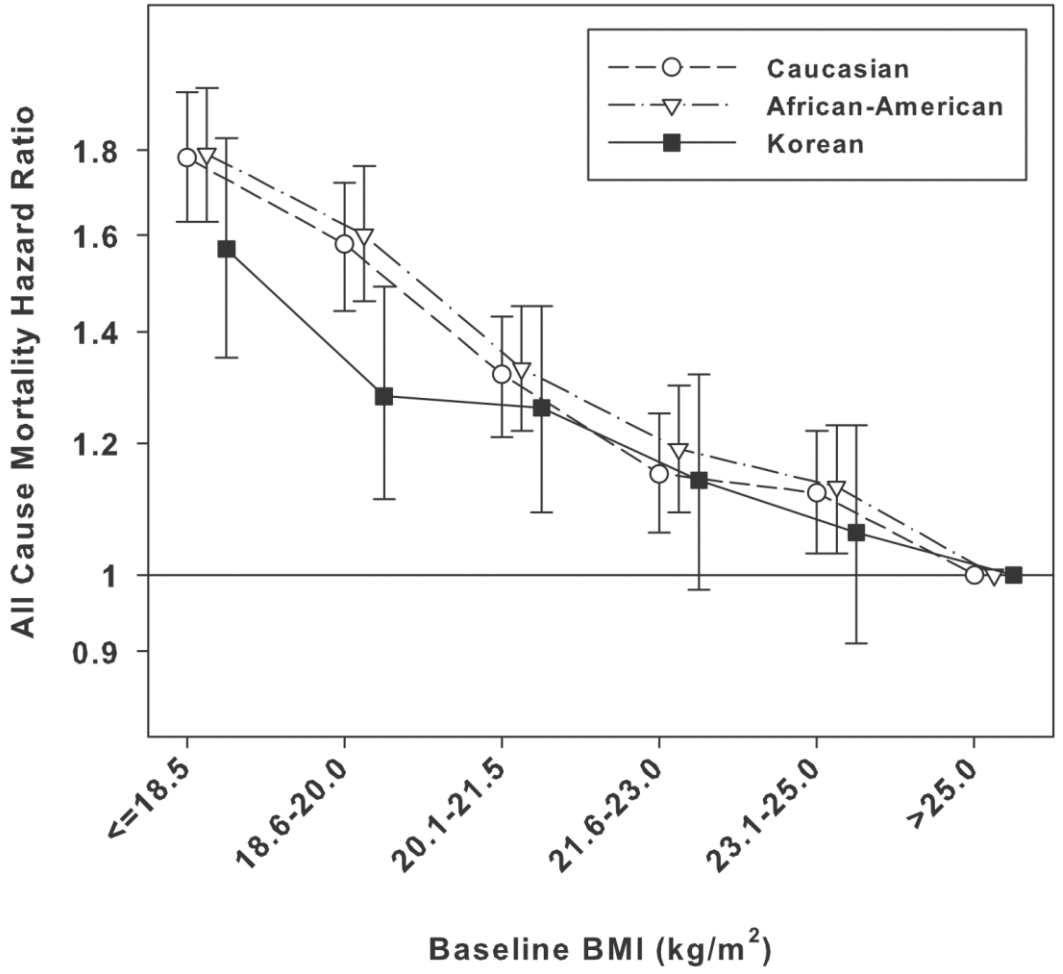


BMI categories shows a U-shaped association with mortality in 453,946 US verterans with eGFR <60 ml/min/1.73m^2.

Model 1: crude
Model 2: age adjusted
Model 3: age + race adjusted
Model 4: age + race + comorbidity + medication adjusted
Model 5: all of above + baseline eGFR

