Carnitine and Renal Disease

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Outline

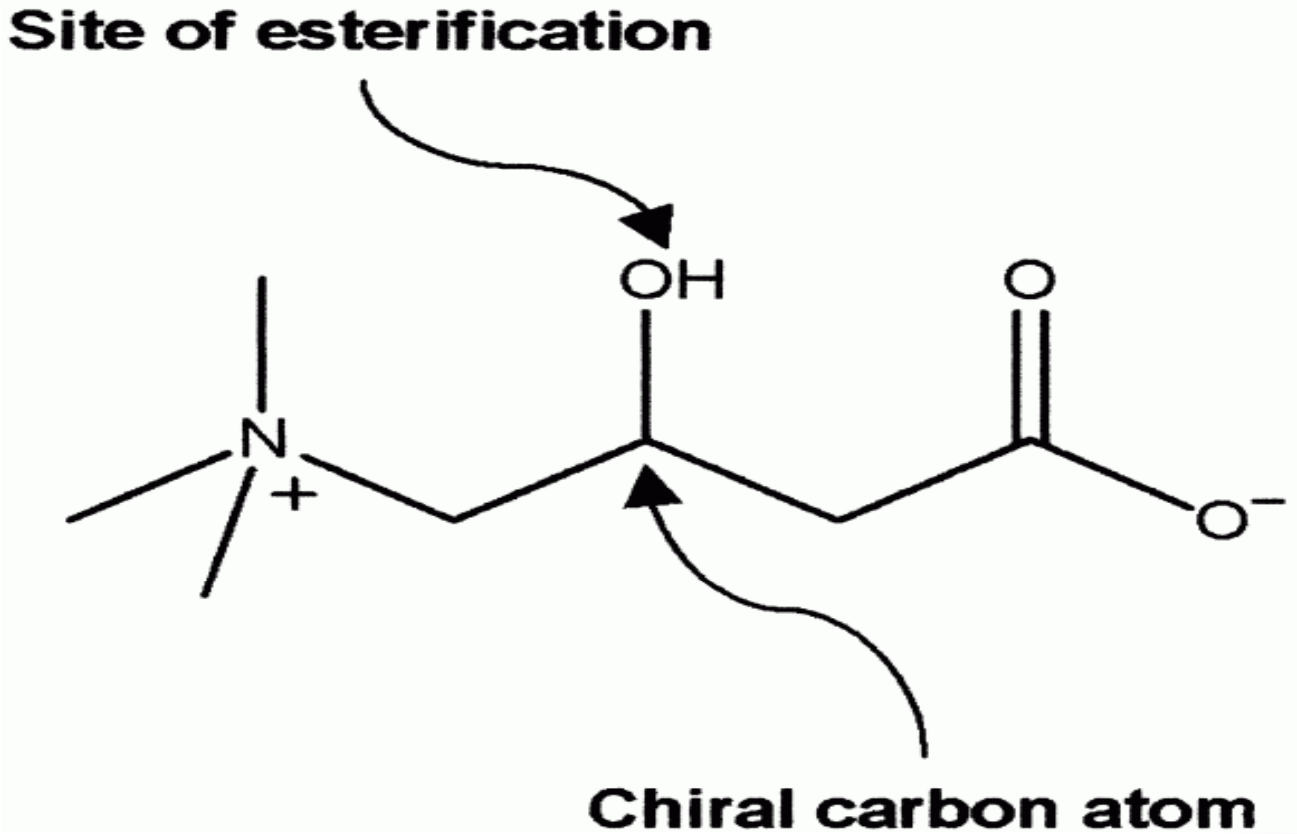
- Introduction to Carnitine
  - National Coverage Policy: FDA
- Alteration of Carnitine Status in Hemodialysis (HD) Patients
- Effects of Carnitine Treatment on HD Patients
- Practice Recommendations

National Coverage Decision for Levocarnitine

- **Effective Jan 1, 2003**
  - **National Coverage Determination for use of L-carnitine - criteria**
    - **L-carnitine deficiency (plasma free carnitine < 40μmol/L) +**
      - **Epo-resistant anemia (resistance to standard modalities to correct anemia = persistent Hct <30%)**
      - **Hypotension on HD that requires intervention & is unresponsive to all usual management measures & interferes with dialysis (min of 2 episodes in 30 days)**
    - **Covered only for 6 mos, if no improvement**

Carnitine:Background

Carnitine Structure



Carnitine Sources

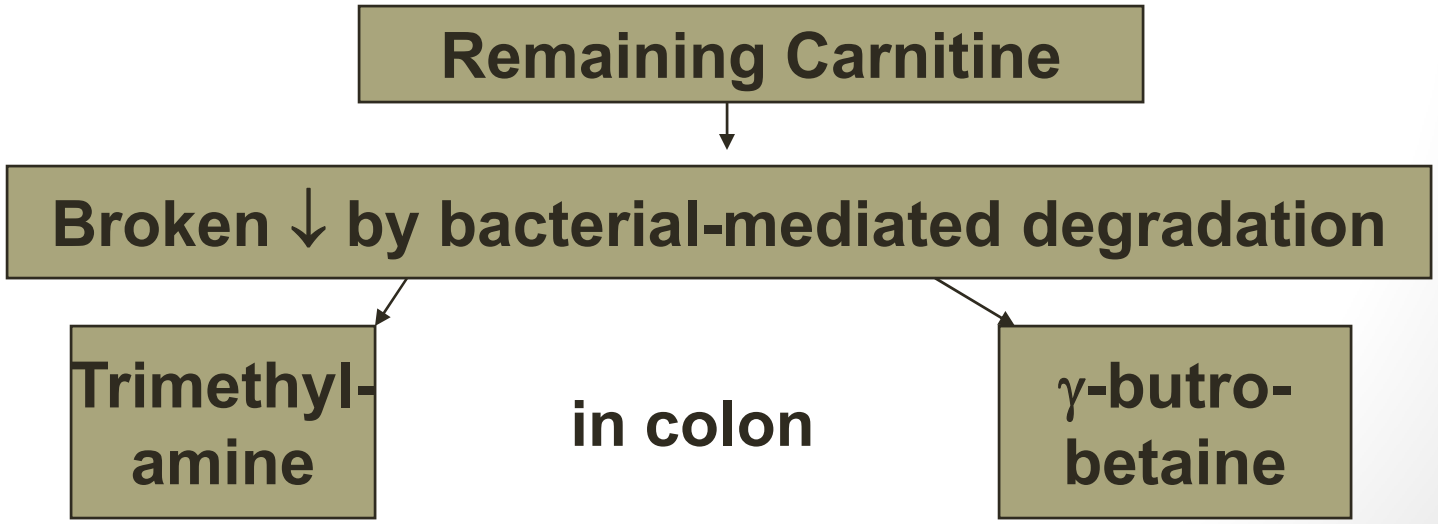
- Exogenous = 75% of body's pool
- Endogenous = 25% of body's pool
- <u>Exogenous sources</u>
  - Red Meats:
    - 50-120mg/100gm
  - Fish, Chicken, Milk:
    - 1.6-6.4mg/100gm
  - Vegetables, Fruits, Grains:
    - <0.05mg/100gm

Herbivore vs Omnivore

- **Carnitine intake:**
  - **Strict vegetarians = 0.1μmol/kg/d**
    - **10-20% decrease in plasma concentrations**
  - **Omnivorous diets = 12 μmol/kg/d**

Bioavailability

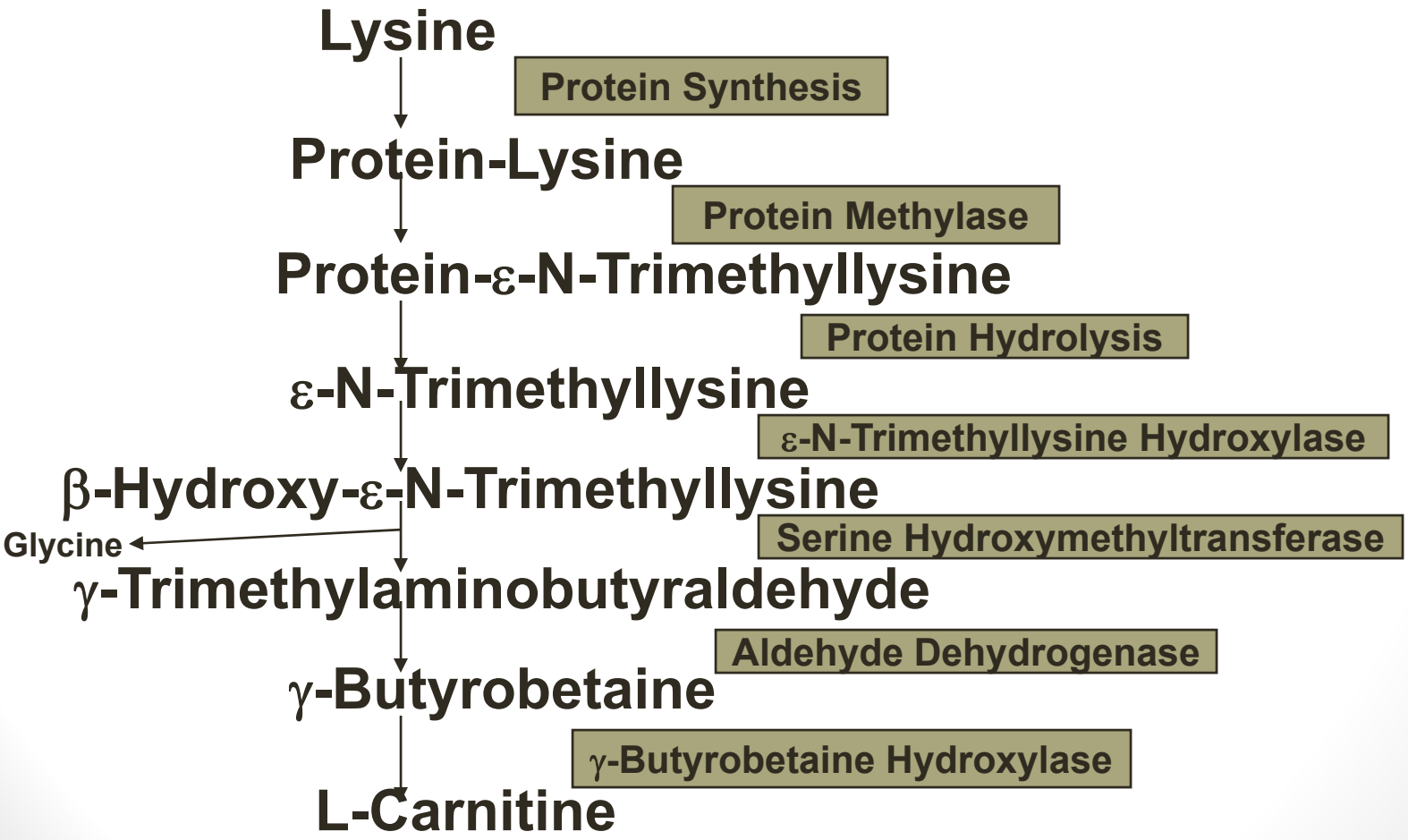
- **Determined by oral load**
  - **High carnitine diet (≥6 g) 5-15% absorbed**
  - **Low carnitine diet 75% absorbed**



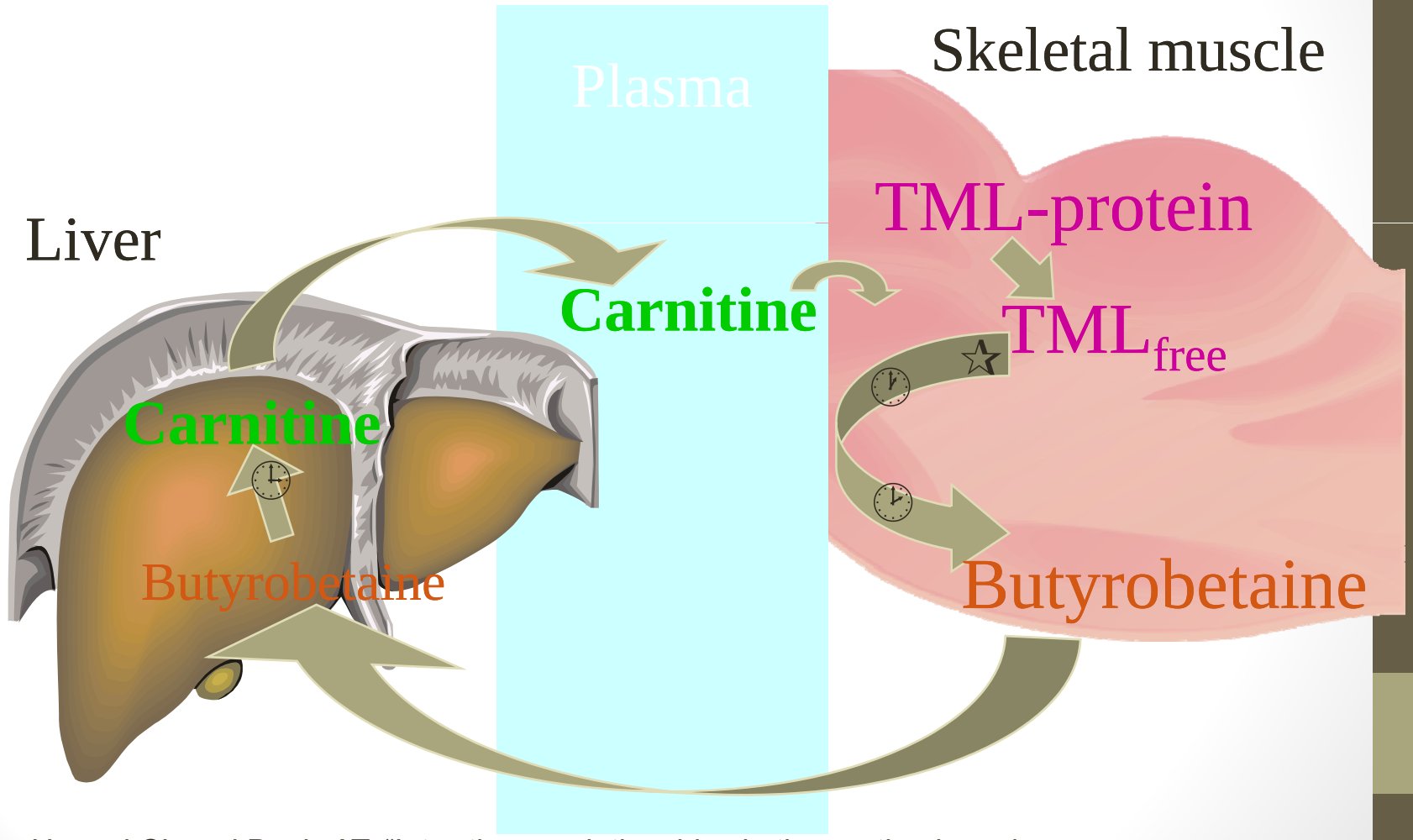
Endogenous sources

- **1-2 μmol/kg/d synthesized by humans (Lomard et al, 1989)**

Endogenous Carnitine Synthesis



Carnitine Biosynthesis



Hoppel CL and Davis AT. “Inter-tissue relationships in the synthesis and distribution of carnitine.” Biochem Soc Trans. 1886

