End stage renal disease and Protein Energy wasting

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www.PassPACES.com/kidney.htm

Introduction

Chronic kidney disease- increasing health burden in many countries.

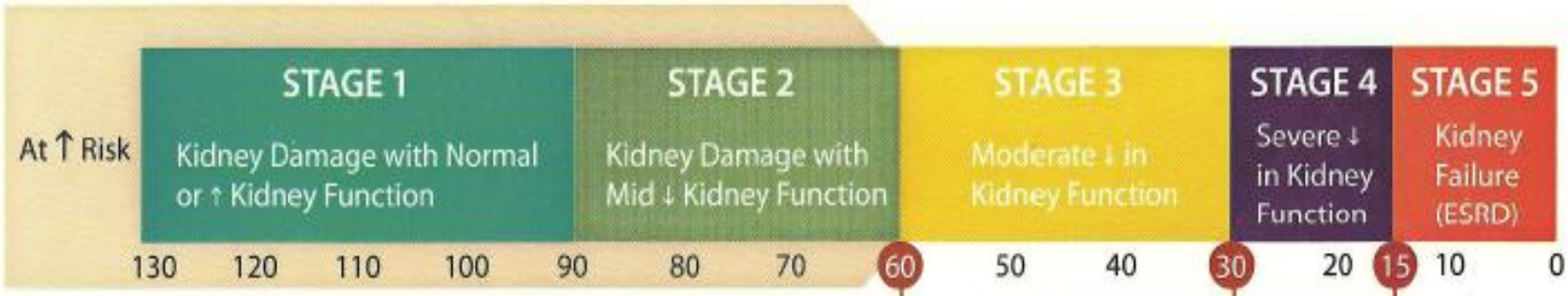
The estimated prevalence of CKD in the US was 16.8% while in Asia the prevalence ranged from 12.1% to 17.5%.

CKD is associated with increased risk of mortality, cardiovascular disease, and progression to renal failure.

Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. Kidney Int 2002; 62: 1109-24.

Appendix 3 : CKD – Stages of CKD

Kidney Function: Glomerular Filtration Rate (GFR) (Guidelines 1 and 2)



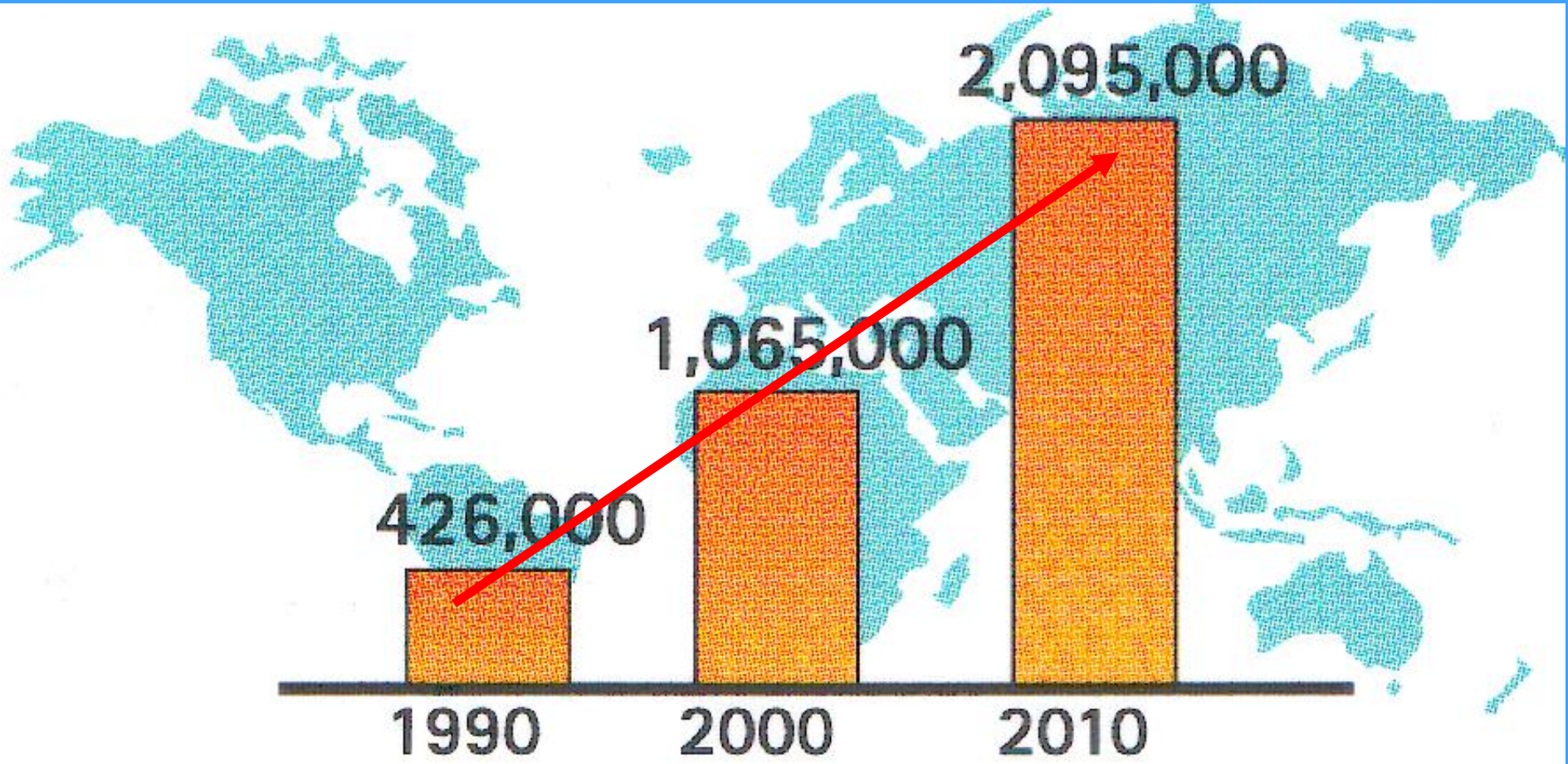
If GFR <60, asess:
- Presence of anemia (Guideline 8): follow K/DOQI Anemia Guidelines
- Nutritional status (Guideline 9): follow K/DOQI Nutritional Guidelines
- Bone Metabolism (Guideline 10): follow K/DOQI Bone Metabolism Guidelines
- Indices of functioning and well-being (Guideline 12)

If GFR <30:
- Refer to nephrologist
- Prepare for Kidney Replacement Therapy (KRT)

If GFR <15, consider initiation of KRT.
Patients who may benefit from KRT at Higher levels of kidney function:
- Living donor transplant recipients
- Older patients
- Those with diabetes (this group is at highest risk for ASCVD)
- Those with ASCVD
- Those with other comorbid conditions

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39, 2002(suppl 1). These Guidelines, as well as all other K/DOQI™ guidelines, can be accessed on the Internet at: www.kdoqi.org NKF Order No. 12-50-0157. Amgen Part No. P35184.

