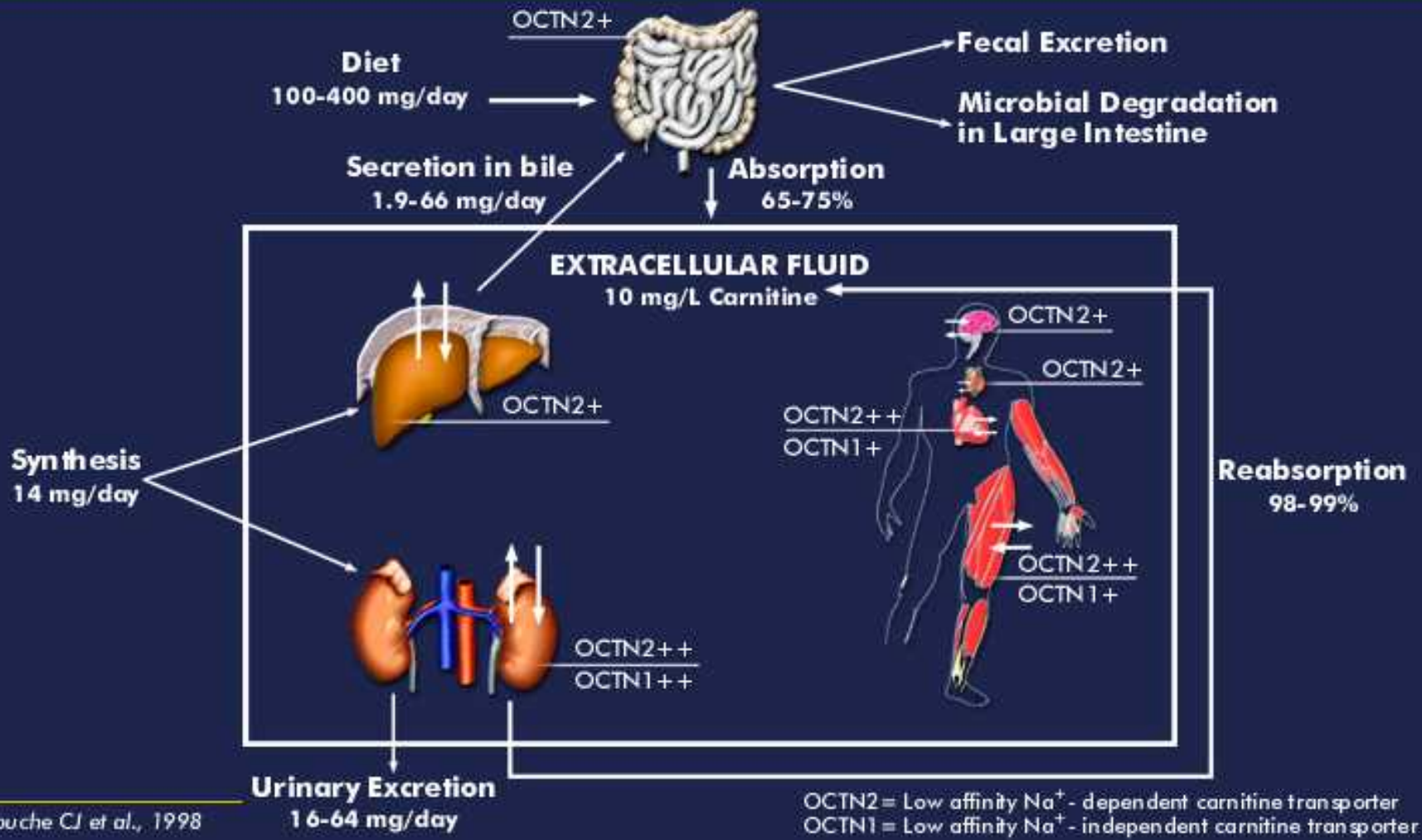


CARNITINE REPLACEMENT IN END-STAGE RENAL DISEASE AND HEMODIALYSIS

MENOTTI CALVANI
Sigma-Tau, Rome, Italy, USA

MARCH 25-26/2004
NATIONAL INSTITUTE OF HEALTH
BETHESDA, MARYLAND

CARNITINE HOMEOSTASIS IN NORMAL SUBJECTS

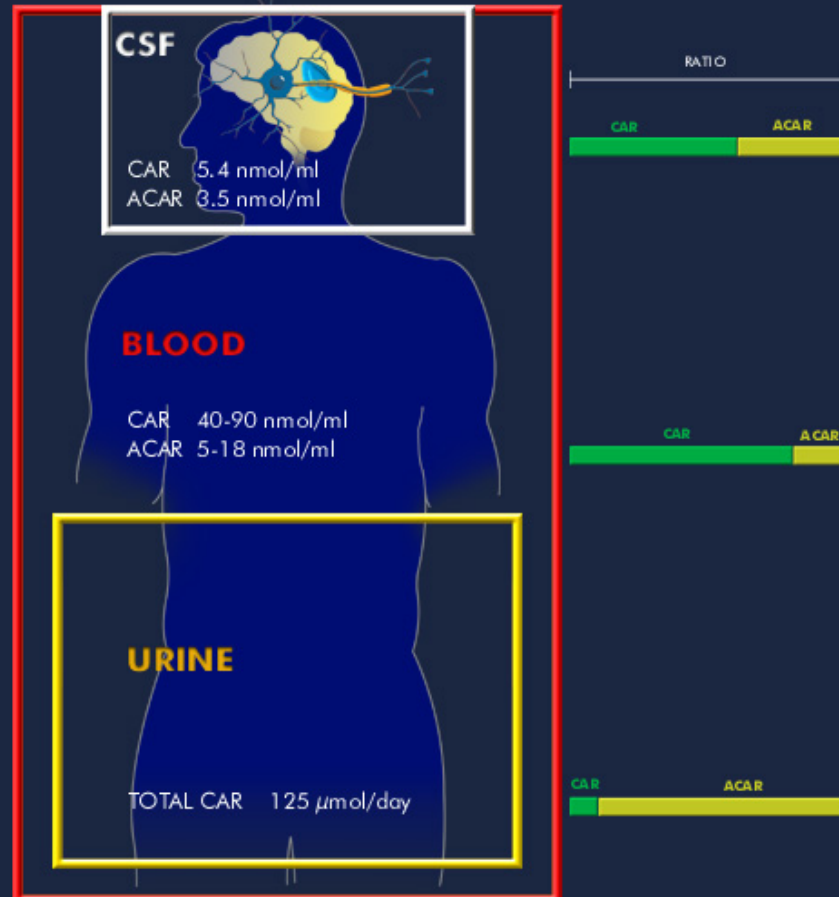


Metabolic Biochem - Jan 2014

Rebouche CJ et al., 1998

OCTN2 = Low affinity Na^+ -dependent carnitine transporter