Carnitine: Normal Excretion

- Tubular resorption in the kidneys
  - 98-99% (free carnitine)
  - 5 μmol/kg/d of acyl + free excreted in urine
- Healthy subject:
  - 2800 μmol/wk (mostly acyl)
- Hemodialysis subject:
  - 350 μmol/txtmt * 3 txtmt/wk = 1050 μmol/wk (equal free and acyl)

Evans et al, 2000; Lombard et al, 1989

Normal Serum Concentration of Carnitine

Type of Carnitine	
Total	46.1 ± 10μm/L *males 51.7±10.8μm/L *females - 43.8±11μm/L
Free	36.7± 7.6μm/L
Short chain acylcarnitine	5.7± 3.5μm/L
Long chain acylcarnitine	3.7 ± 1.5μm/L

* Borum et al, 1996, all others Brass and Hoppel, 1978

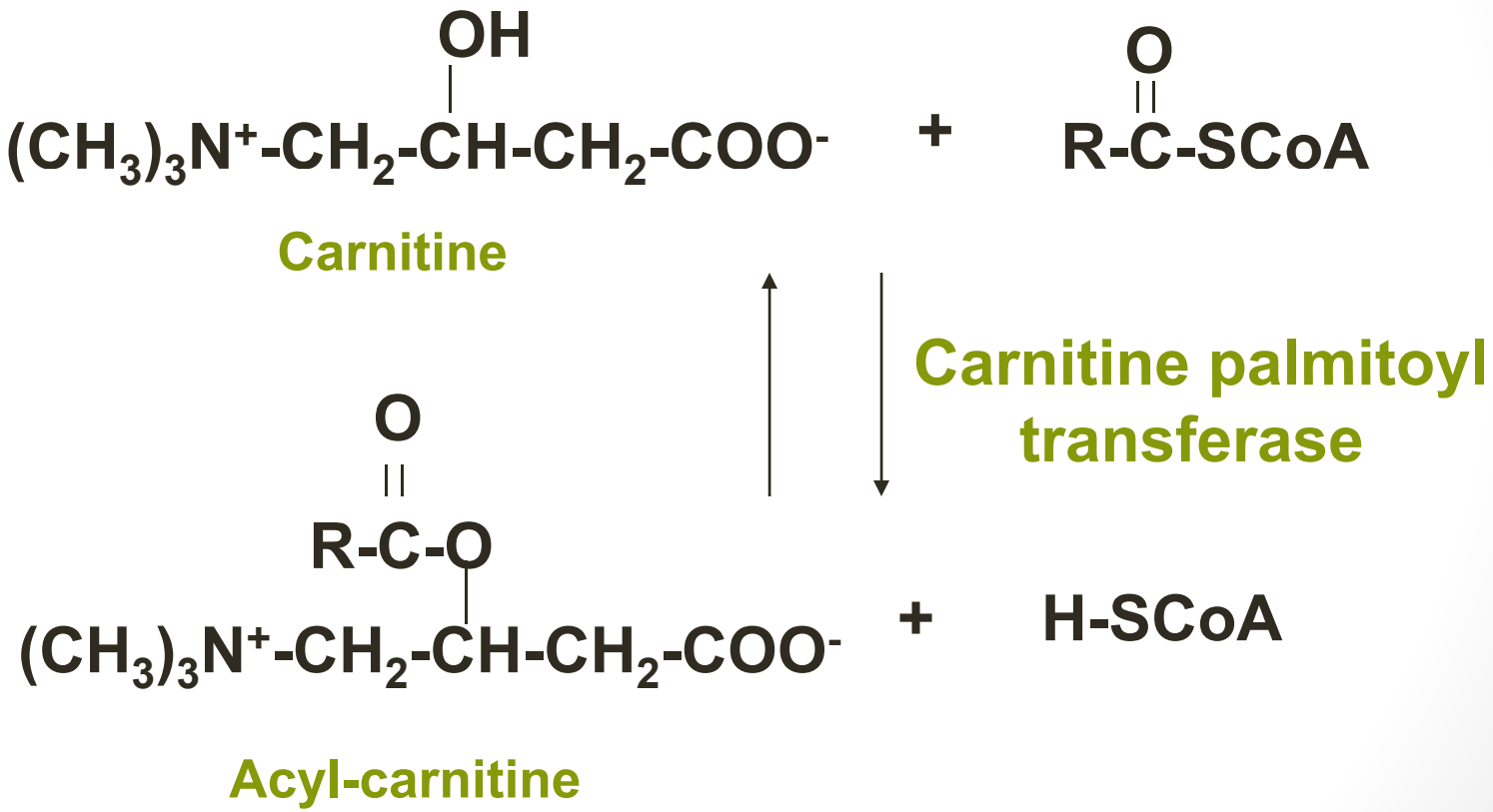
Normal Serum Concentrations of Carnitine

Type of Carnitine (plasma)	Historical Norms* μm/L	Reuter Norms μm/L	Hoppel Norms μm/L
Total	46±10	NA	29.3-72.9
Free	36.8±11	NA	23.3-57.9
Acetyl (c2)	SCAC 5.7±3.5 LCAC 3.7±1.5	6.43±2.01	3.01-13.5
Propionyl (c3)	NA	0.52±0.17	<0.64

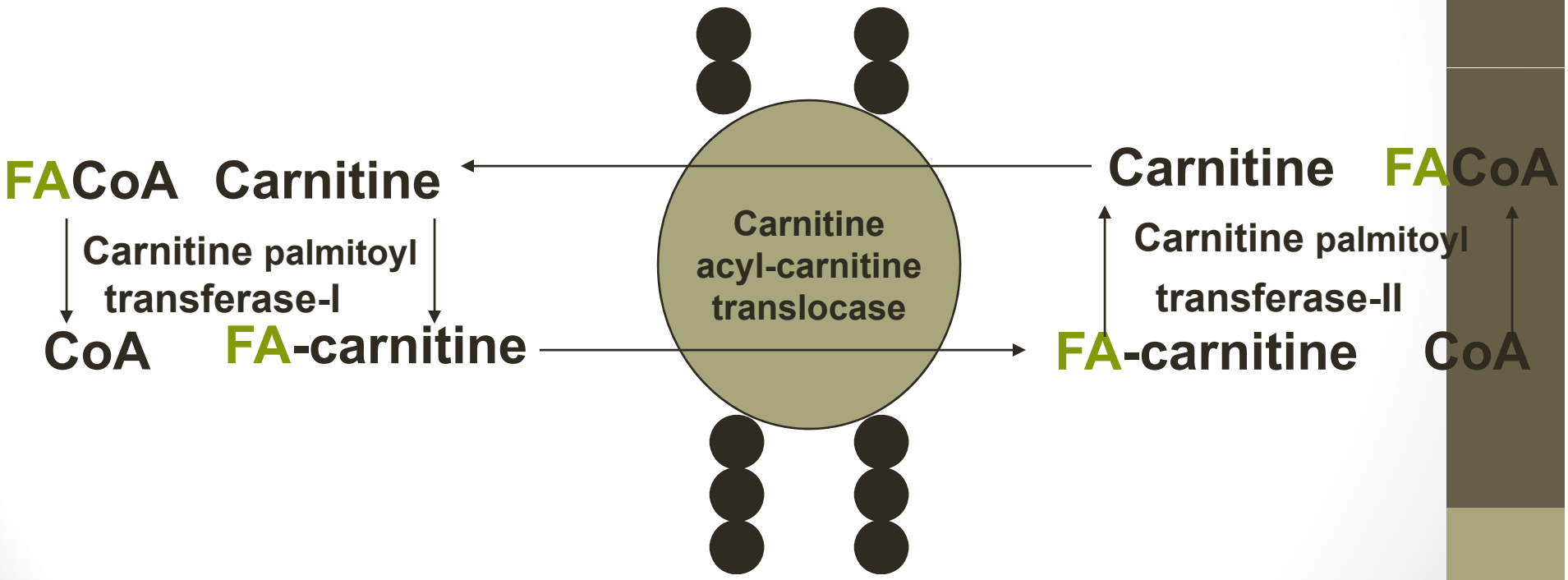
*** Borum et al, 1996, all others Brass and Hoppel, 1978**