Global maintenance dialysis population from 1990 to 2010



Lysaght, *J Am Soc Nephrol*, 2002

Prevalence of ESRD

(per million population),

2005

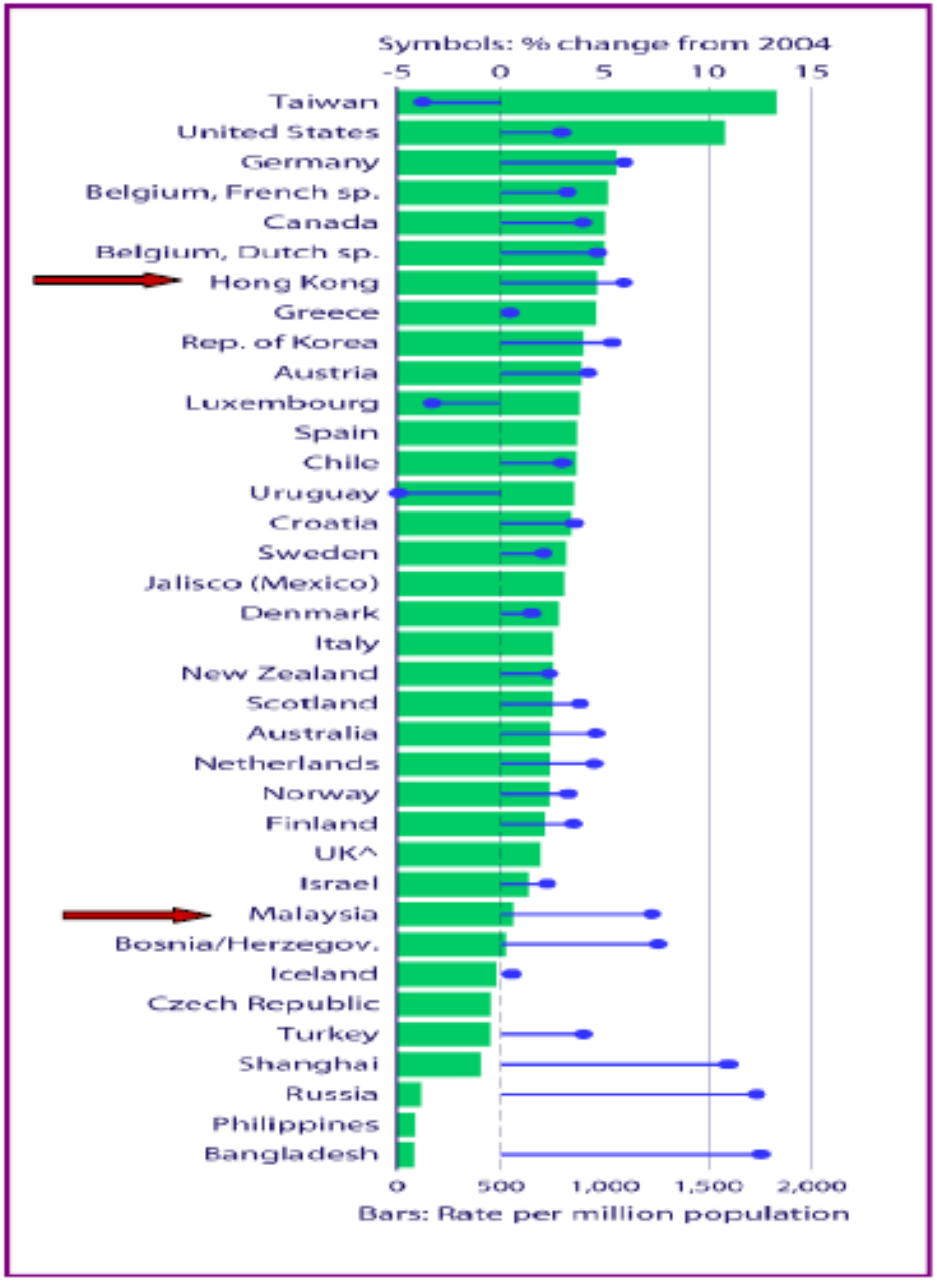
1. **Taiwan 1,830**
2. **USA 1,585**
3. **Germany 1,057**

7. HK 965

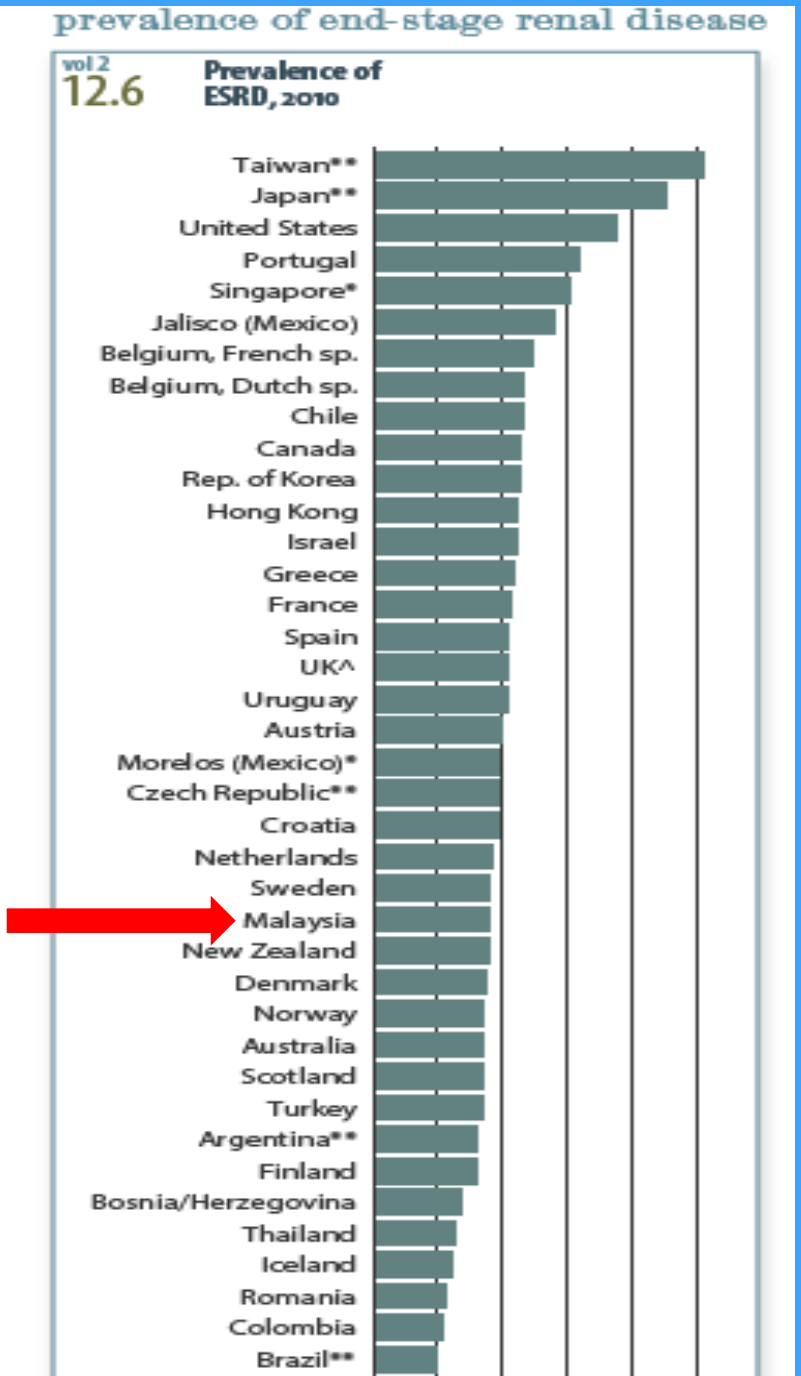
28. Malaysia 560

(Japan – no data - No. 1 in 2003)