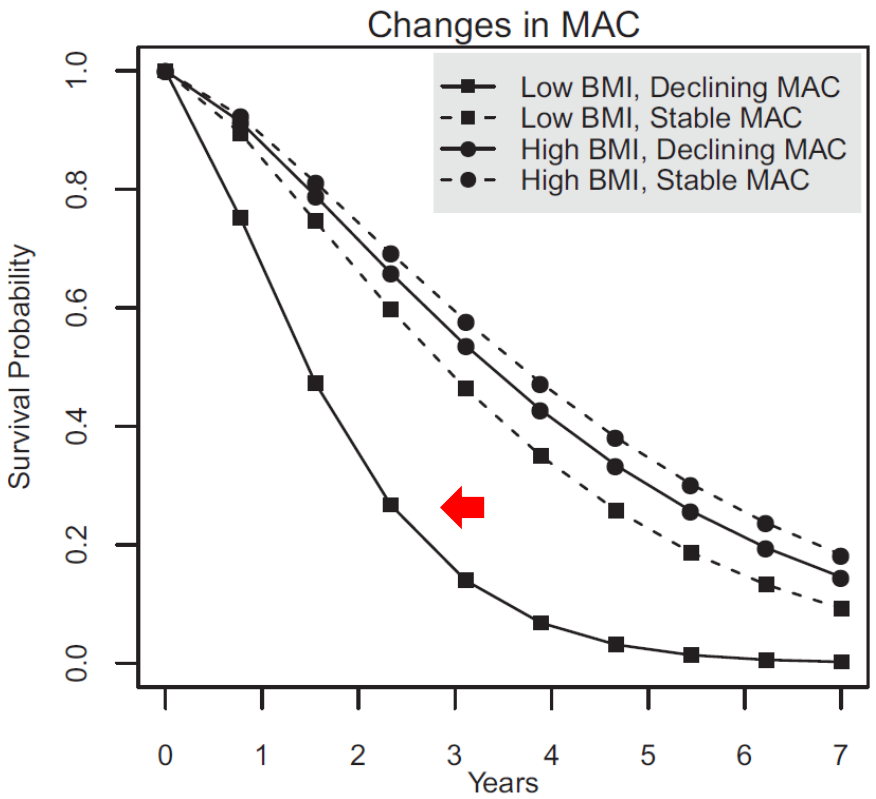
Lu et al. JASN, 2014

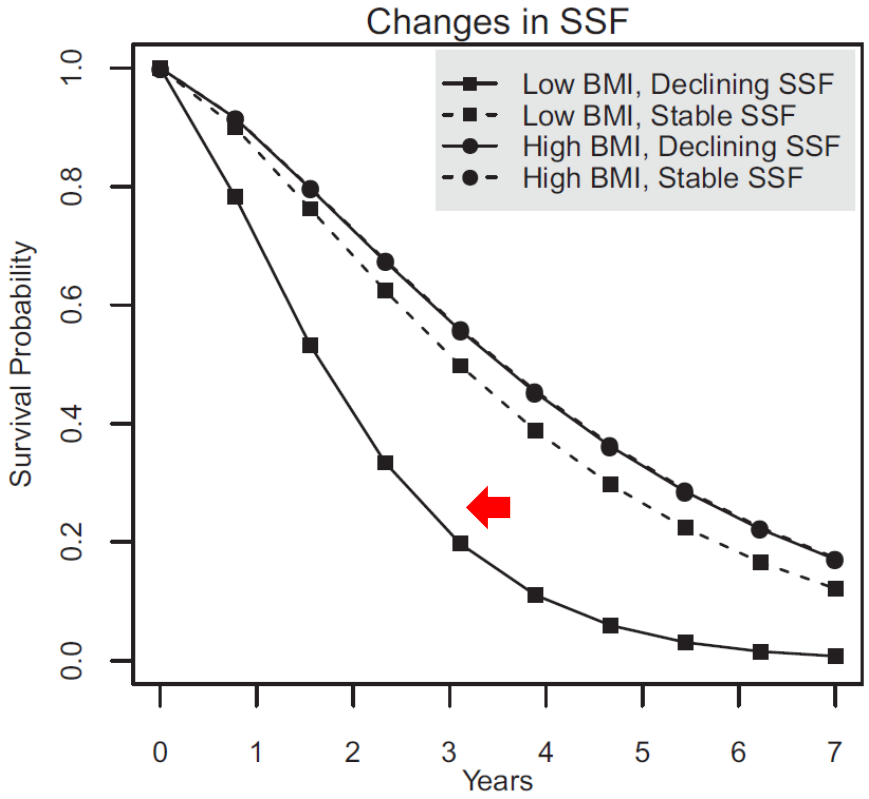
IMPACT ON OUTCOME



Park et al. Mayo Clin Proc, 2013

IMPACT ON OUTCOME





Predicted survival curves based on an adjusted joint-model with midarm circumference (MAC) or SSF (sum of skinfolds over 3 sites: subscapular, triceps and biceps) in HD patients