Carnitine Functions

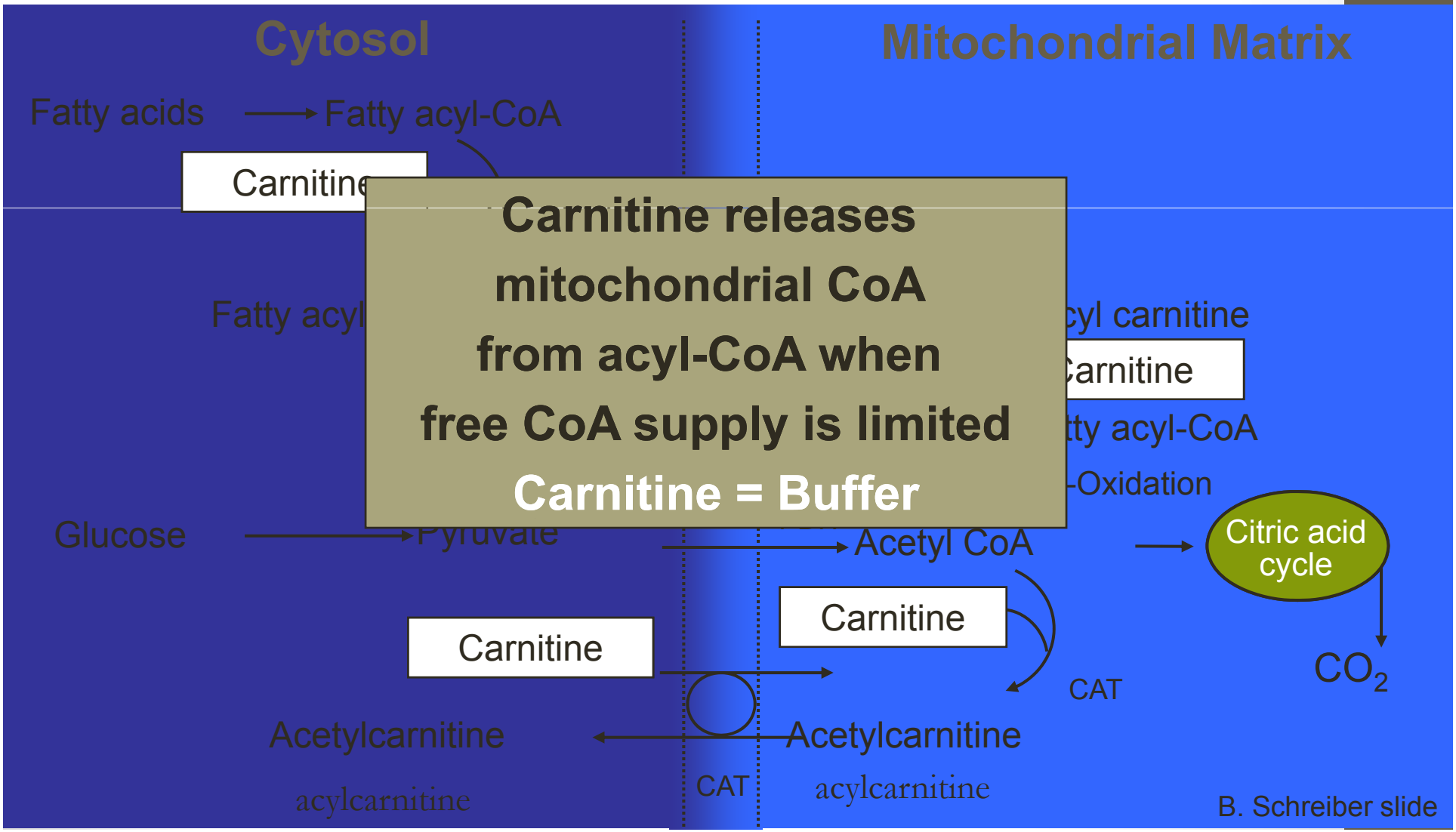
Acylation of Carnitine



Transport of LCFA across mitochondrial border

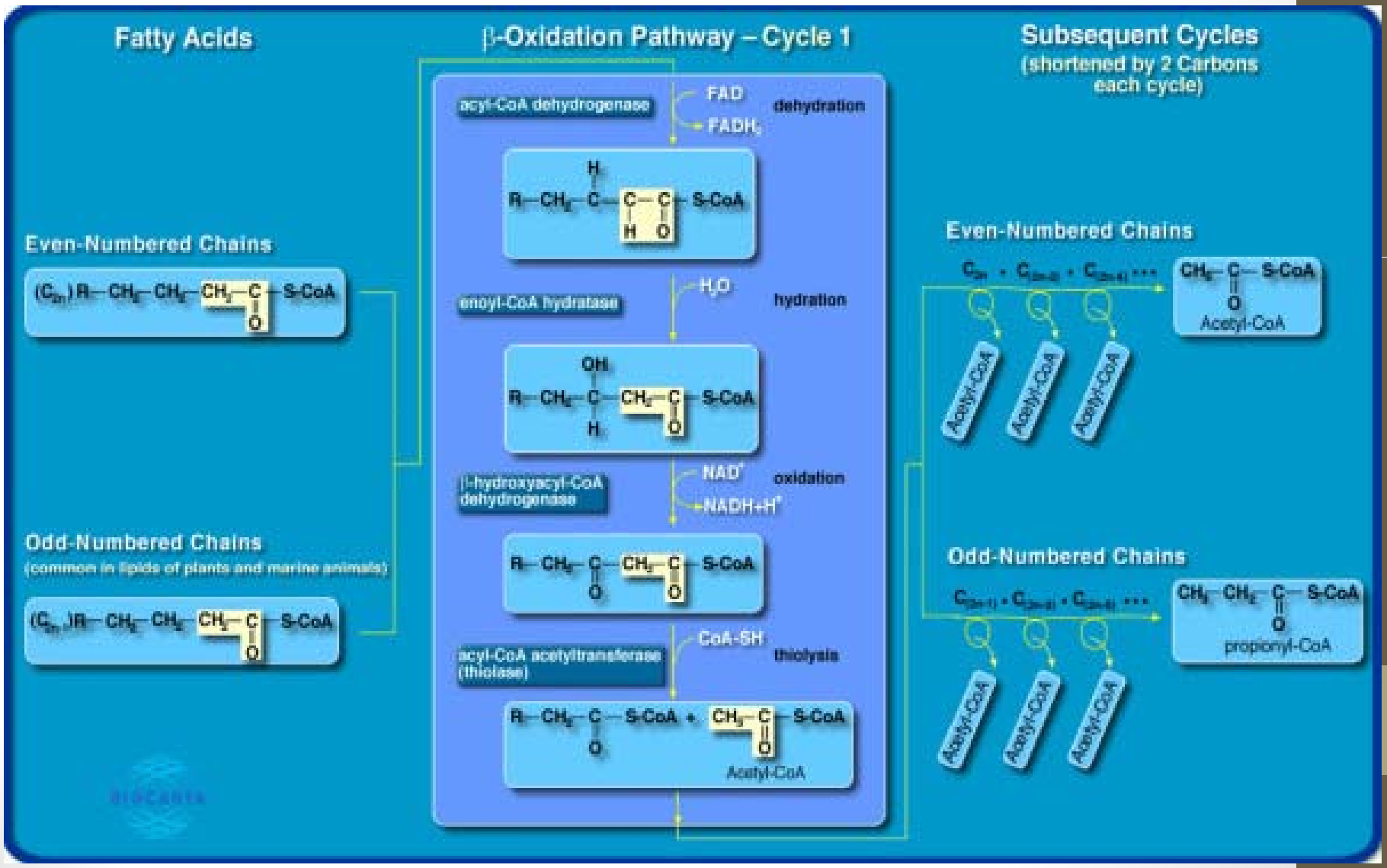


Fatty Acid Metabolism

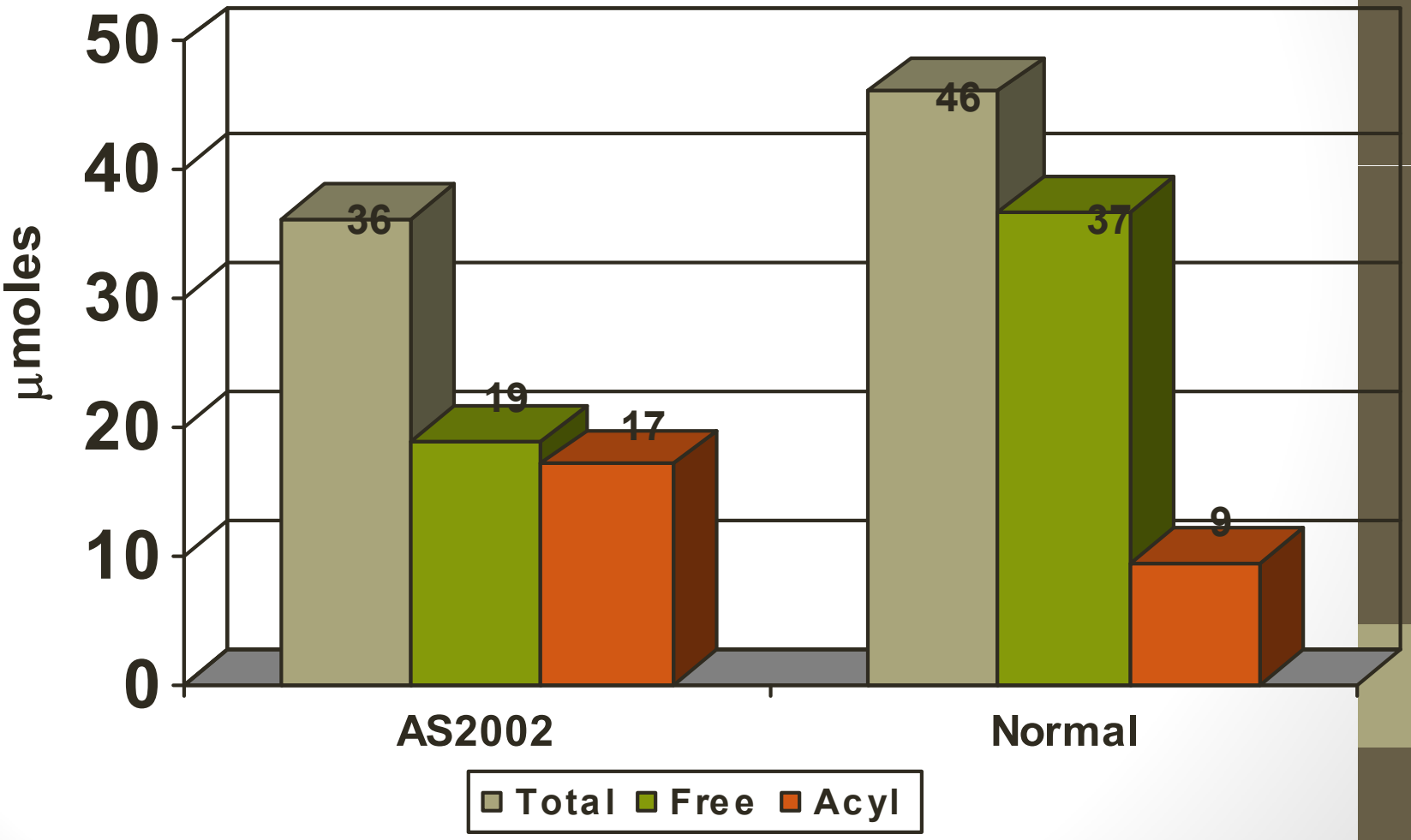


Carnitine and CKD

Beginnings and Endings

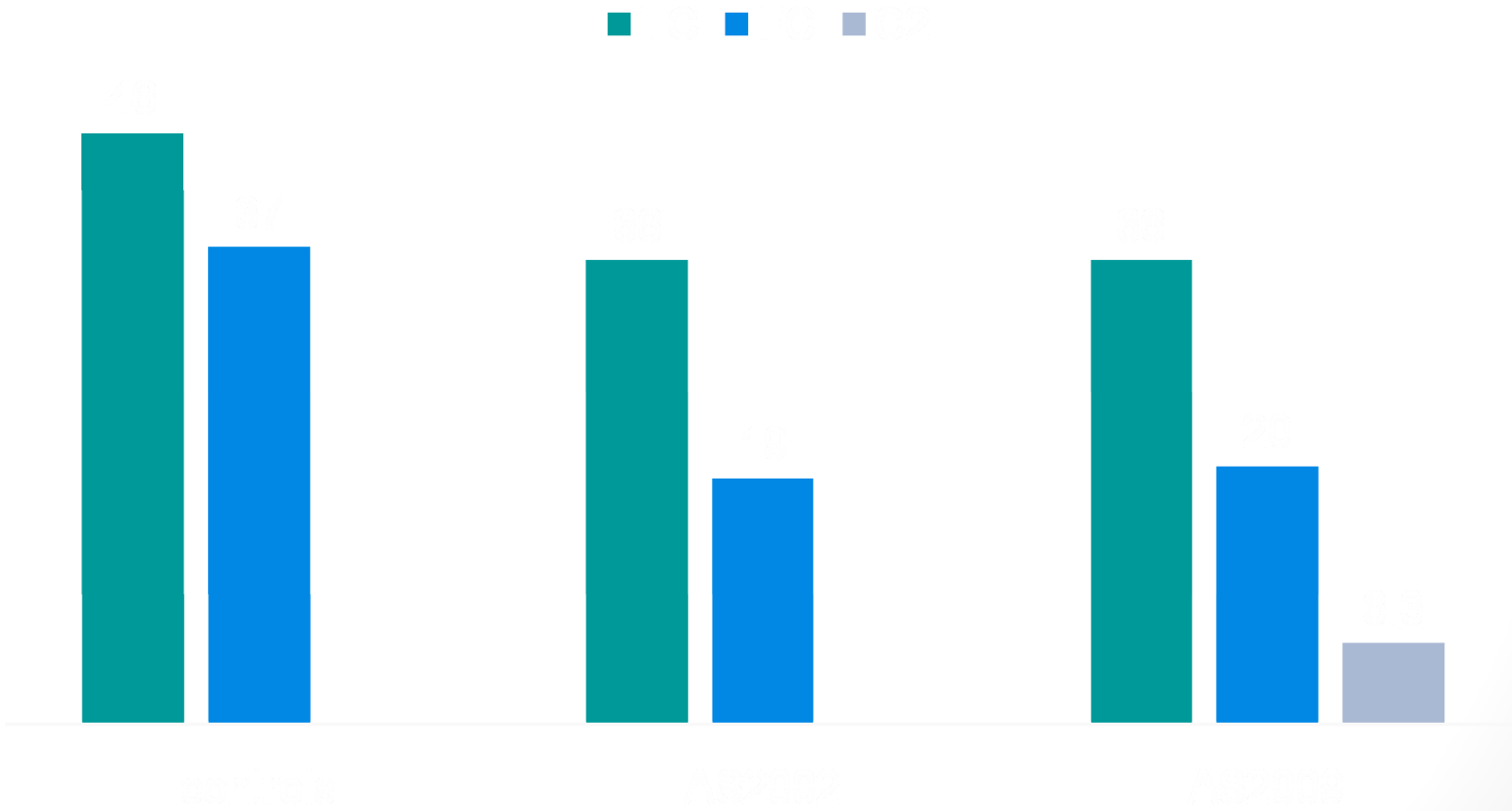


Comparison of Mean Carnitine Concentrations



Steiber. Clincal Nutr. 2004

Comparison of Mean Carnitine Concentrations

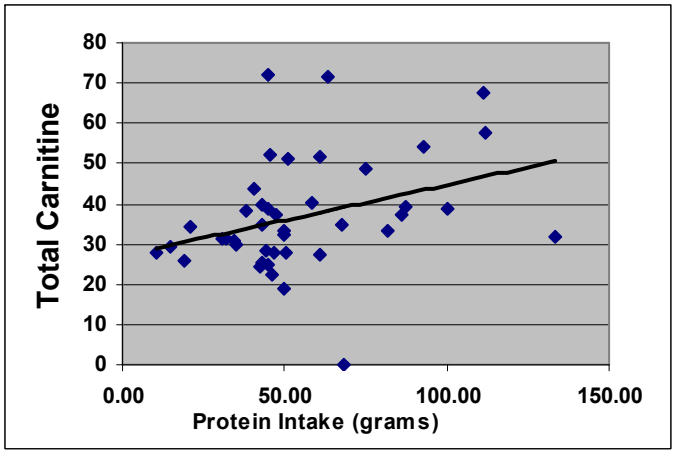


Steiber. Clincal Nutr. 2004

Why altered carnitine status in HD patients?

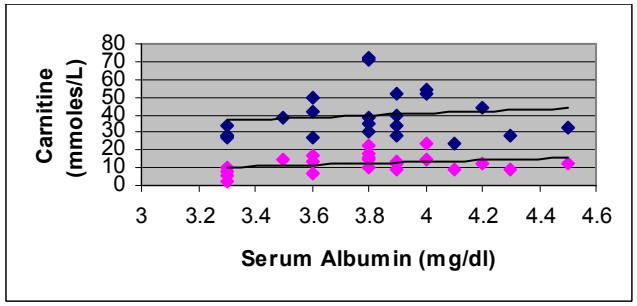
- ↓ intake (uremia)
- Loss of free carnitine in dialysate
- Abnormal fatty acid metabolism
- Protein-Energy Wasting
  - Decreased Fat Free Mass

Correlation Between Total Carnitine and Protein Intake (g)