USRDS 2007



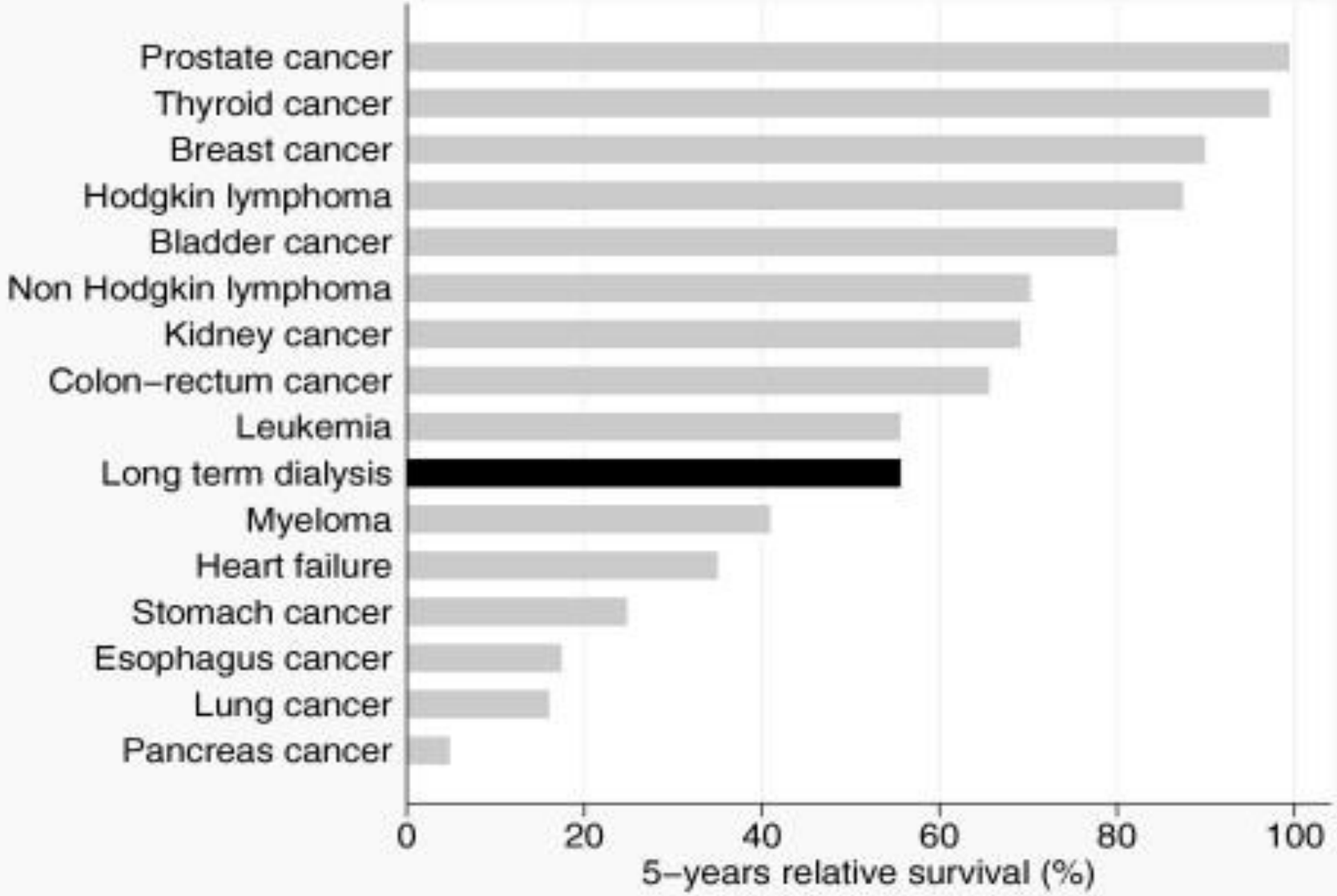
prevalence of end-stage renal disease



Taiwan and Japan continued to report the highest rates of prevalent ESRD, at 2,584 and 2,260 per million population, respectively, in 2010. The next highest rate was reported by the United States, at 1,870, followed by Portugal, Singapore (2009), and Jalisco (Mexico) at 1,590, 1,524, and 1,402. The lowest rates were reported by Bangladesh and Russia, at 158 and 186.

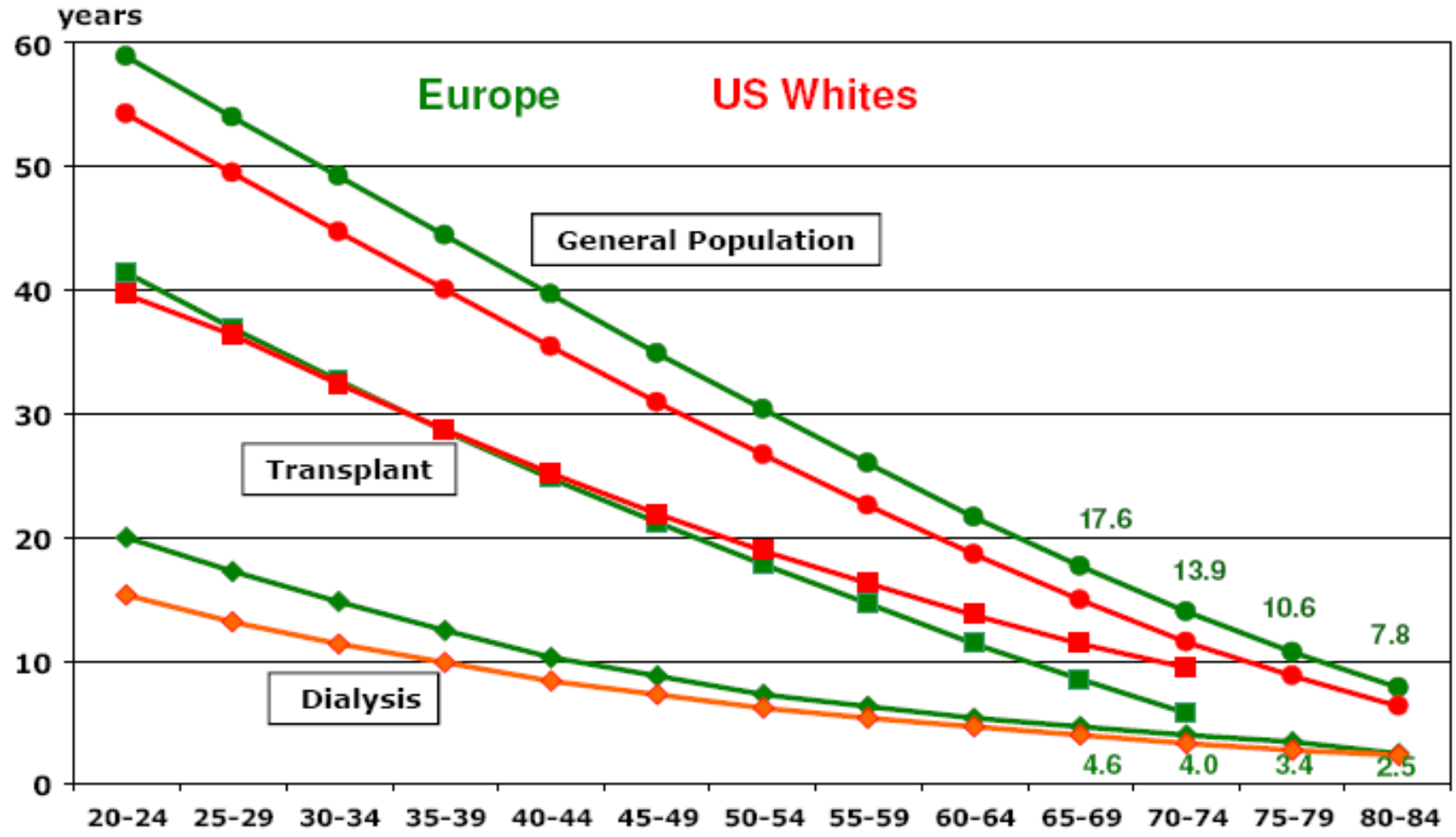
1) Taiwan 2584 pmp
2) Japan 2260 pmp
3) USA 1870 pmp

25) Malaysia 812 pmp



Maurizio Nordio et al 2012,AJKD

Expected remaining lifetimes in adult CKD Stage 5 as compared to the General Population