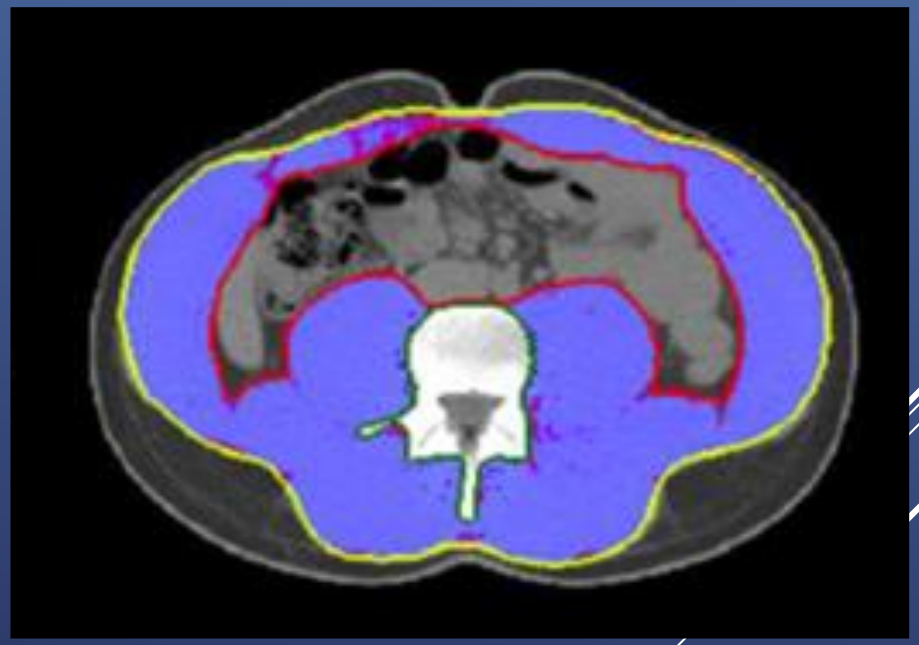
Su et al. AJKD, 2013

SARCOPENIA

	sarcopenia	**PEW**	frailty	cachexia
Malnutrition		v		v
Abnormal biochemistry		v		v
Low BMI/weight loss		v	v	v
Decreased muscle mass	v	v		
Decreased muscle strength	v		v	v
Fatigue/exhaustion			v	v
Decreased gait speed	v		v	
Decreased physical activity			v	

SARCOPENIA

- **Automated measure of muscle mass using abdominal CT & AI algorithm**
  - L3 level
  - Cross-sectional area of:
    bilateral psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, rectus abdominis
  - -30 ~ 150 hounsefield unit area



INTERVENTION – NUTRITIONAL

- Recommended minimum protein and energy intake for CKD patients

	CKD(ND)	HD
protein	0.6-0.8 g/kg/day on illness 1.0 g/kg/day	>1.2 g/kg/day
Energy*	30-35 kcal/kg/day	30-35 kcal/kg/day

* Based on physical activity level. In sedentary elderly adults, recommended energy intake is 30 kcal/kg/day. All recommendations are based on ideal body weight.

INTERVENTION – NUTRITIONAL

- Proposed algorithm for nutritional support in CKD patients

Indications for nutritional interventions despite preventive measure

- poor appetites and oral intake
- **DPI <0.7 (CKD 3-4) or <1.2 (CKD5D); DEI <30 kcal/kg/d**
- **serum Alb <3.8 g/dL** or serum preAlb <28 mg/dL
- unintentional weight loss >5% of IBW or estimated DW over 3 months
- SGA in PEW range

Start CKD-specific oral nutritional supplementation

- CKD 3-4: DPI target >0.8 g/kg/d +/- amino acid/keto acid
- CKD 5D: DPI target >1.2 g/kg/d (oral nutritional supplement at home or in-center meals)