TC
p<0.
Steibe

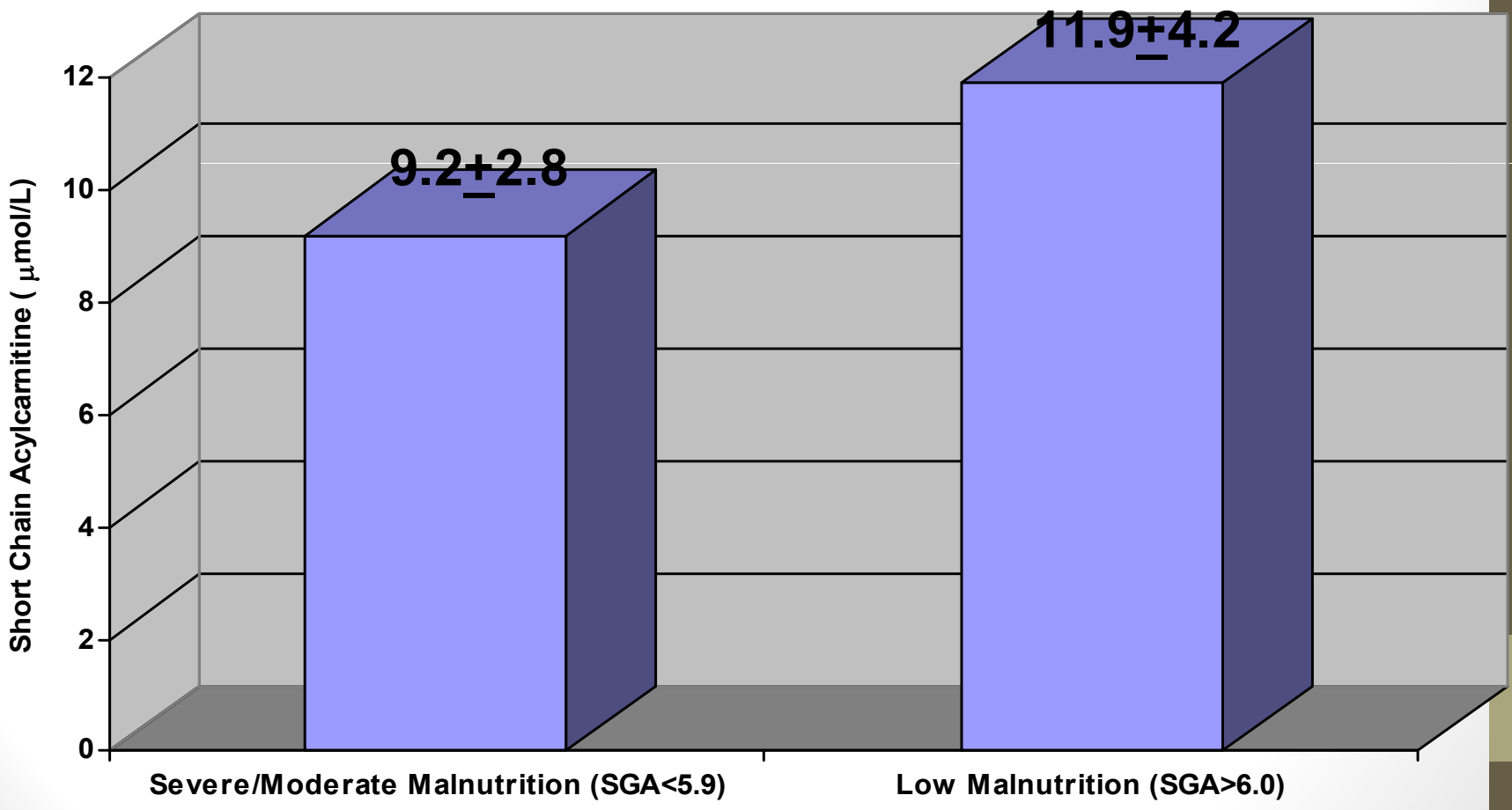
Serum Albumin & Carnitine



Steiber et al, unpublished

p<0.05, TC r=0.37, SCAC r=0.45

Carnitine and SGA



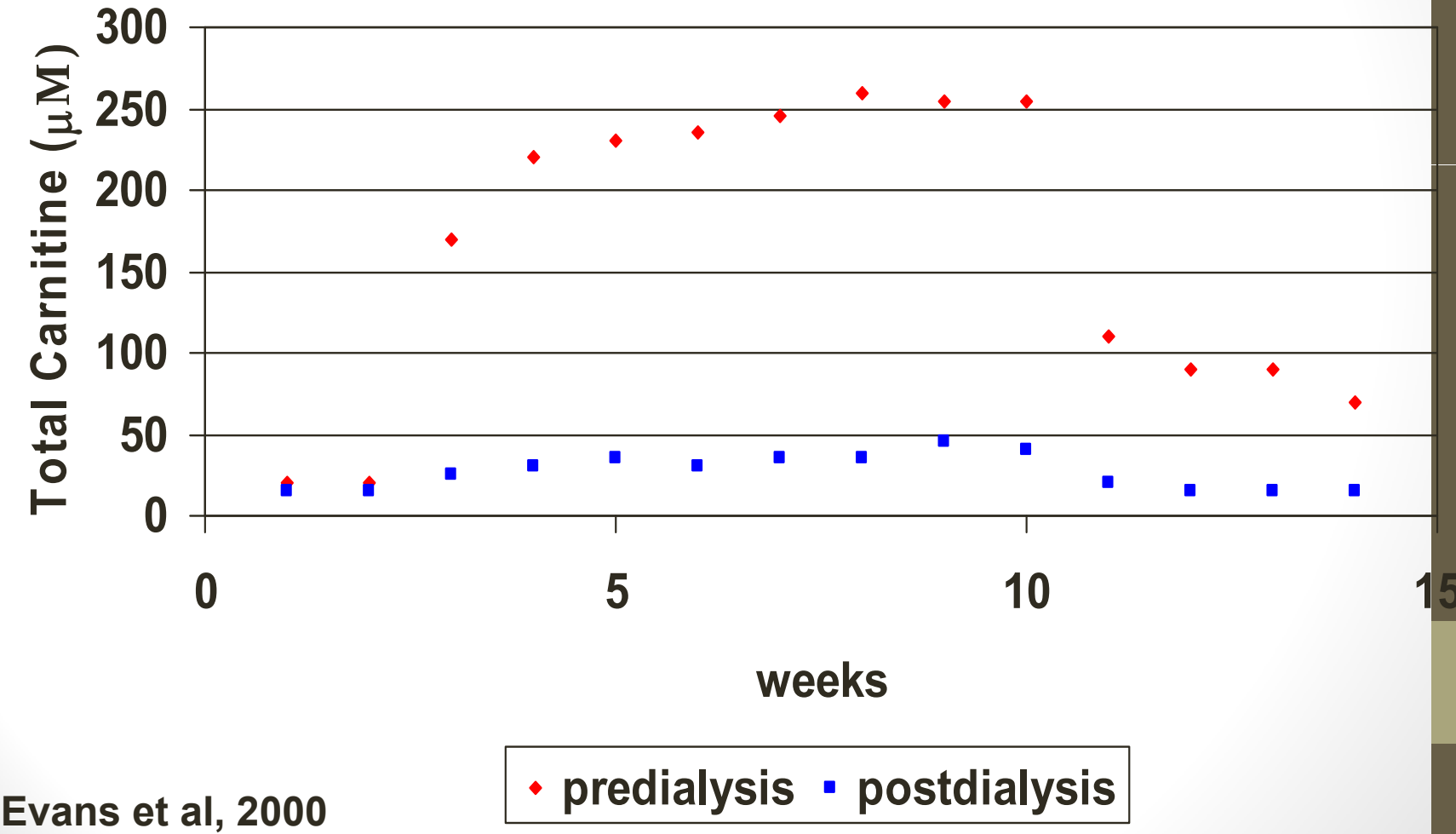
Steiber et al, unpublished

Mean Carnitine Loss via HD

Carnitine Moiety	Pre-dialysis (μmol/L)	Post-dialysis (μmol/L)	% Loss	Total μmol Lost
Free Carnitine	19.5±5.6	5.6±1.9	71	250
Acetyl-Carnitine	7.2±1.9	2.3±0.9	68	95

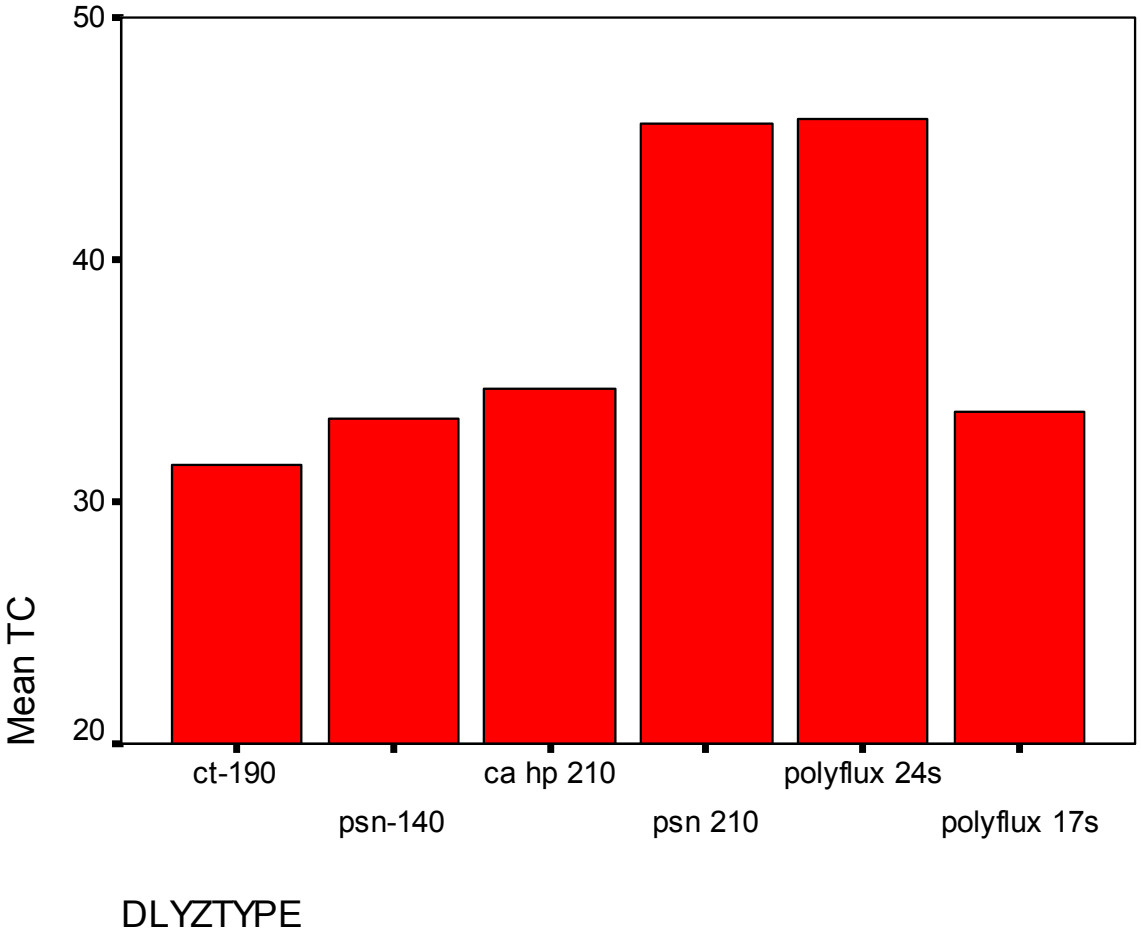
Evans et al, 2000

Pre & Post-dialysis Carnitin



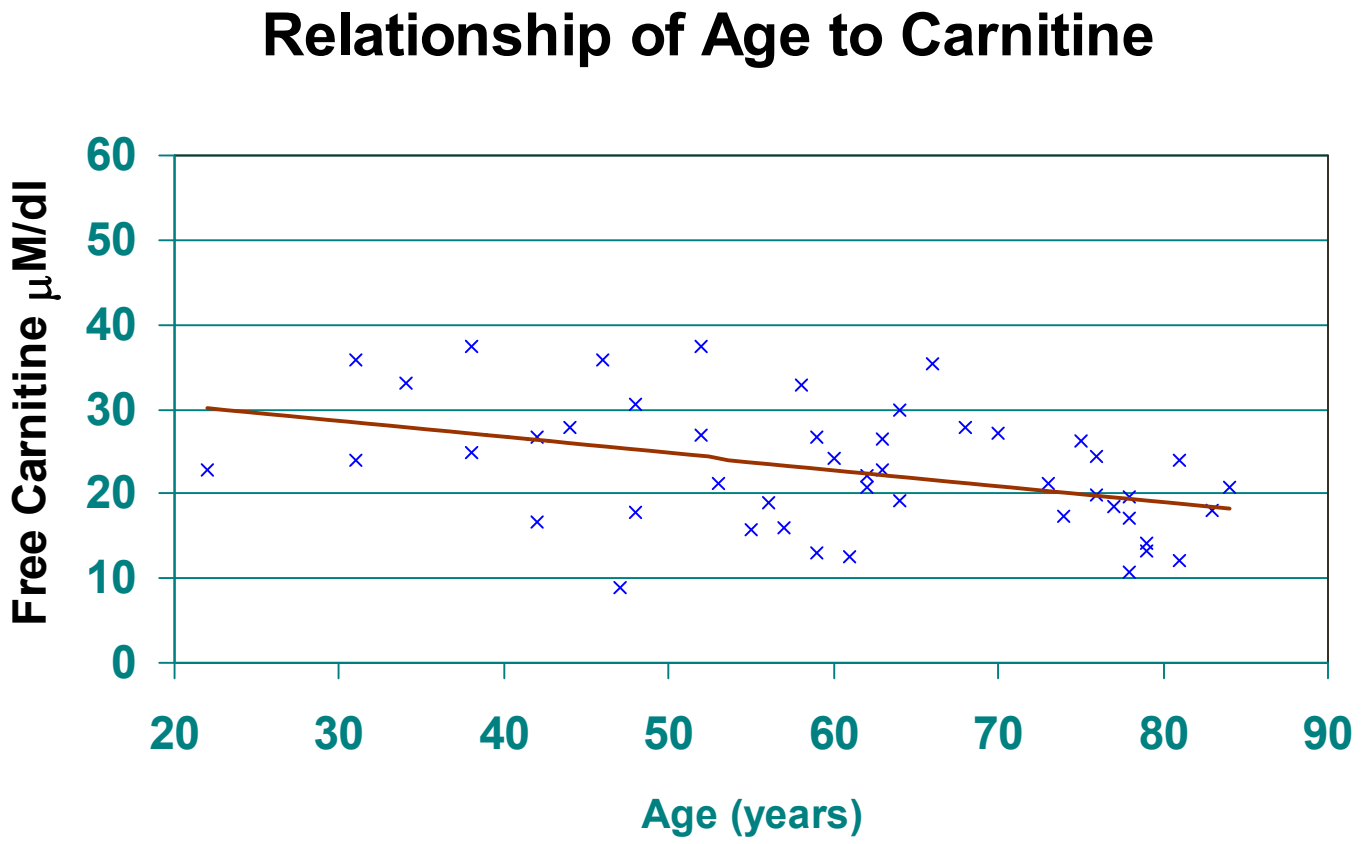
Evans et al, 2000

Total Carnitine by Dialyzer Type (Baseline)



p<0.002, TC in μmol/L
Steiber et al, 2003

Relationship of Age to Free Carnitine



r = -0.41, p <0 .001
Steiber et al., JPEN 2006

Carnitine Supplementation

Clinical Outcomes Possibly Affected By or Affecting Carnitine Status

- **Lean Body Mass and fat stores**
  - **97% of carnitine is stored in the muscle mass**
  - **Indication of weight loss and functional status**
- **Kcal/protein intake/nPCR/BUN**
  - **Kcal and Protein intake may impact**
    - **Carnitine status itself**
    - **Malonyl-CoA regulation on CAT-I & thereby FA oxidation**
    - **Malonyl-CoA inhibition**
      - **regulated by insulin to glucagon ratio which is regulated by energy intake**

Clinical Outcomes Possibly Affected

- Erythropoeitin
  - Mean erythropoietin dose per month
  - Serum Hct
  - Hgb concentration
- Quality of Life Indicator
  - Short-Form-36 (SF-36)
  - Correlation found between SF-36 physical composite score & acyl-to-free ratio

Clinical Outcomes Possibly Affected

- **Muscle Cramping/Interdialytic Weight Gain**
  - **Carnitine supplementation has been shown to ↓ muscle cramping due to fluid removal**
- **Parathyroid Hormone**
  - **PTH concentrations have been associated with carnitine**
  - **PTH concentrations have been postulated to interfere with CAT-I action in uremic patients (Perna et al, 1988)**

Outcome Parameters Affected by Carnitine Treatment

Nutritional Status

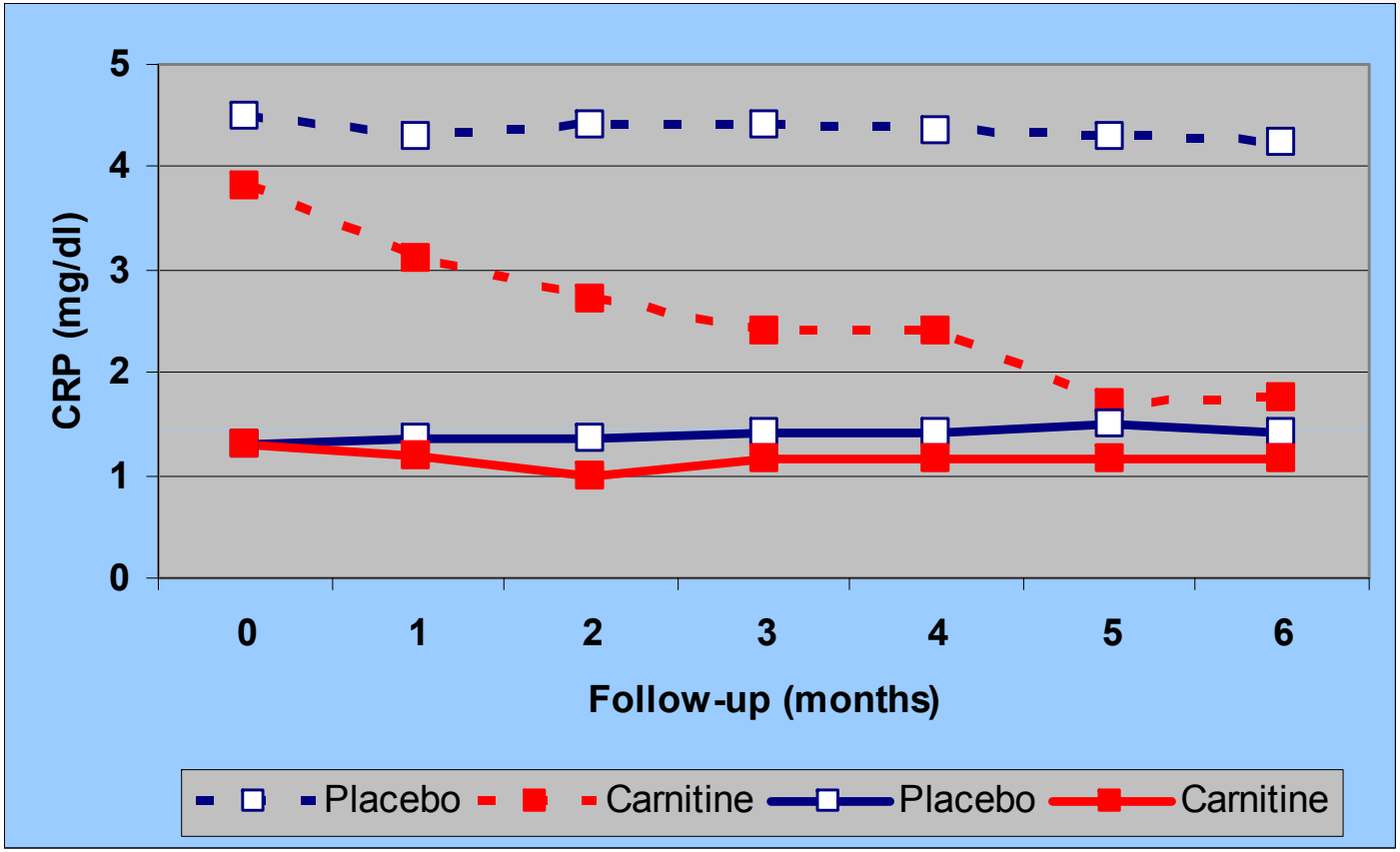
Body composition & visceral protein status

Savica 2005

- 48 patients treated with L-carnitine 20mg/kg 3x/week for 6 months
- 65 patients treated for 6 months with placebo
- Assignment by center