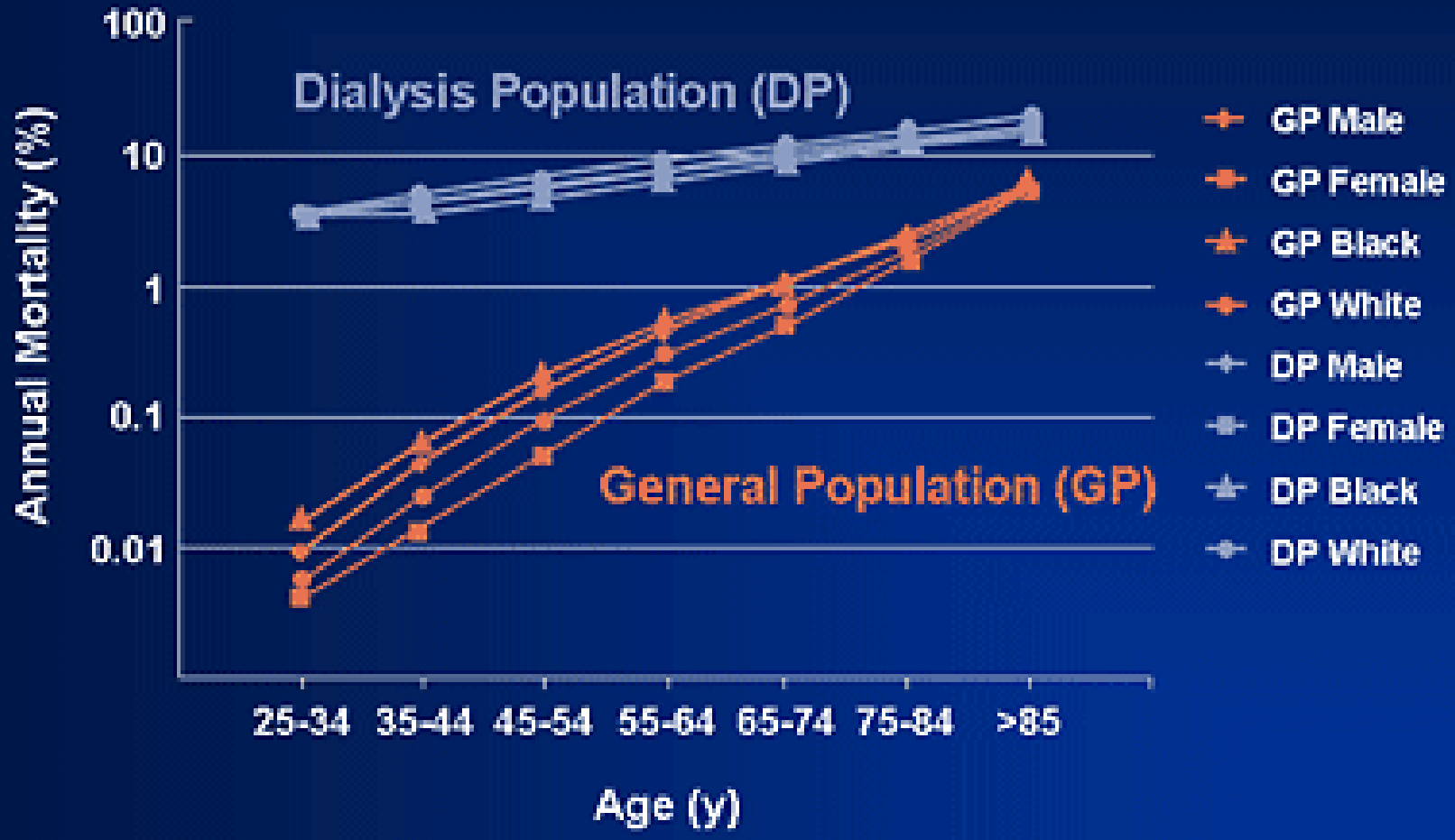


ERA-EDTA Registry data and USRDS data

If a cure is not achieved, the kidneys will pass on the disease to the heart

Huang Ti Nei Ching Su Wen
The Yellow Emperor's Classic of Internal Medicine
~2000 B.C.

Cardiovascular Mortality



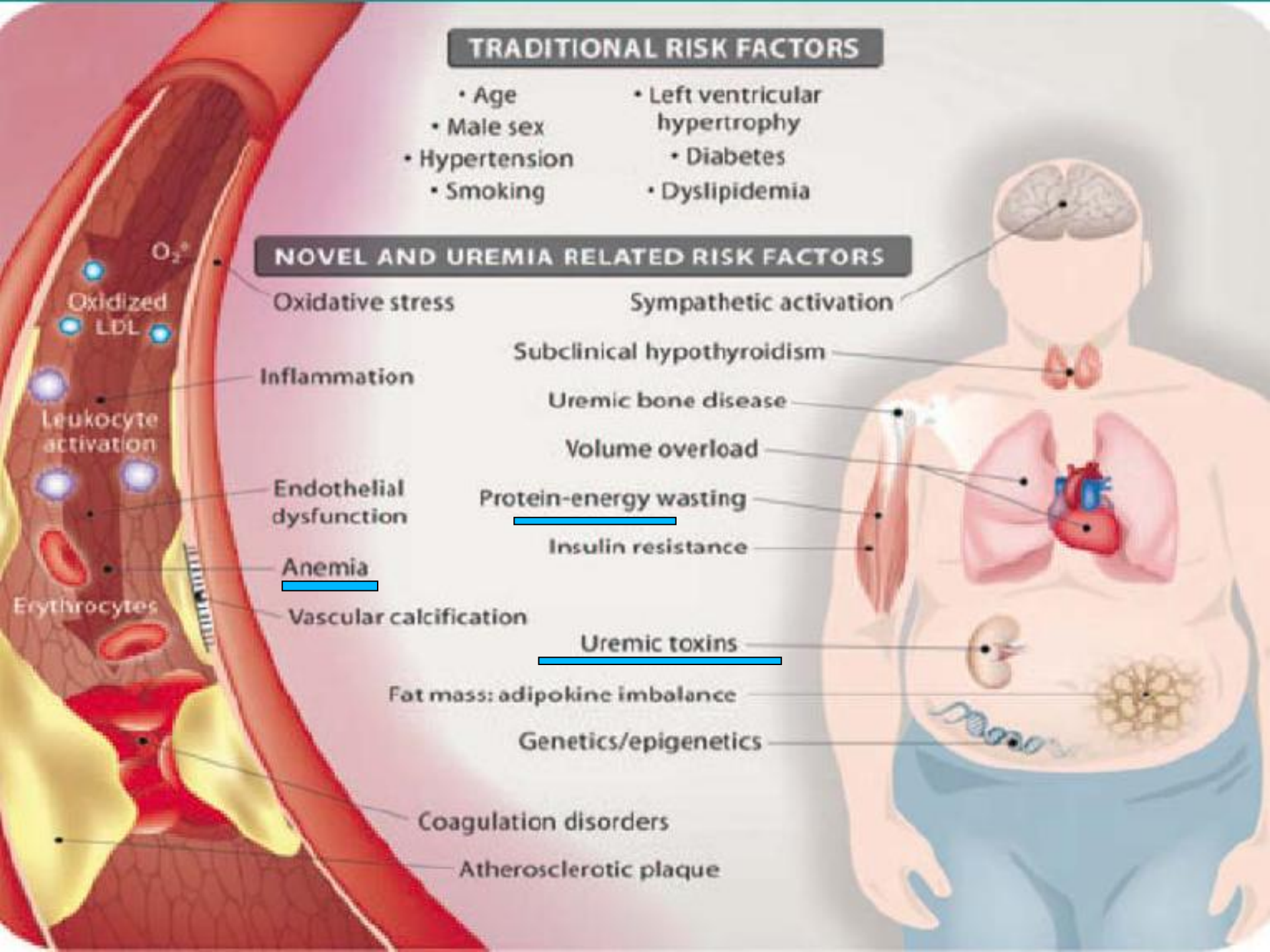
Adapted from Sarnak MJ, et al. *Am J Kidney Dis.* 2000;35(4 suppl 1):S117-S131.

Table 3.1.2: Causes of Death on Dialysis 2001-2010

Year / Causes of Death	2001		2002		2003		2004		2005	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	221	26	313	33	341	28	341	26	376	25
Died at home	228	27	212	22	290	24	307	23	320	21
Sepsis	134	16	148	15	197	16	166	13	179	12
PD peritonitis	30	4	16	2	14	1	13	1	22	1
GIT bleed	18	2	24	3	29	2	24	2	29	2
Cancer	18	2	18	2	28	2	20	2	28	2
Liver disease	11	1	16	2	25	2	29	2	26	2
Withdrawal	20	2	18	2	26	2	9	1	11	1
Others	89	10	104	11	161	13	325	25	406	27
Unknown	81	10	90	9	100	8	84	6	116	8
TOTAL	850	100	959	100	1211	100	1318	100	1513	100

Year / Causes of Death	2006		2007		2008		2009		2010	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	517	28	516	26	682	31	871	34	871	34
Died at home	354	20	343	17	423	19	492	19	507	20
Sepsis	235	13	222	11	336	15	570	22	605	24
PD peritonitis	22	1	16	1	25	1	30	1	34	1
GIT bleed	26	1	31	2	43	2	44	2	51	2
Cancer	41	2	34	2	53	2	54	2	69	3
Liver disease	35	2	37	2	44	2	26	1	31	1
Withdrawal	23	1	27	1	24	1	34	1	29	1
Others	392	22	552	28	366	17	195	8	108	4
Unknown	170	9	206	10	194	9	262	10	269	10
TOTAL	1815	100	1984	100	2190	100	2578	100	2574	100