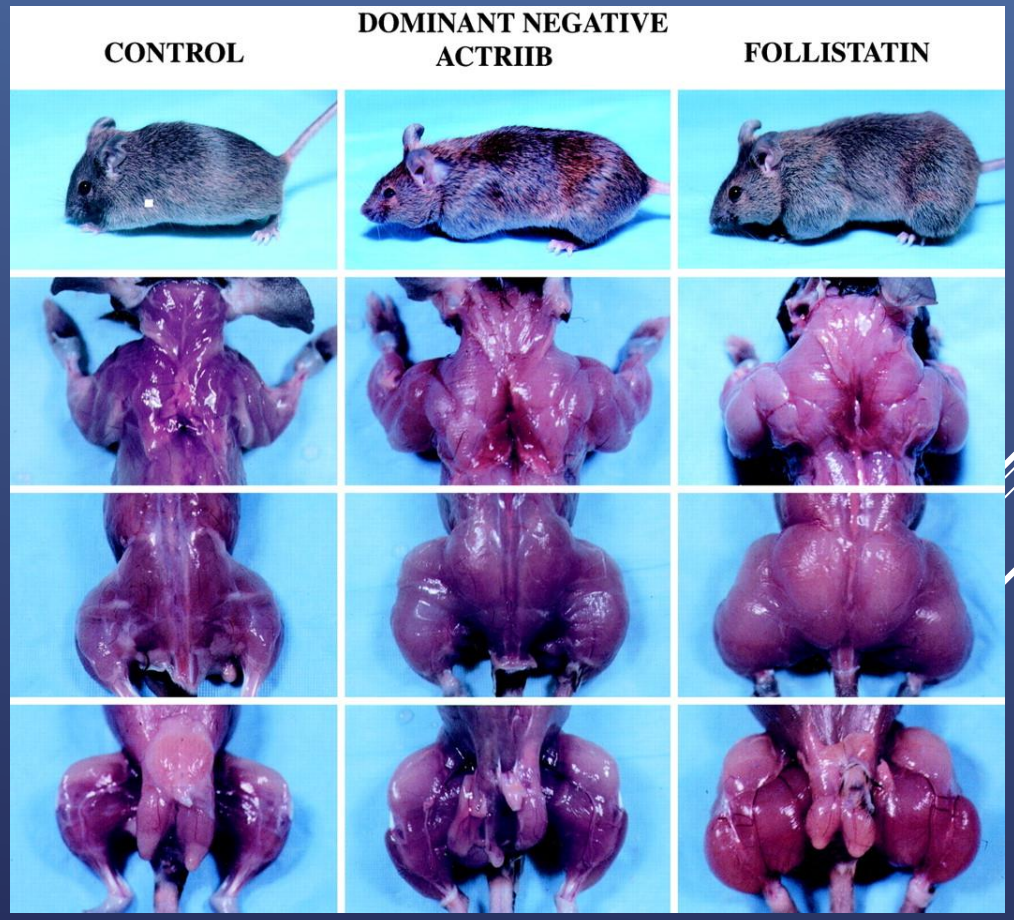
INTERVENTION - EXERCISE

- Examples of recent exercise studies in patient with CKD

Ref		Days/ week	Duration/day	Duration (weeks)	Intensity	Outcome
Van Craenenbroeck	Aerobic	Daily	4, 10-min bouts	12	90% HR at anaerobic threshold	↑ VO2 peak ↑ QOL → Vas Fx
Gregory	Aerobic	3x	Up to 55 min	48	50-60% VO2 peak	→ IGF → Kid Fx ↑ VO2 peak
Headley	Aerobic	3x	Up to 55 min	16	50-60% VO2 peak	↑ VO2 peak → Vas Fx
Watson	Resistance	3x	3 sets of 10 reps	8	70% predicted max	↑ Muscle mass ↑ Vcross-sec area (8%) ↑ Strength
Balakrishman	Resistance	3x	3 sets of 8 reps		80% 1 rep max	↑ mtDNA copy no.

INTERVENTION - PHARMACOLOGICAL

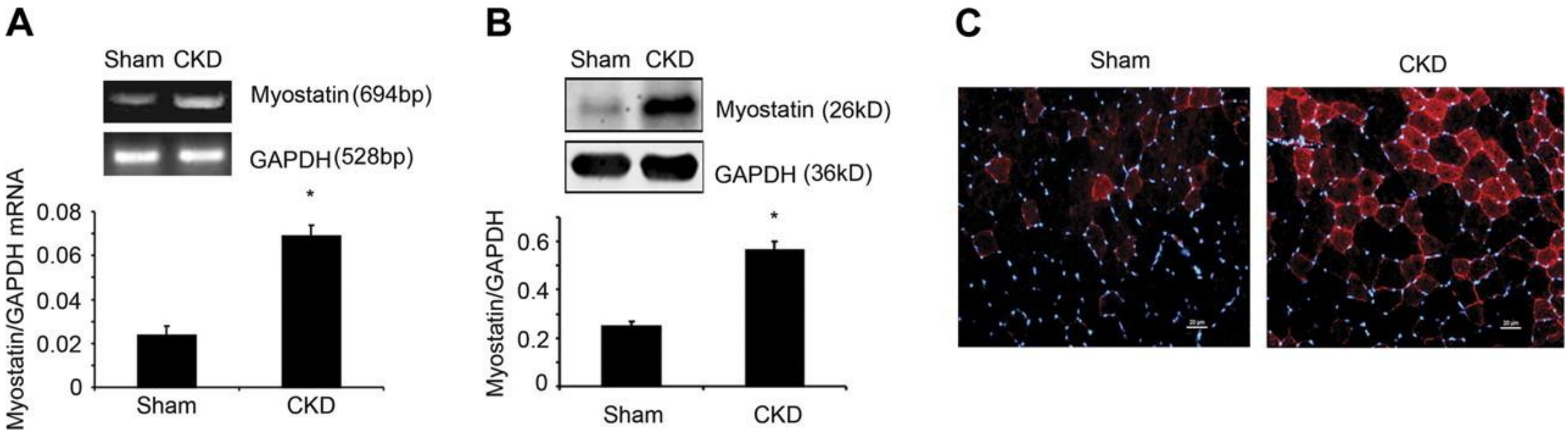
- Myostatin
  - Transforming growth factor-β family
  - Binding to activin receptor type IIB (ActRIIB)
  - **Inhibiting skeletal muscle growth**
- Follistatin
  - Activin-binding protein
  - Myostatin antagonist