Savica V Journal of Renal Nutrition 2005 15(2) 225-230

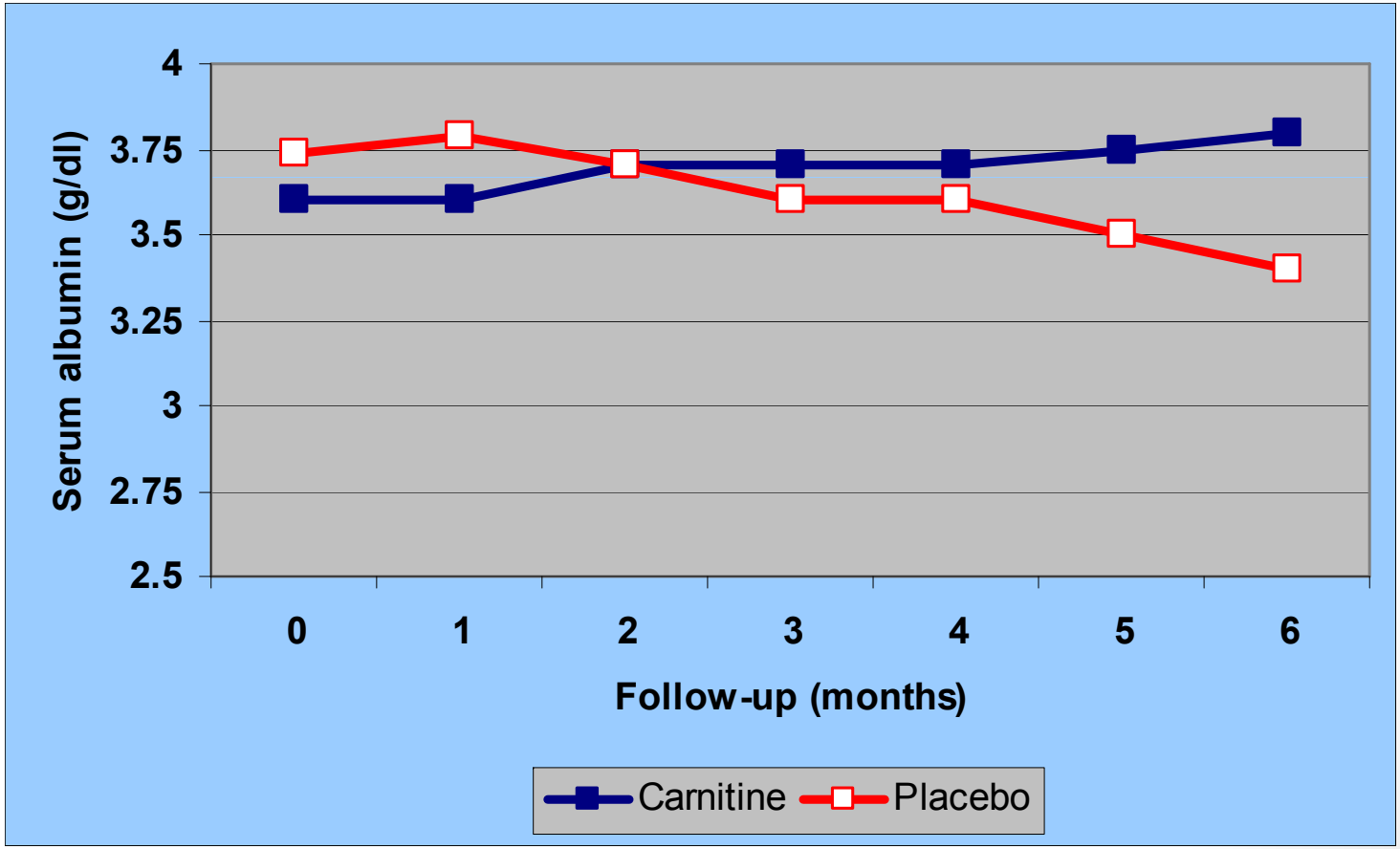
Decrease in CRP in Patients with High Baseline



Patients with CRP levels <3 mg/dL at baseline (carnitine, n = 38, versus placebo, n = 52) and at the end of the follow-up (carnitine, n = 47, versus placebo, n = 54). Mean ± standard deviation CRP levels at the sixth month of follow-up: 1.1 ± 0.2 versus 1.3 ± 0.1 ($P < .0001$). Patients with CRP levels ≥3 mg/dL at baseline (carnitine, n = 10, versus placebo, n = 13) and at the end of the follow-up (carnitine, n = 1, versus placebo, n = 11). Mean ± standard deviation CRP levels at the sixth month of follow-up: 1.6 ± 0.7 versus 4.2 ± 0.3 ($P < .01$).

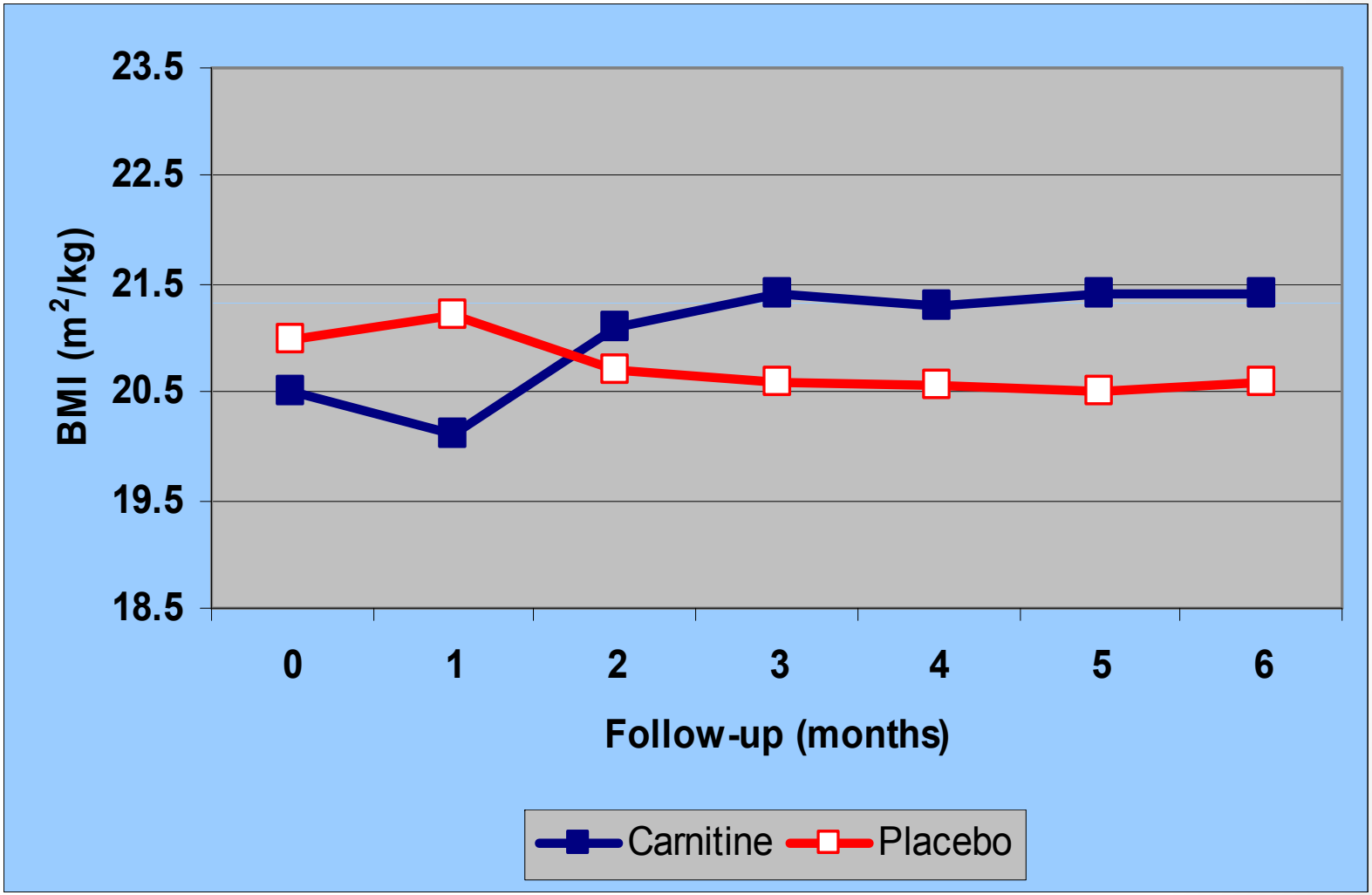
Serum Albumin Increase

Serum albumin concentrations (g/dL) in MHD patients treated with L-carnitine or placebo for 6 months



Savica V.Journal of Renal Nutrition 2005 15(2) 225-230

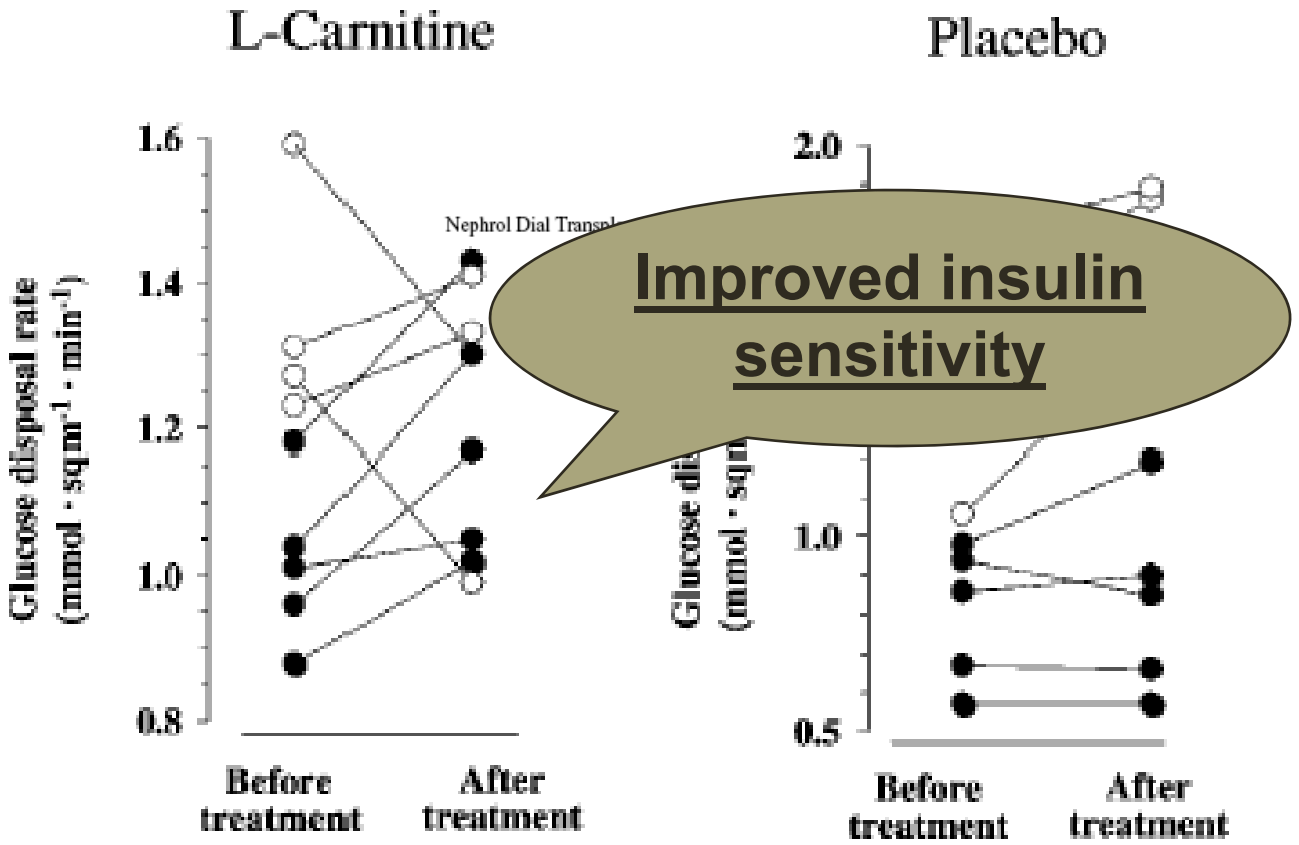
Increase In Body Mass Index



Savica V.Journal of Renal Nutrition 2005 15(2) 225-230

Insulin action on glucose and protein metabolism during L-carnitine supplementation in maintenance haemodialysis patients

Gianni Biolo[1], Manuela Stulle[1], Francesco Bianco[2], Giuseppe Mengozzi[3], Rocco Barazzoni[1], Alfonso Vasile[3], Giovanni Panzetta[2] and Gianfranco Guarnieri[1]



Nephrol Dial Transplant (2008) 23: 991–997

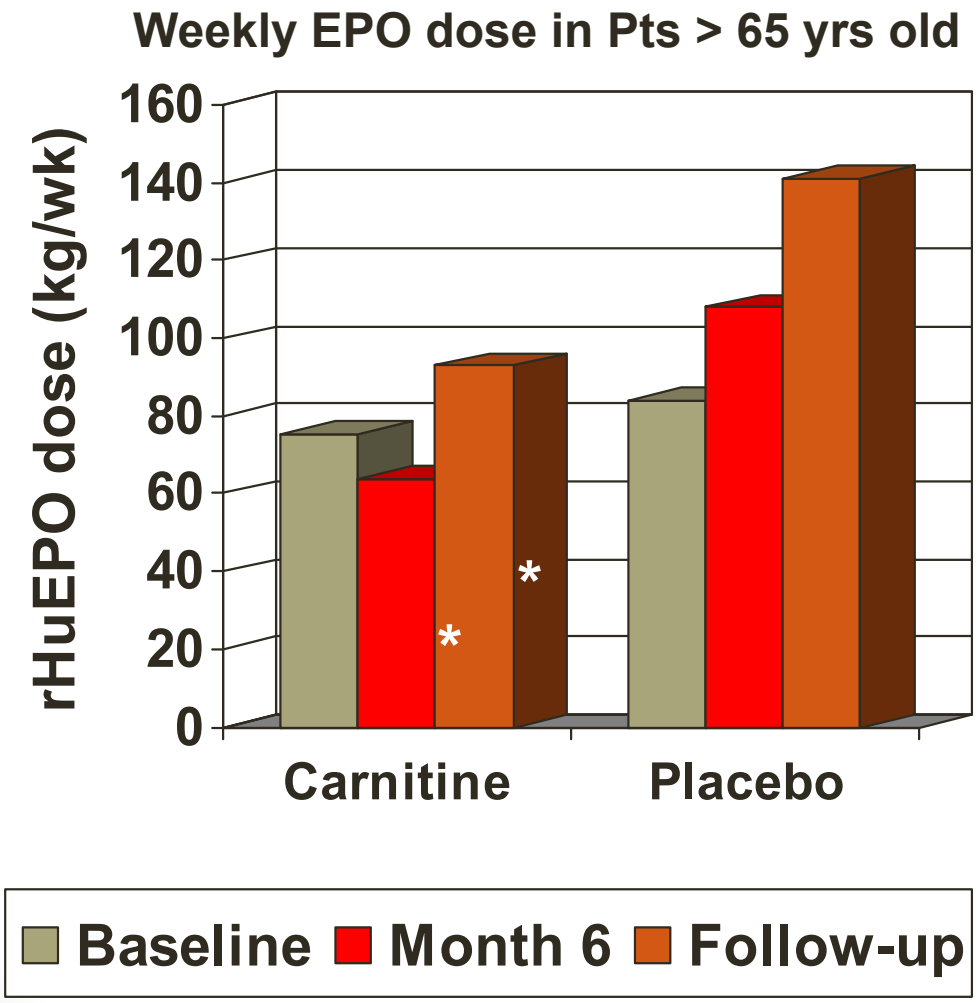
Table 2. Whole-body leucine kinetics in haemodialysis patients in the basal postabsorptive state and during euglycemic hyperinsulinemic clamp before and after L-carnitine supplementation or placebo