18th MDTR report 2010, Malaysia


TRADITIONAL RISK FACTORS
• Age
• Male sex
• Hypertension
• Smoking
• Left ventricular hypertrophy
• Diabetes
• Dyslipidemia
NOVEL AND UREMIA RELATED RISK FACTORS
O_2^-
Oxidized LDL
Oxidative stress
Sympathetic activation
Subclinical hypothyroidism
Inflammation
Uremic bone disease
Leukocyte activation
Volume overload
Endothelial dysfunction
Protein-energy wasting
Insulin resistance
Anemia
Erythrocytes
Vascular calcification
Uremic toxins
Fat mass: adipokine imbalance
Genetics/epigenetics
Coagulation disorders
Atherosclerotic plaque

Definition

Protein-energy wasting (PEW) is common in patients with chronic kidney disease (CKD)

The International Society of Renal Nutrition and Metabolism (ISRNM) expert panel has defined PEW as a, “state of decreased body stores of protein and energy fuels (body protein and fat masses)”

Other terms used

Uremic malnutrition,

uremic (renal) cachexia,

protein–energy malnutrition,

malnutrition–inflammation atherosclerosis syndrome, or

malnutrition–inflammation complex (or cachexia) syndrome

CKD and Malnutrition

Complication	GFR category (ml/min/1.73 m^2)				
	≥90	60-89	45-59	30-44	<30
Anemia[1]	4.0%	4.7%	12.3%	22.7%	51.5%
Hypertension[2]	18.3%	41.0%	71.8%	78.3%	82.1%
25(OH) Vit D deficiency[3]	14.1%	9.1%	10.7%		27.2%
Acidosis[4]	11.2%	8.4%	9.4%	18.1%	31.5%
Hyperphosphatemia[5]	7.2%	7.4%	9.2%	9.3%	23.0%
Hypoalbuminemia[6]	1.0%	1.3%	2.8%	9.0%	7.5%
Hyperparathyroidism[7]	5.5%	9.4%	23.0%	44.0%	72.5%

Kidney international , 2013, 73-90

Surveys using classic measures of nutritional status indicate that approximately 18–75% of patients with CKD undergoing maintenance dialysis therapy show evidence of wasting

Malnutrition is Common in Dialysis Patients

HEMO Study (2002): Nutritional status of 1000 patients analyzed.

- 76% had mean energy intake below KDOQI standard of care(28kcal/kg/d)
- 61% had a mean protein intake below the KDOQI standard of care (1g/kg/d)
- 79% had a mean serum albumin level < 4.0g/dL
- 28% had a mean serum albumin level <3.5g/dL

Pre-albumin levels and patient survival both drop with increasing time on dialysis

Rocco et al. *Am J Kidney Dis* 2002
Chertow et al. *Kidney International* 2000

Potential causes of protein-energy wasting syndrome in kidney disease

Anorexia, acidosis, anemia

Endocrine disorders, vitamin D deficiency, ↑PTH, diabetes, decreased insulin / IGF signalling

↑ Production of inflammatory cytokines

Oxidative and carbonyl stress

Volume overload

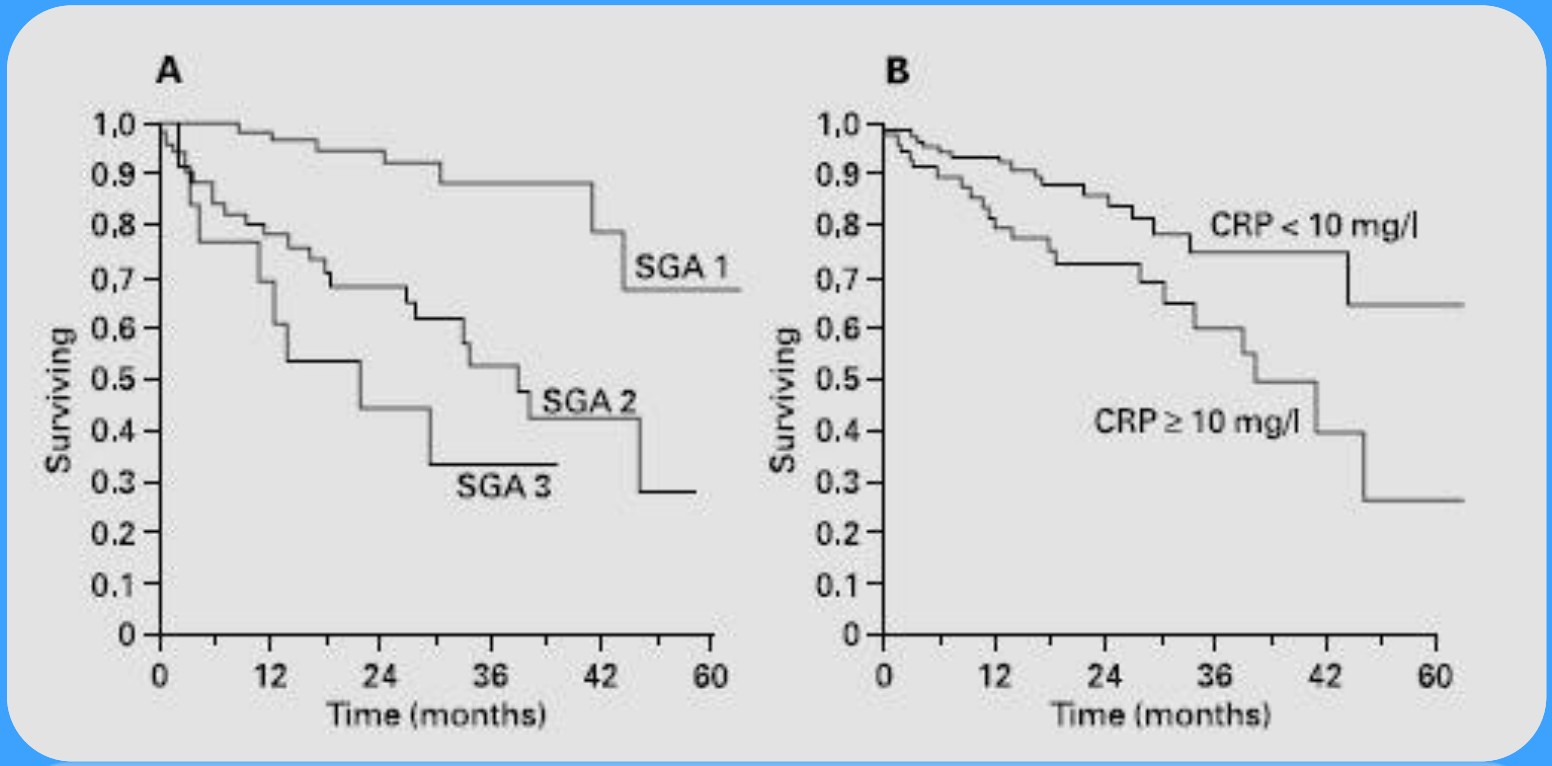
↓ Nutrient intake, prescribed dietary restrictions

Nutrient loss during dialysis

Dialysis treatment–related factors, AV graft, dialysis membrane

Comorbid conditions: DM, cardiovascular disease, infection, aging

Markers of Malnutrition and Inflammation are Independent Predictors of Mortality



Peter Stenvinkel. Blood Purification 2001

Association of Albumin and Mortality

Lowrie et al (*Am J Kidney Dis* 1990)

- 12,000 US hemodialysis patients were evaluated.
- Serum albumin < 4g/dL was the variable most hightly associated with death
- 2/3 had low albumin

Iseki et al (*Kidney International* 1993)

- 1982 Okinawan dialysis patients were recruited between 1971-1990 and observed until 1992.
- Albumin (along with age, male sex and serum creatinine) was identified as a significant predictors of death (52% died of cardiovascular causes)
- Patients had incrementally higher survival rates when albumin went from <3.5g/dL (HR1) to 3.5-3.9 g/dL (HR0.4) to 4 (HR0.27)

Lowrie EG, Lew NL. *Am J Kidney Dis*, 15(5) 1990
Iseki et al. *Kidney International*, Vol.44 (1993)