McPherron et al. PNAS, 2001

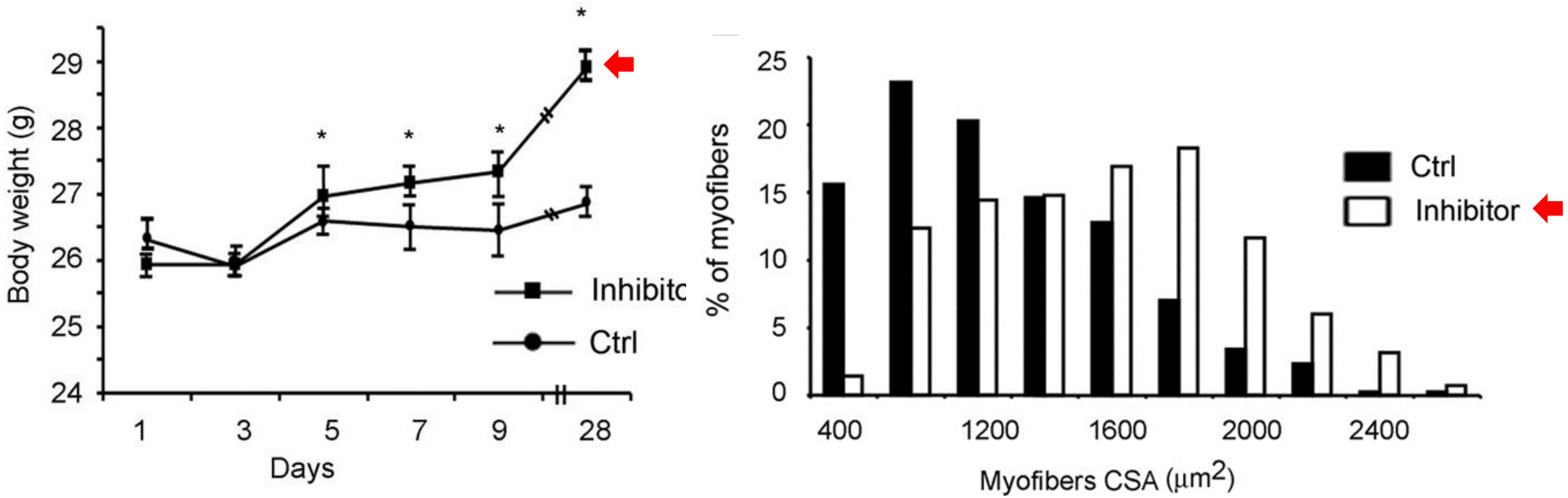
INTERVENTION - PHARMACOLOGICAL

CKD stimulates myostatin expression in muscle



Zhang et al. FASEB J, 2011

Inhibition of myostatin increases body weight and reduces muscle atrophy in CKD mice



Zhang et al. FASEB J, 2011

INTERVENTION - PHARMACOLOGICAL

- Anabolic steroid
  - Testosterone, nandrolone, oxymetholone etc
- Anti-inflammatory agents
  - Pentoxifylline, ertanercept, IL-1 receptor antagonist etc.

INTERVENTION - PHARMACOLOGICAL

- Appetite stimulants
  - Megestrol acetate, dronabinol, cyproheptadine, melatonin, ghrelin etc
- Others: growth hormone, vitamin D etc

SUMMARY

- PEW is common and closely associated with high mortality and morbidity in CKD patients
- PEW is caused by multiple CKD-related factors, as well as inadequate nutrient intake
- Prevention and treatment of PEW, including optimal nutritional support and exercise, should be integrated clinical practice in CKD patients
- Potential pharmacologic agent needs to be studied further.