	L-carnitine			
	Basal	Clamp		
Rate of appearance (μmol·sqm^{-1}·min^{-1})				
Before treatment	68 ± 3	56 ± 2*	68 ± 3	55 ± 3*
After treatment	62 ± 3**	53 ± 3*	68 ± 4	56 ± 3*
Changes	−5.1 ± 1.5***	−3.4 ± 1.5***	0.4 ± 1.2	1.0 ± 1.0
Oxidation (μmol·sqm^{-1}·min^{-1})				
Before treatment	5.3 ± 0.3	4.7 ± 0.3	5.1 ± 0.6	3.9 ± 0.2
After treatment	4.6 ± 0.4	3.9 ± 0.2	5.0 ± 0.5	3.8 ± 0.3
Changes	−0.7 ± 0.4	−0.8 ± 0.4***	−0.2 ± 0.4	−0.1 ± 0.3

Protein-sparing affect of CN

Anemia Management

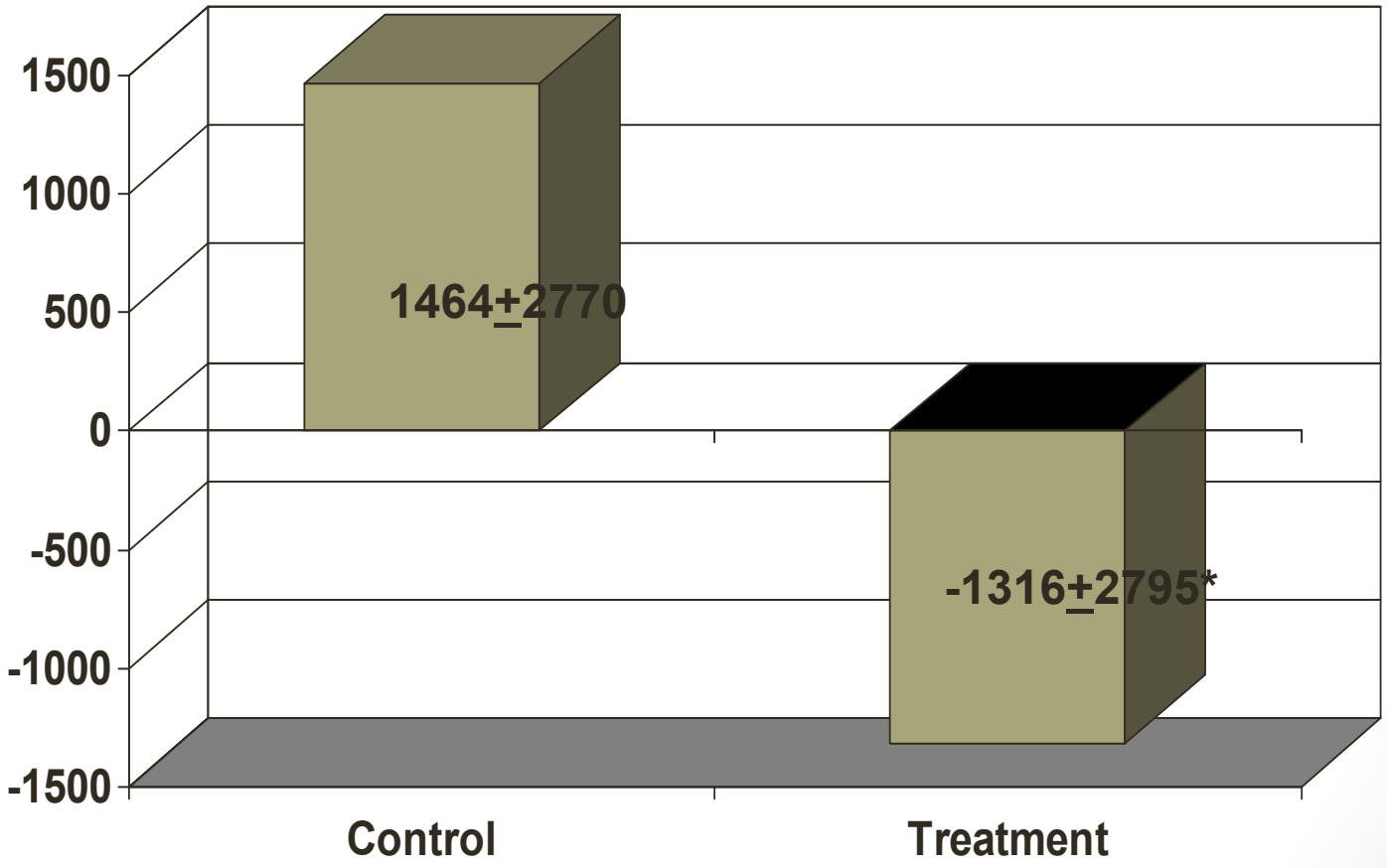
Carnitine and Anemia



Caruso et al, 1998 - IV

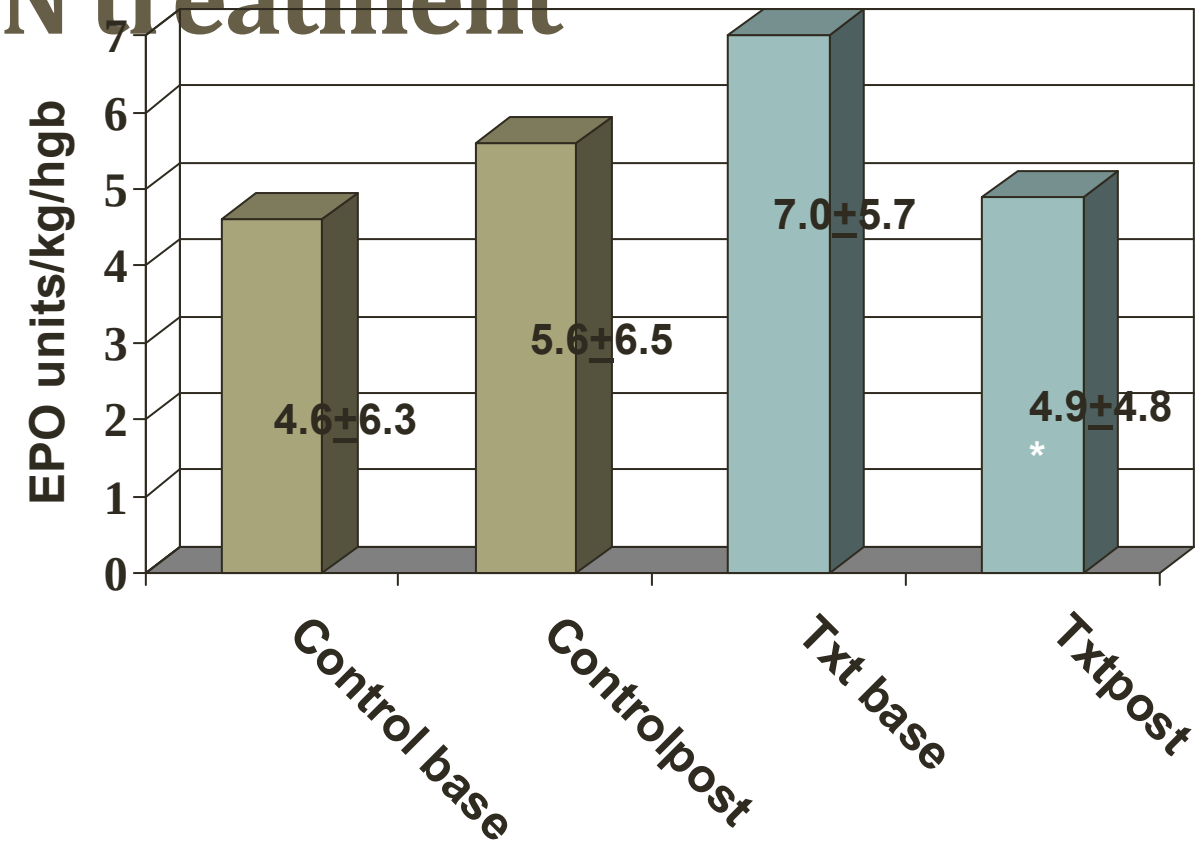
- **Possible mechanisms:**
  - **Stabilization of erythrocyte membrane**
    OR
  - **↑ Na/K ATPase activity**

Epogen Dose Change: post-24 wks of CN treatment



* p<0.01 using a one-way ANOVA between groups, n = 34
20 mg/kg/txt Steiber et al., 2006

Erythropoietin Resistance Index (EPO/kg/mg hgb) – post 24 wks of CN treatment



*= p<0.05

Steiber et al., 2006

ERI and EPO Responsiveness

Table 2. Patient demographic and dialysis data; data expressed as mean ± SD

Parameter	All patients	Low ERI patients	High ERI patients
Subjects (*n*)	87	75	12
Age (years)	59.1 ± 13.8	58.6 ± 13.8	61.8 ± 14.2
Gender	56 males/ 31 females	53 males/ 22 females	3 males/ 9 females
Dialysis age (years)	2.78 ± 2.72	2.47 ± 2.04	4.70 ± 5.02
Dialysis session duration (hours)	4.10 ± 0.461	4.09 ± 0.452	4.17 ± 0.531

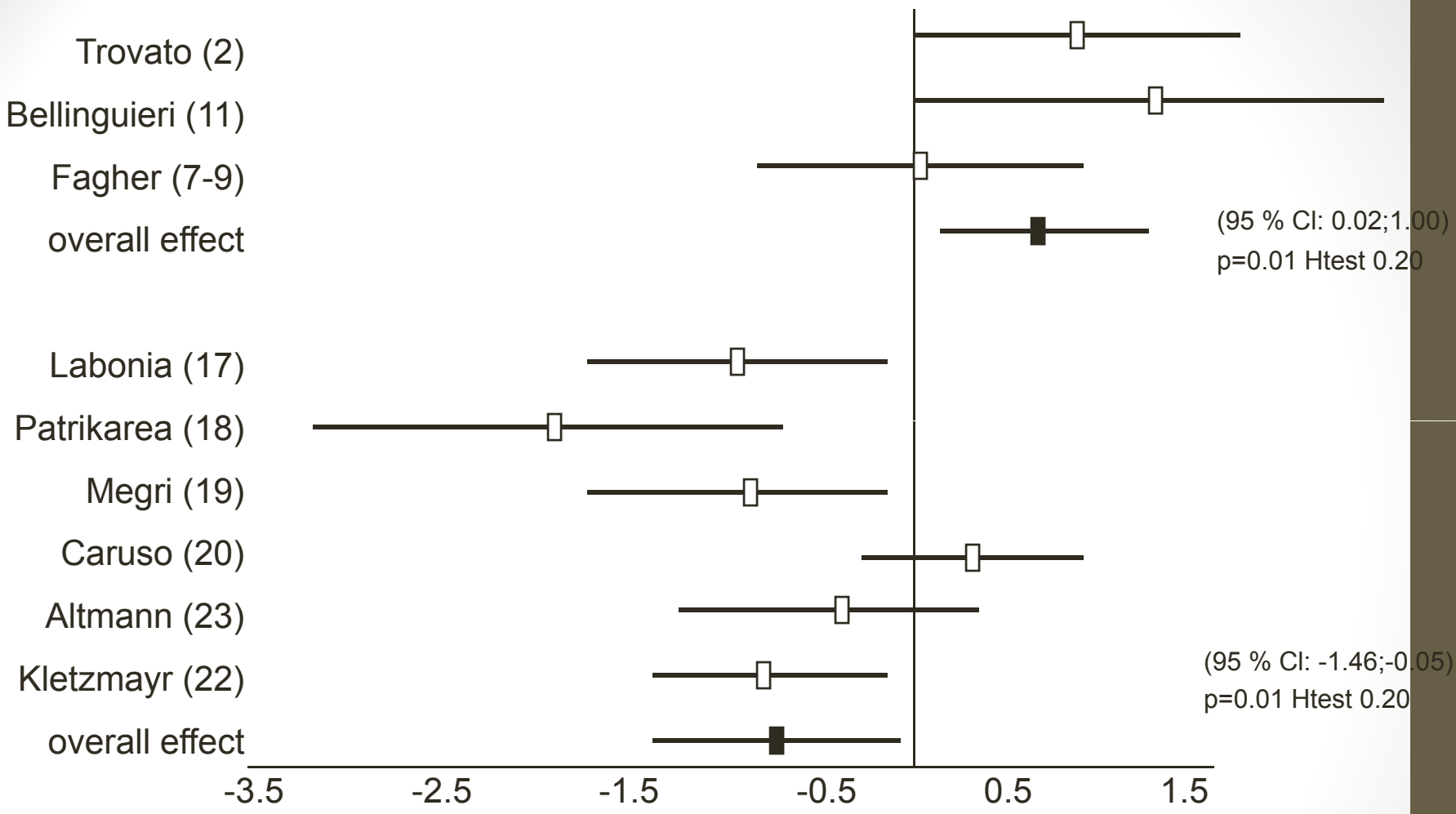
ERI = erythropoietin resistance index.

Table 3. Endogenous plasma carnitine levels for all subjects and each erythropoietin resistance index (ERI) subgroup; data expressed as mean ± SD

Parameter	All patients	Low ERI patients	High ERI patients
LC	22.8 ± 8.62 μM	23.8 ± 8.67 μM	17.0 ± 5.47 μM*
TC	38.6 ± 13.7 μM	39.9 ± 13.9 μM	30.6 ± 9.29 μM*
AcylLC	15.8 ± 5.93 μM	16.1 ± 6.01 μM	13.6 ± 5.13 μM
AcylLC-C2	7.80 ± 2.57 μM	7.83 ± 2.37 μM	7.59 ± 3.74 μM
LC/TC	0.588 ± 0.0608	0.593 ± 0.0585	0.558 ± 0.0685
AcylLC/TC	0.412 ± 0.0608	0.407 ± 0.0585	0.422 ± 0.0685
AcylLC-C2/ TC	0.211 ± 0.0556	0.205 ± 0.0504	0.248 ± 0.0733*

*$P < 0.05$, compared to the Low ERI group.