Readily utilizable criteria for the clinical diagnosis of protein energy wasting in chronic kidney disease criteria

1. **Serum chemistry**
   Serum albumin < 3.8 g 100 ml^{-1} (Bromcresol Green)[a]
   Serum prealbumin (transthyretin) < 30 mg 100 ml^{-1} (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5)[a]
   Serum cholesterol < 100 mg 100 ml^{-1}[a]
2. **Body mass**
   BMI < 23[b]
   Unintentional weight loss over time: 5% over three months or 10% over six months
   Total body fat percentage < 10%
3. **Muscle mass**
   Muscle wasting: Reduced muscle mass 5% over three months or 10% over six months
   Reduced mid-arm muscle circumference area[c] (reduction > 10% in relation to the fiftieth percentile of reference population)
   Creatinine appearance[d]
4. **Dietary intake**
   Unintentional low DPI < 0.80 gkg^{-1} day^{-1} for at least two months[e] for dialysis patients or < 0.6 g kg^{-1} day^{-1} for patients with CKD stages 2 – 5
   Unintentional low dietary energy intake (DEI) < 25 kcal kg^{-1} day^{-1} for at least two months[e]

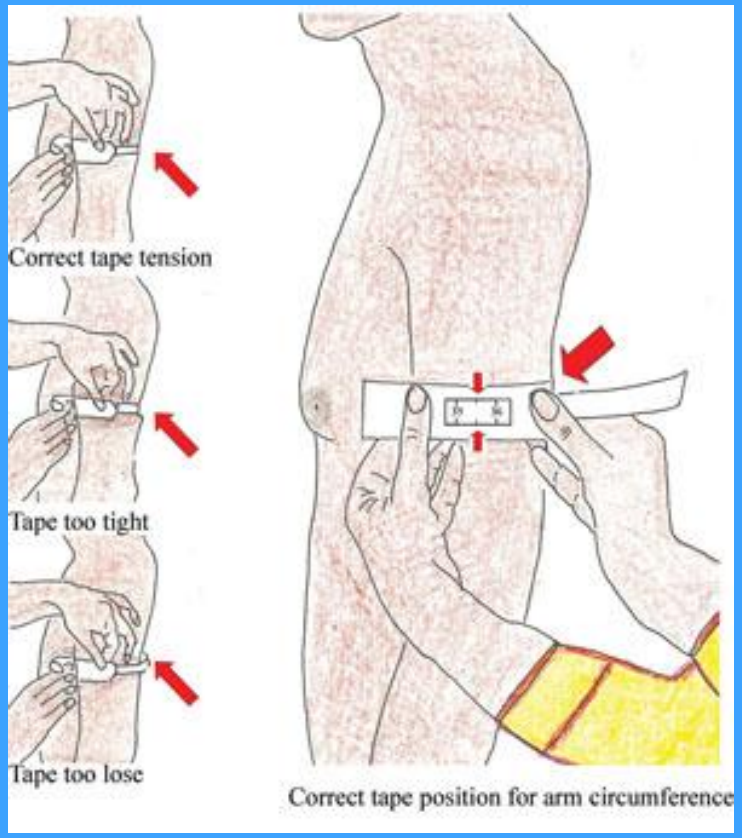
At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease–related PEW. Optimally, each criterion should be documented on at least three occasions, preferably two-to-four weeks apart.

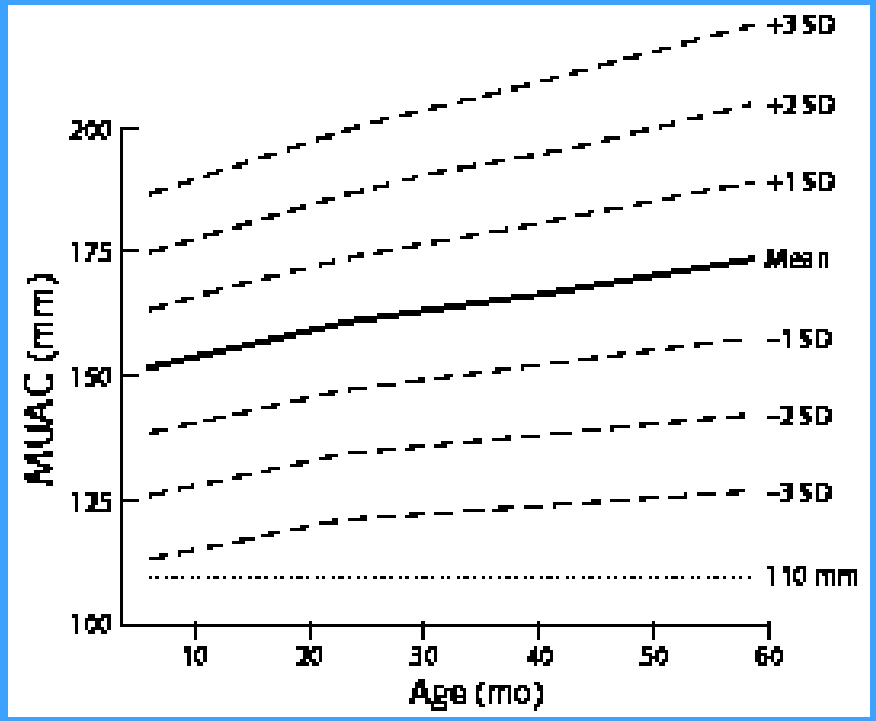
Dietary energy intake (DEI), dietary protein intake (DPI), nPCR normalized protein catabolic rate, and nPNA normalized protein nitrogen appearance,

a. Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines
b. A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, post-dialysis dry weight
c. Measurement must be performed by a trained anthropometrist
d. Creatinine appearance is influenced by both muscle mass and meat intake
e. Can be assessed by dietary diaries and interviews, or by protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR), as determined by urea kinetic measurements

Simplified Assessment

1) Biochemistry- Albumin level, serum choleterol (38g-bromcresol green technique and 2.59umol)
2) BMI or body fat content (<23 and < 10%)
3) Muscle mass- reduced mid arm circumference


Correct tape tension
Tape too tight
Tape too lose
Correct tape position for arm circumference


+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
110 mm
MUAC (mm)
200
175
150
125
100
10
20
30
40
50
60
Age (mo)

4) Dietary intake- protein intake less than 0.8g/kg for 2 months in dialysis patients or energy intake of less than 25 kcal/kg/day.

Must be 3 out of 4 criteria above

Selected nutritional parameters for varying levels of kidney disease

Nutritional Parameter	Stages 1 – 4 CKD	Stage 5 Hemodialysis	Stage 5 Peritoneal Dialysis
Calories (kcal / kg / d)	35 < 60 years 30 - 35 ≥ 60 years	35 < 60 years 30 - 35 ≥ 60 years	35 < 60 years 30 - 35 ≥ 60 years, include kcals from dialysate
Protein (g / kg / d)	0.6 - 0.75	1.2	1.2 - 1.3
Fat (% total kcal)	For patients at risk for CVD, < 10% saturated fat, 250 - 300 mg cholesterol / d		
Sodium (mg / d)	2000	2000	2000
Potassium (mg / d)	Match to laboratory values	2000 - 3000	3000 - 4000
Calcium (mg / d)	1200	≤ 2000 from diet and medicines	≤ 2000 from diet and medicines
Phosphorus (mg / d)	Match to laboratory values	800 - 1000	800 - 1000
Fluid (mL / d)	Unrestricted with normal urine output	1000 + urine	Monitor; 1500 - 2000

*Represents initial guidelines; individualization to patient's own metabolic status, and coexisting metabolic conditions are essential for optimal care

American Dietetic Association guidelines

Albumin = Marker of Nutrition?