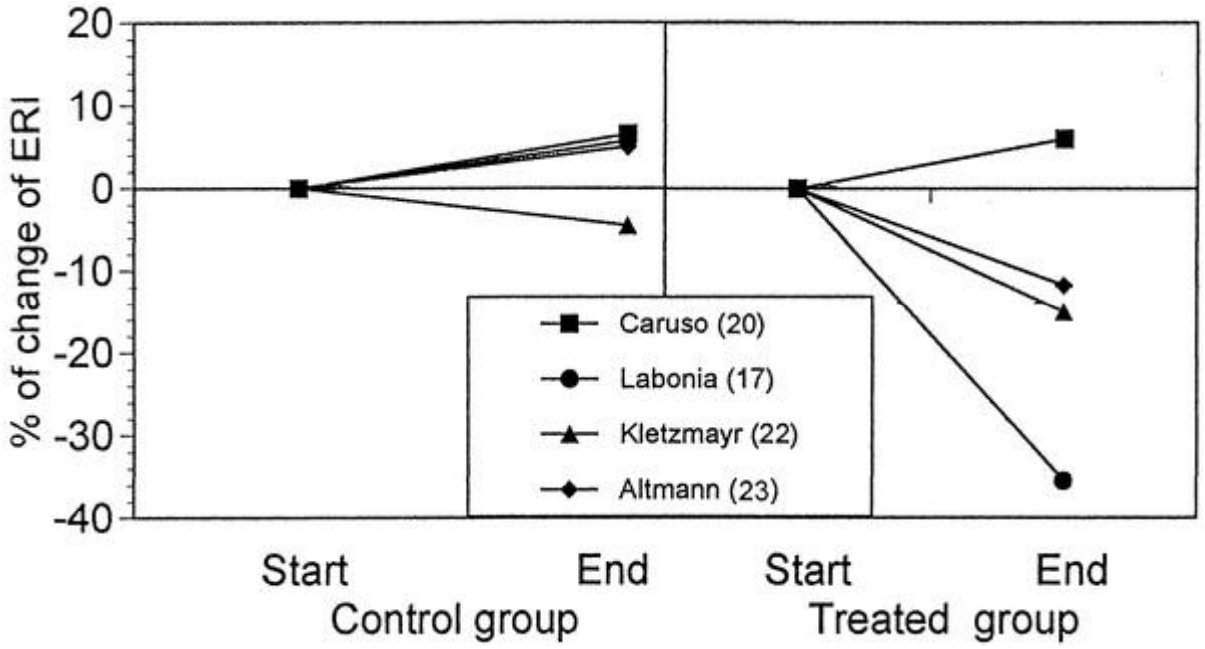
Reuter et al, NDT 2009



The effect of L-carnitine on anemia control (top; fixed model analysis) and erythropoietin dose reduction (bottom; random model analysis). Open boxes indicate the effect of each individual trial, and the closed boxes the overall effect of treatment. The *P* value is given for overall treatment effect and is significant for values ≤ 0.01. Heterogeneity of treatment effect among trials is present if H test value is < 0.10.

Hurot JM, et al. *J Am Soc Nephrol.* 2002;13:708-714

Erythropoietin Resistance Index



Hurot JM, et al. *J Am Soc Nephrol.* 2002;13:708-714

Quality of Life (QOL) Results

Improved Fatigue: Post-6 months of CN treatment

Table 3. Effect of L-Carnitine Supplementation on Quality of Life Assessed by KDQ for All Patients

	Placebo				L-Carnitine				
		Baseline	24 Weeks	Change	No. of Patients	Baseline	24 Weeks	Change	P*
Total sc			5.29 ± 1.08	0.29 ± 0.74	121	4.83 ± 1.12	5.27 ± 1.03	0.44 ± 0.76	0.10
Physical symptoms	57	4.20 ± 1.11	4.88 ± 1.36	0.68 ± 1.22	118	4.23 ± 1.17	5.04 ± 1.11	0.81 ± 1.15	0.76
Fatigue	59	4.90 ± 1.34	5.14 ± 1.22	0.24 ± 0.89	121	4.65 ± 1.26	5.09 ± 1.28	0.44 ± 0.95	0.03
Depression	59	5.38 ± 1.37	5.53 ± 1.39	0.16 ± 1.14	121	5.07 ± 1.48	5.36 ± 1.29	0.29 ± 0.99	0.11
Relationship with others	59	5.38 ± 1.06	5.59 ± 1.09	0.20 ± 0.86	121	5.23 ± 1.06	5.55 ± 1.00	0.32 ± 0.83	0.13
Frustration	59	5.00 ± 1.34	5.28 ± 1.44	0.28 ± 1.25	121	4.91 ± 1.54	5.23 ± 1.29	0.33 ± 1.08	0.59

NOTE. Values expressed as mean ± SD.

*Change in placebo versus change in L-carnitine patients.

Fatigue, domain ↑significantly in CN group

Brass et al, AJKD, 2001

SF36 Domains improve with CN treatment

PF, GH, VT & PCS significantly↑ in CN group

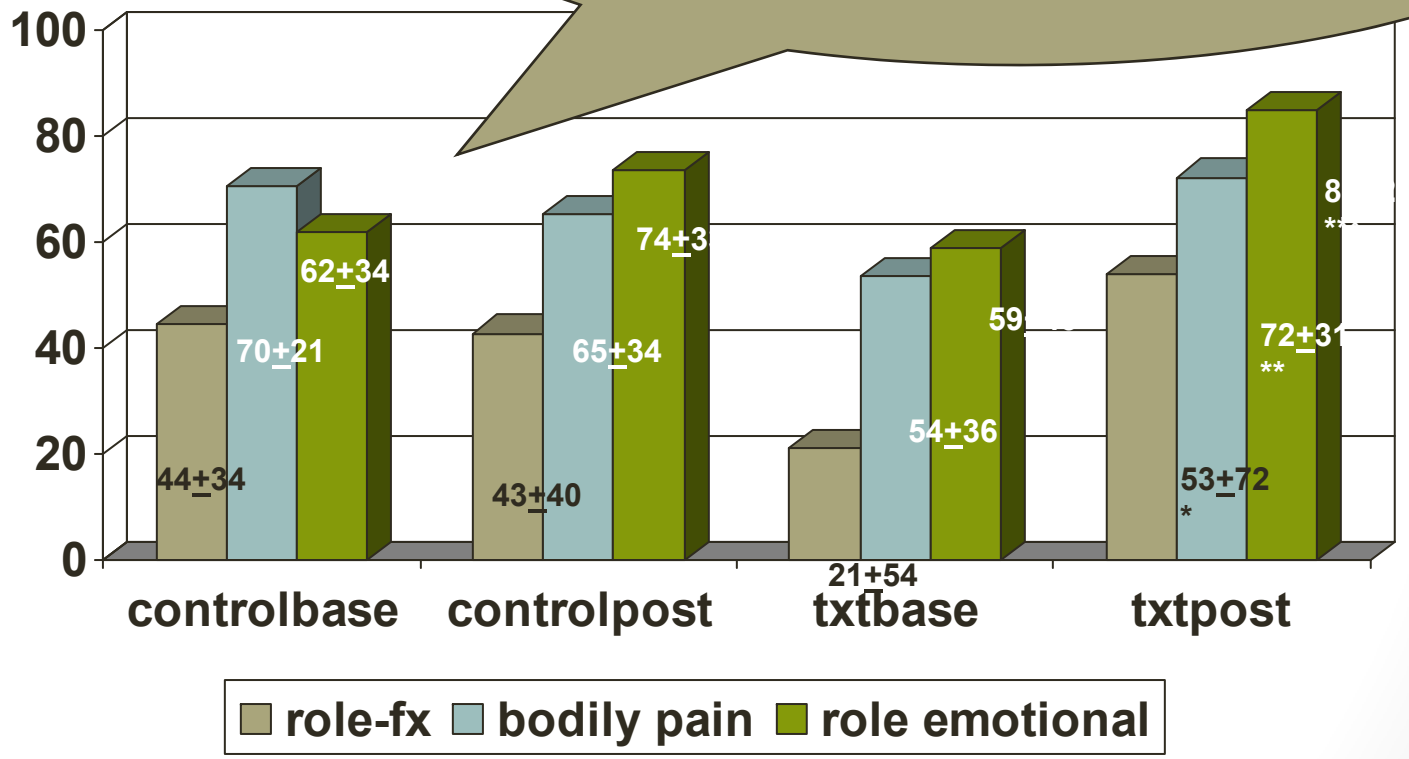
Table 2: Effect of L-carnitine versus pla… HD patients

Parameter	L-carnitine				difference*			P value
PF	29.50 ± 17.70	35.00 ± 25.27	56.00 ± 23.06	30.50 ± 21.00	26.50 ± 20.28 (13.92 - 39.07)	-4.50 ± 31.66 (-24.1 - 15.12)	32.5 (12.5)	-2.5 (43.75)	0.02
RP	35.00 ± 21.08	42.50 ± 16.87	50.00 ± 11.78	47.50 ± 7.90	15.00 ± 21.08 (1.93 - 28.06)	5.00 ± 19.70 (-7.22 - 17.22)	0 (25)	0 (0)	0.33
BP	30.90 ± 19.80	35.80 ± 16.27	48.60 ± 22.80	39.20 ± 17.03	7.70 ± 133.01 (-2.76 - 38.16)	3.40 ± 24.29 (-11.65 - 18.45)			0.28
GH	24.50 ± 16.23	35.90 ± 23.51	46.50 ± 17.92	29.20 ± 19.71	22.00 ± 22.90 (7.80 - 36.19)	-6.70 ± 22.38 (-20.57 - 7.17)			0.01
Vitality	28.50 ± 17.48	43.00 ± 26.58	39.50 ± 23.97	24.00 ± 16.63	11.00 ± 30.62 (-7.98 - 29.98)	-19.00 ± 32.30 (-39.01-1.01)			0.04
SF	47.50 ± 24.15	56.25 ± 22.24	61.25 ± 12.43	35.00 ± 11.48	13.75 ± 30.30 (-5.03 - 32.53)	-21.25 ± 25.71 (-37.19 - -5.30)			0.01
RE	20.00 ± 28.10	36.66 ± 18.92	50.00 ± 28.32	46.66 ± 17.21	30.00 ± 36.68 (7.26 - 52.73)	10.00 ± 27.44 (-7.00 - 27.00)	33.33 (66.66)	0 (25)	0.22
MH	43.20 ± 25.90	55.60 ± 25.60	53.60 ± 18.39	37.20 ± 13.86	10.40 ± 24.95 (-5.06 - 25.86)	-18.40 ± 25.52 (-34.21 - -2.58)			0.02
PH	29.68 ± 9.89	38.44 ± 14.05	48.12 ± 12.48	34.08 ± 11.18	18.44 ± 15.41 (8.88 - 27.99)	-4.36 ± 16.37 (-14.51 - 5.79)	20.8 (10.1)	-2.5 (16.8)	0.005
MH	32.70 ± 15.61	45.48 ± 18.25	50.17 ± 11.10	34.41 ± 12.66	17.43 ± 15.02 (8.11 - 26.74)	-11.07 ± 21.12 (-24.16 - 2.02)			0.002
Total SF-36	32.38 ± 11.47	42.58 ± 13.97	50.68 ± 9.83	36.15 ± 10.22	18.29 ± 12.71 (10.41 - 26.17)	-6.4 ± 16.39 (-16.59 - 3.73)			0.001

Rathod, Indian J Med Sci, 2006

SF-36 Doma

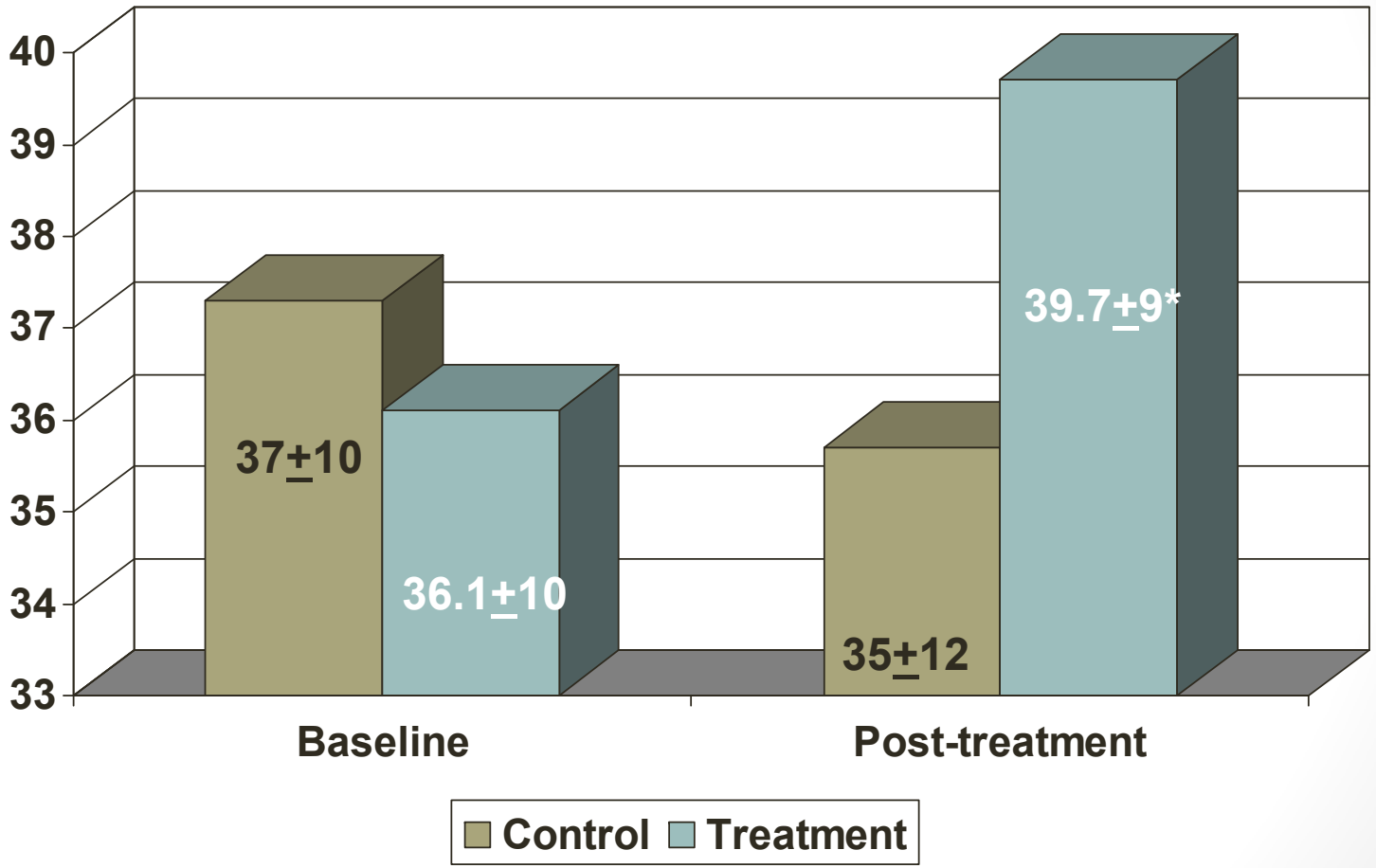
Role physical, bodily pain ↑ significantly in CN treatment group