Albumin influenced by nutrition as well as inflammation

- Albumin may be Low even in apparently well nourished patients suggesting it is not a pure marker of nutritional status

Albumin is regulated by multiple factors including protein malnutrition, inflammation and external losses

Inflammation via acute phase proteins (ie. CRP) are correlated with reductions in serum albumin

Halliwell B. *Haemostasis* 23 (Suppl 1), 1993
Stenvinkel P et al. *Nephrol Dial Transplant* 1998

Table 7.1.1: Distribution of serum albumin, HD patients, 1997-2012

Year	Number of patients	Sr. Albumin (g/L)				Patient Distribution			
		Mean ± SD	Median	LQ	UQ	% patients <30g/L	% patients 30-<35g/L	% patients 35-<40g/L	% patients ≥40g/L
1997	1644	40.9 ± 6.2	41	37.7	44.3	3	8	30	59
1998	2075	41.2 ± 6.5	41	37.5	44.7	3	9	28	59
1999	2755	39.7 ± 6.1	39.7	36.3	43	4	13	35	49
2000	3731	38.6 ± 7	39	36	42	5	11	41	43
2001	4666	39 ± 5.6	38.5	36	41.8	3	15	44	38
2002	5568	39.2 ± 5.6	39	36.5	42	3	12	42	43
2003	6524	39.9 ± 5.4	40	37.3	42.5	3	9	35	52
2004	7581	39.9 ± 5.3	40	37	42.8	3	10	34	53
2005	8706	40 ± 5.2	40.3	37.5	42.8	3	9	33	56
2006	10928	39.8 ± 5.4	40.3	37.3	42.8	3	10	33	54
2007	12315	39.7 ± 5.3	40	37	42.5	3	10	35	52
2008	14548	39.4 ± 5.1	40	37	42.3	3	10	36	50
2009	16940	39.4 ± 5.1	40	37	42.3	3	11	35	51
2010	18757	38.9 ± 4.9	39.3	36.3	41.8	4	13	40	44
2011	21830	38.7 ± 5	39	36.3	41.5	4	13	41	43
2012	24789	38.7 ± 5	39.2	36.3	41.5	4	13	41	43

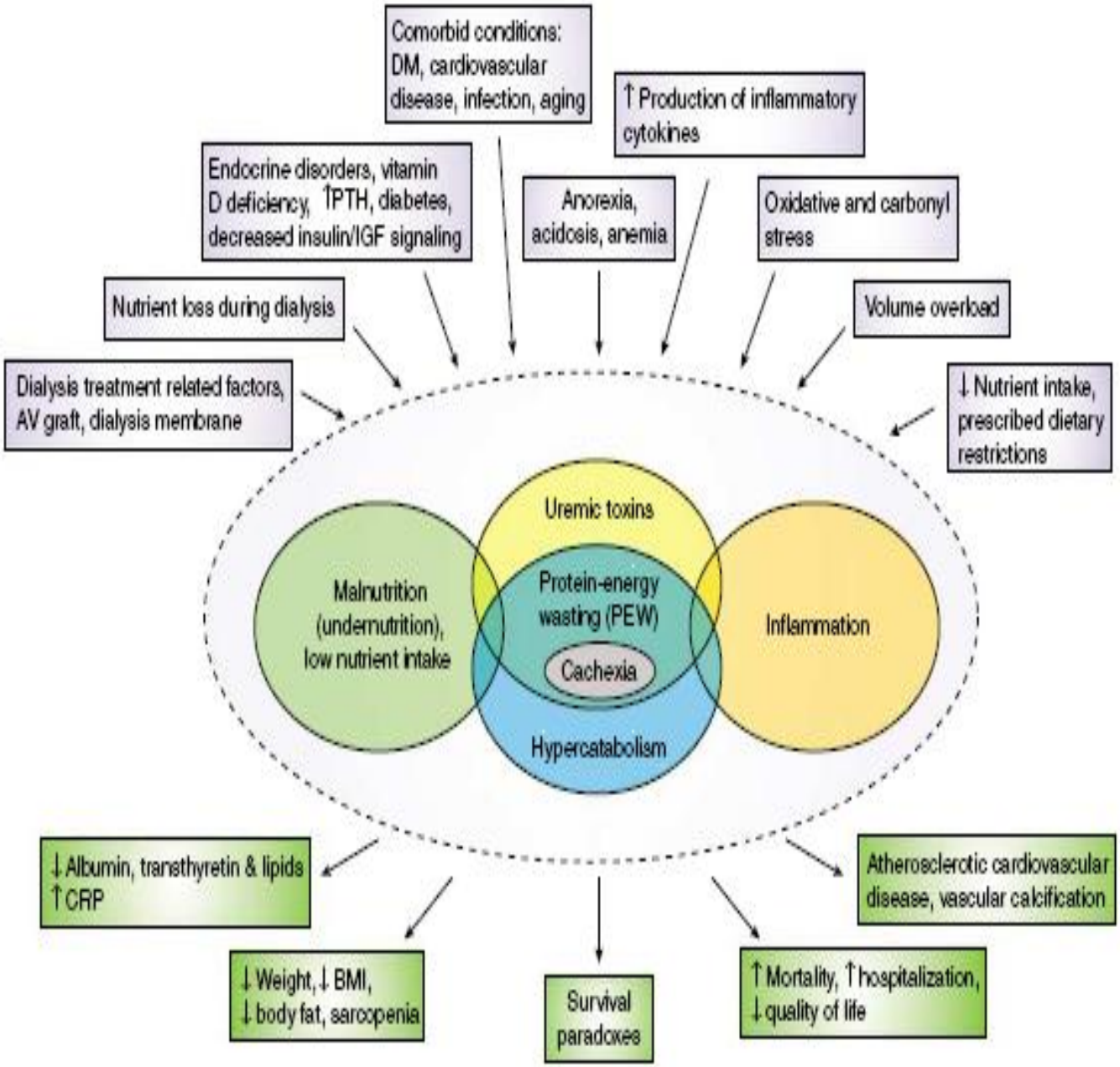


Figure 1 | Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease.

Oral Nutritional Supplements: Useful!

All HD patients with

albumin ≤3.5 g/dL

>4000 matched pairs

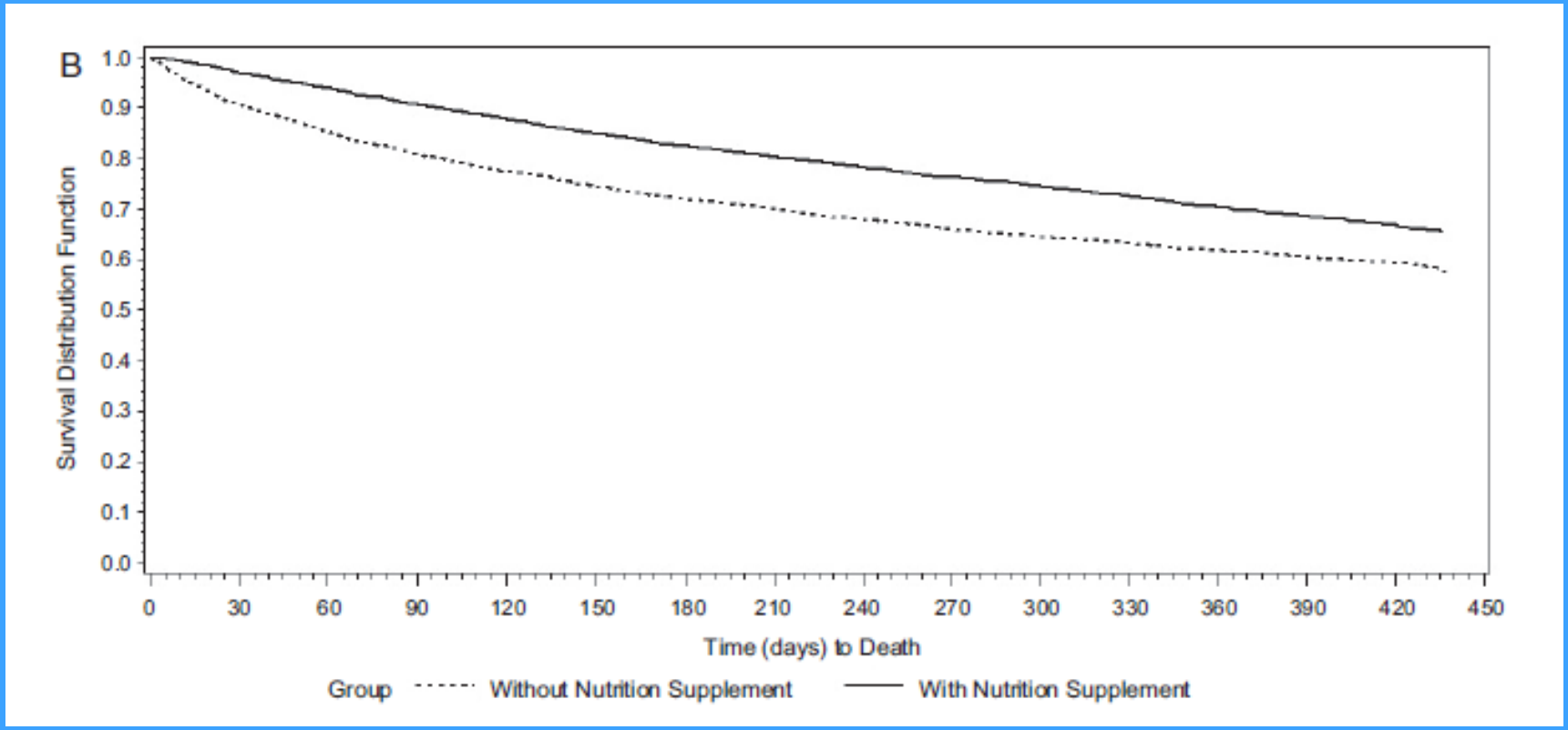
Nepro, or pure protein supplement at dialysis