*, **, *** = p<0.05, n = 27

Steiber et al JPEN 2006 Vol30(1) pp10-15

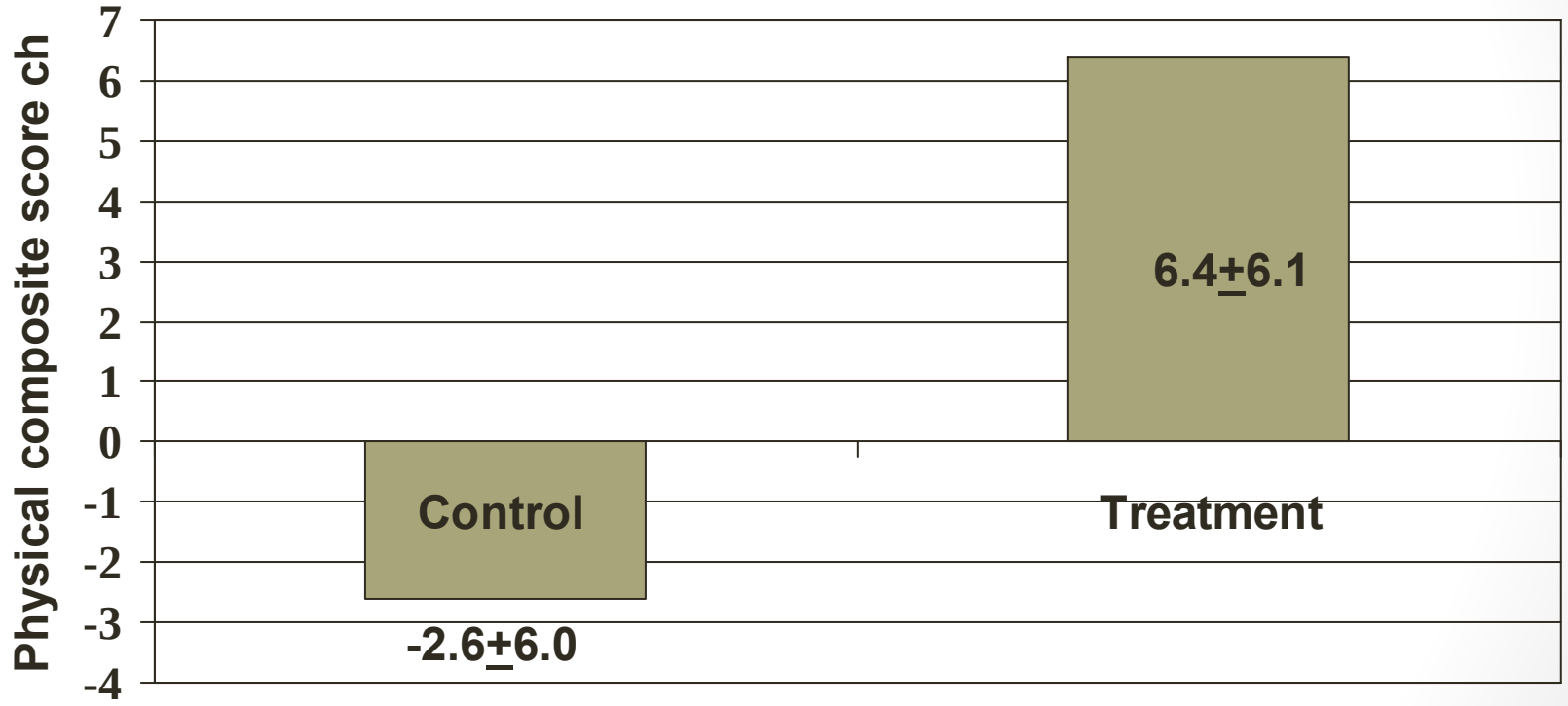
SF36 Physical Composite Score



* = p=0.078

Steiber et al., JPEN, 2006

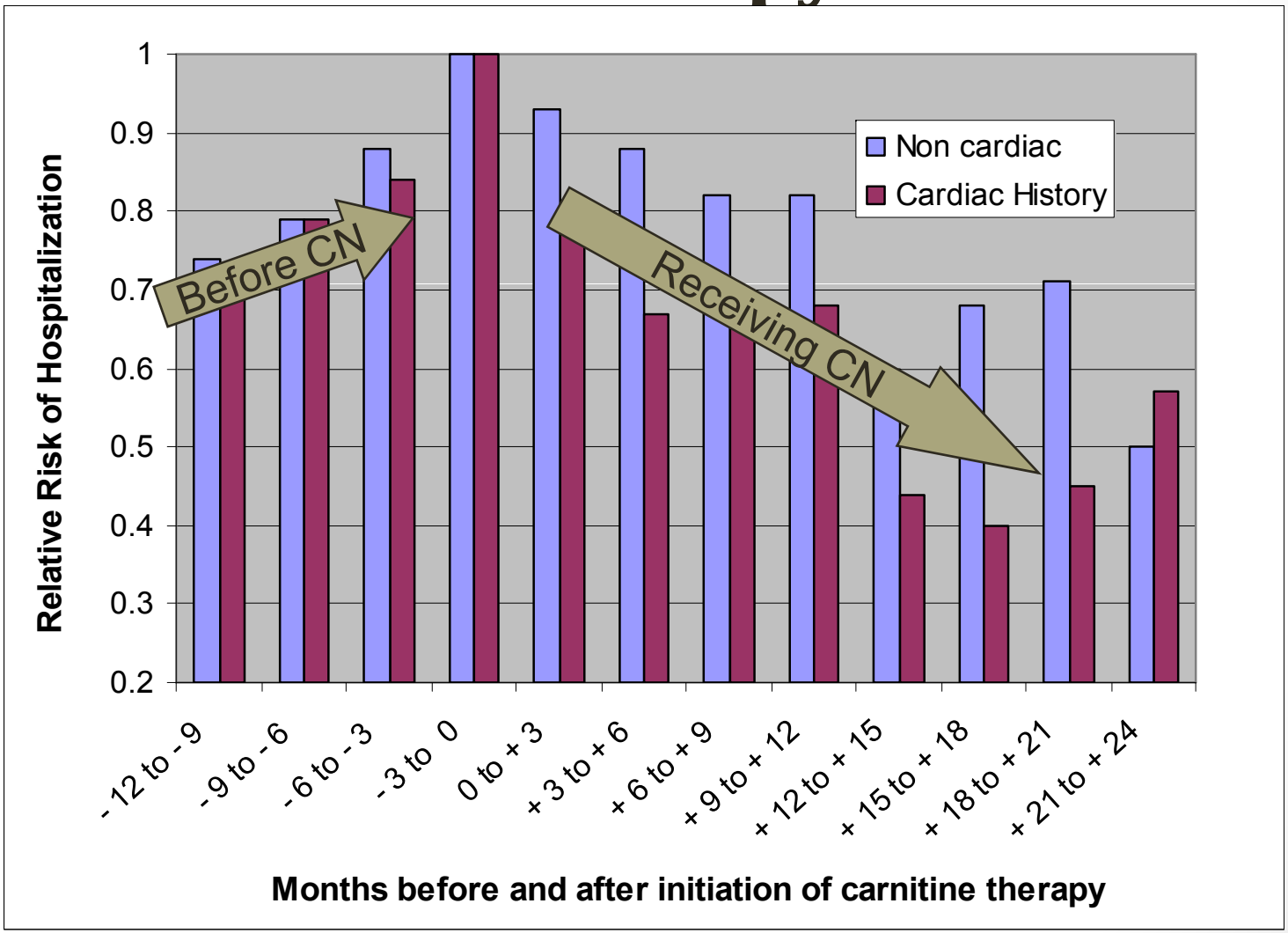
Initially compromised patients improve significantly: baseline SF36-PCS <35



p<0.05, n = 7 per group
Steiber et al., unpublished

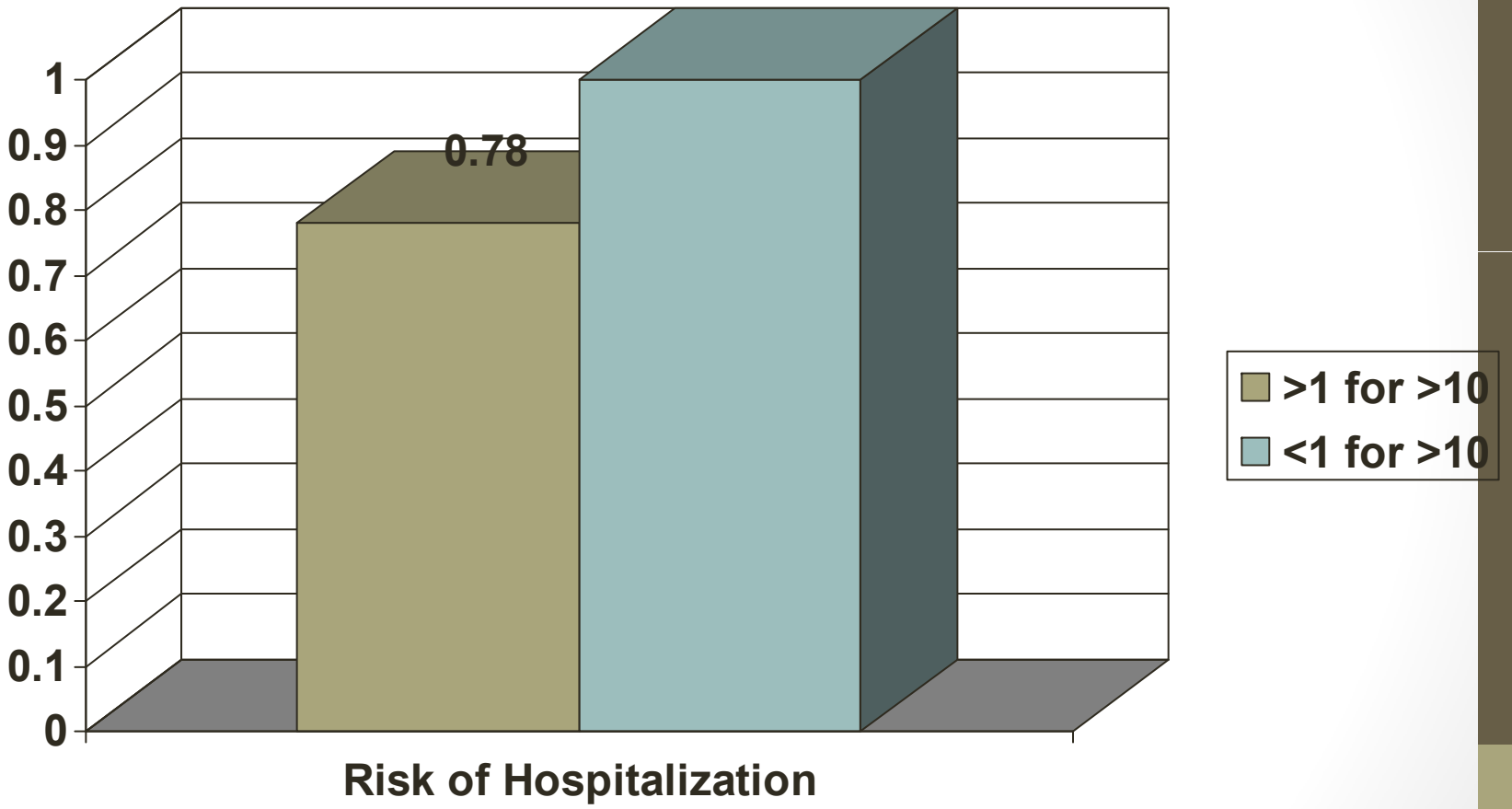
Risk of Hospitalization

Decrease in Hospitalization With Levocarnitine Therapy-FMC



Kazmi WH, et al. *Am J Nephrol.* 2005;25:106-115.

Carnitine Treatment Decreases Risk of Hospitalization



Weinhandl et. al. AJKD, 2007

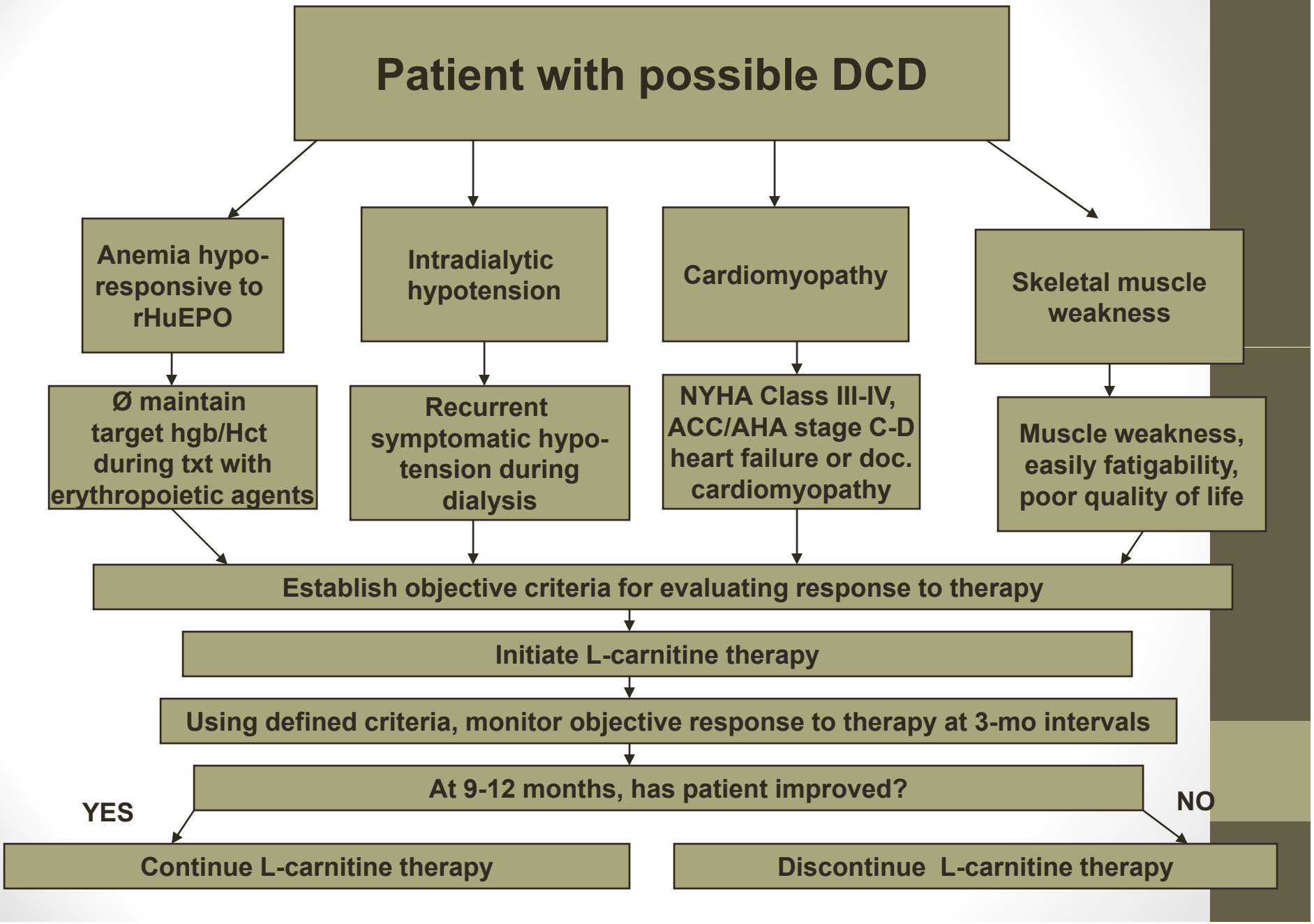
Reduction in Hospital Days by Model and Methods

Repeated Measures Model ≥ 10g of LC during preceding month*	Repeated Measures Model ≥ 3g of LC per 7 outpatient days**	Marginal Structural Model ≥ 10g of LC during preceding month*	Marginal Structural Model ≥ 3g of LC per 7 outpatient days **
10.80%	7.00%	21.70%	15.40%

Weinhandl et. al. AJKD, 2007

Practical Considerations

Replicated from fig 1 of Eknoyan et al, AJKD, 2003



Take Home Message

- **For a sub-sample of HD patients carnitine is a safe, potentially effective treatment for improving**
  - **nutritional status,**
  - **quality of life,**
  - **high erythropoietin doses, and**
  - **reducing the risk of hospitalization.**
- **This is evidenced based practice in 2008!**

Thank you!

For questions please email:

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