Survival improved in the supplement group by 9% (ITT) or 34% (as-treated) compared with matched controls

Subjects with serum albumin <3.5 g/dL who were prescribed and received supervised ONSP exhibited significantly better one-year survival

Lacson et al. *Am J Kidney Dis.* 2012 Oct;60(4):591-600

KM survival curves – As Treated



Lacson et al. *Am J Kidney Dis.* 2012 Oct;60(4):591-600

Strategies to enhance oral intake

Avoid diet restrictions in patients with poor intake
Offer oral liquid supplements and snacks
Treat gastroparesis and other gastrointestinal conditions
Achieve glycemic control
Correct electrolyte abnormalities
Evaluate for and address depression

Guidelines for Nutrition Intervention

PEW is one of the strongest predictors of mortality in CKD patients

Provision of meals or oral nutritional supplements improves outcomes as well as patient adherence and satisfaction to dietary recommendations

Kalantar-Zadeh K et al. *Nat Rev Nephrol*. 2011;7:369-3

Nutrition Intervention now Supported by Nephrology Societies

Expert recommendations:

	KDOQI[1]	ESPEN[2]	EBPG[3]
Nutrition Support	Individuals undergoing maintenance dialysis who are unable to meet their protein and energy requirements with food intake for an extended period of time **should receive nutritional support**	**Special formula products for HD** treatment can be useful, especially in malnourished patients who are not able to increase their nutrient intake	Oral nutritional supplements should be prescribed if nutritional counseling does not achieve an increase in nutrient intake to a level that covers minimum recommendations. **Products specifically designed for dialysis patients should be prescribed**

THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

European Best Practice Guidelines

1. NKF K/DOQI Clinical practice guidelines for nutrition in chronic renal failure. *AJKD*, 2000; 35:S1-S140.
2. Cano N, et al. *Clin Nutr*, 2006; 25:295-310.
3. Fouque D, et al. *NDT,* 2007; 22(suppl 2):ii45-ii87.

Assisted Enteral Feeding

The hospitalized patients may benefit from a period of nasogastric feeding until the acute illness resolves

If the feeding tube placement is discussed as an important and beneficial part of their overall care, a patient is much more likely to agree to NGT placement

Parenteral Nutrition

Parenteral nutrition should be reserved only for those patients who are unable to receive enteral nutrients

Renal Specific Nutrition Therapy

Clinical studies have shown that renal-specific nutrition offers advantages over standard nutrition.

- Phosphorus levels were lower with the renal-specific nutrition than with the standard nutrition[1]
- Less fluid and potassium in renal-specific nutrition offers advantages over standard nutrition[2]

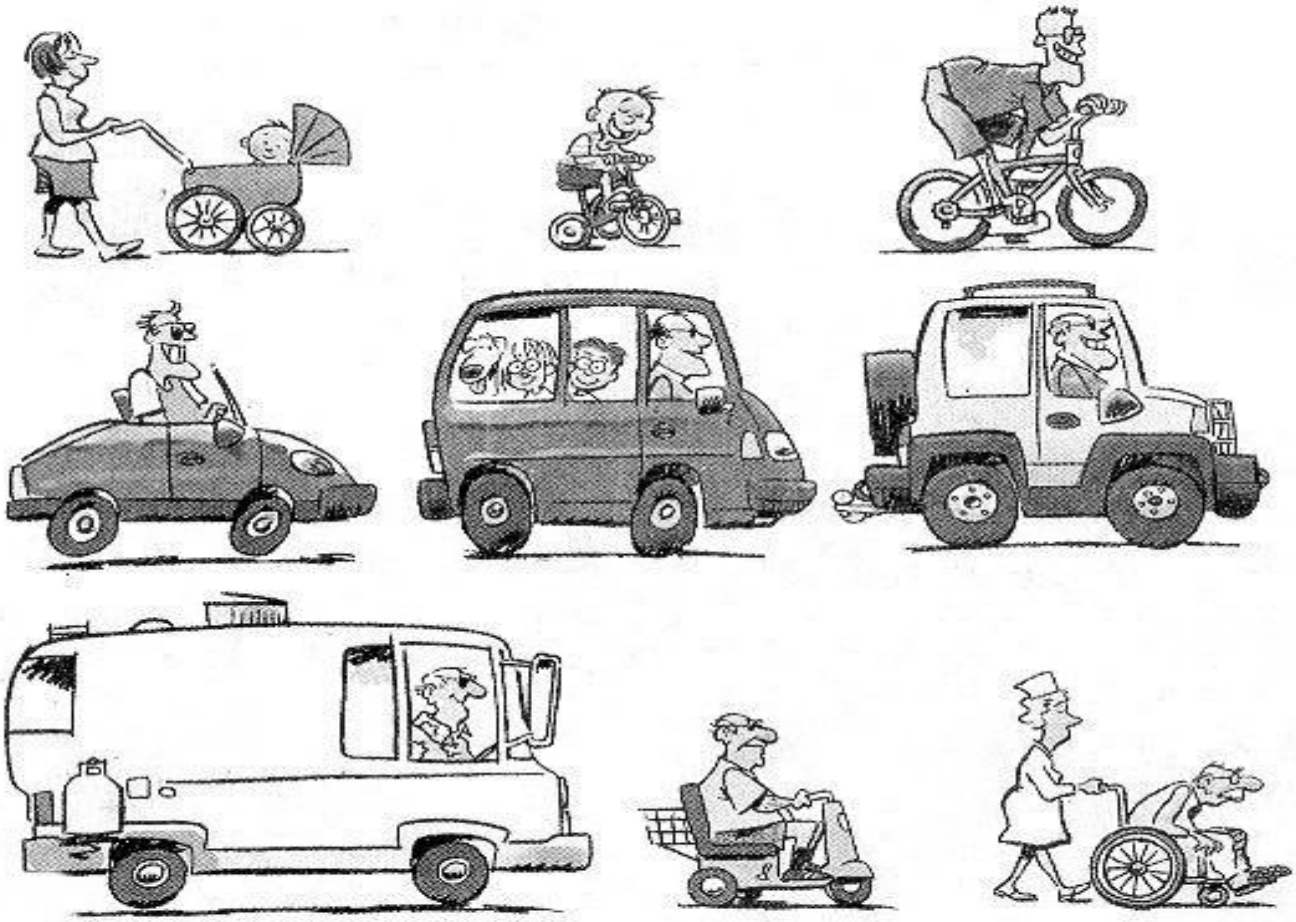
1. Cockram DB et al. *J Ren Nutr*. 1998;8:25-33.
2. Williams RF, Summers AM. *J Ren Nutr*. 2009;19:183-188.

SUMMARY

Summary

- Protein Energy wasting is common among chronic kidney disease patients and it is multifactorial
- PEW in CKD/dialysis patient is linked to increased CV disease, atherosclerosis Mortality
- Various strategies can be employed to treat PEW and studies show promising results in improving survival

The Wheels of Life



Thank You