 OCTN1 = Low affinity Na^+ -independent carnitine transporter

CARNITINE/ACETYLCARNITINE RATIO IN FLUIDS



CAR = CARNITINE

ACAR = ACETYLCARNITINE

CSF = CEREBROSPINAL FLUID

Rubio JC et al., *J Neurol Sci* 155:192-195, 1998

Hoppel CL. In *Hommes FA* (ed.) New York: Allen R. Liss, pp 309-326, 1991

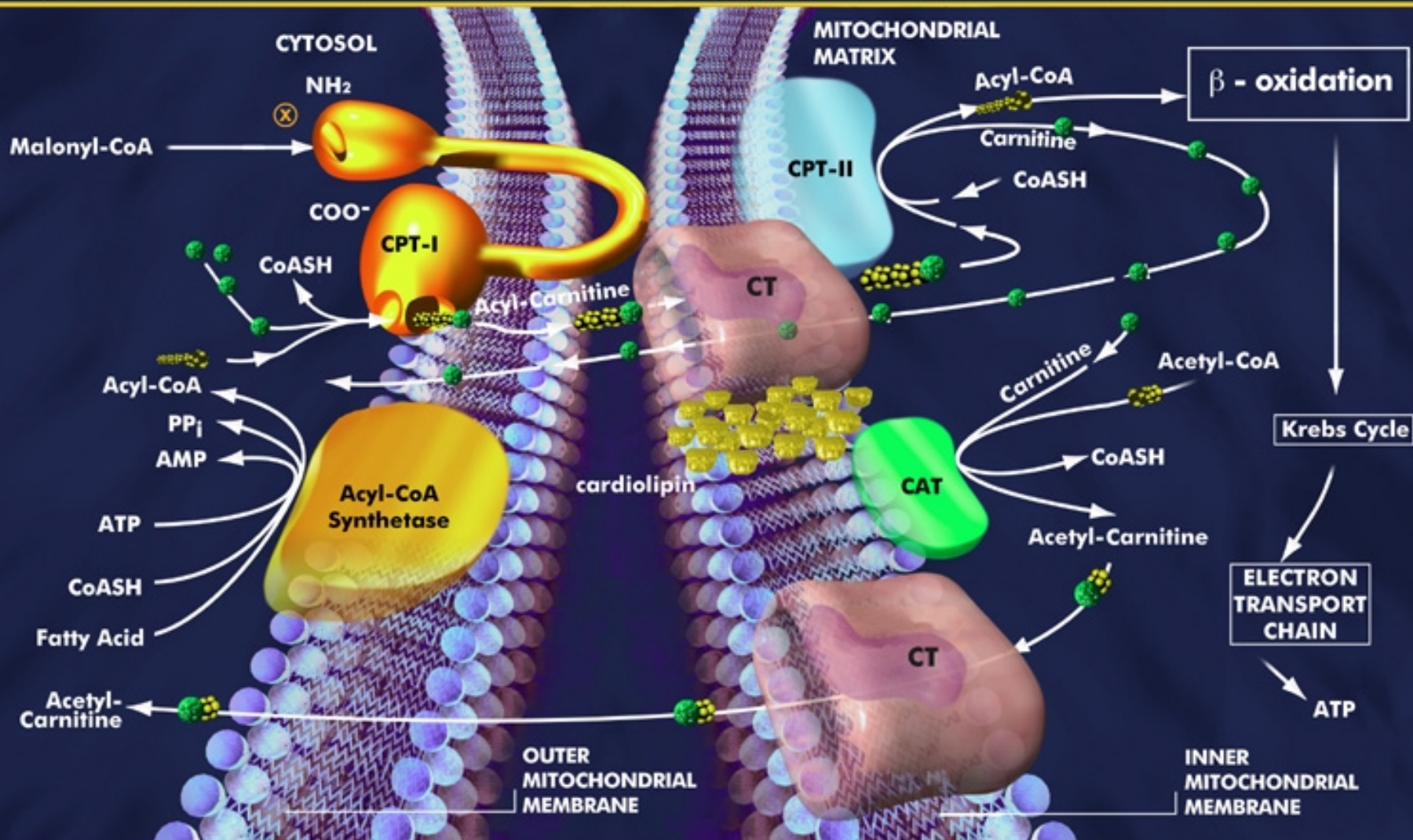
Scientific Department 

DISTRIBUTION OF THE CARNITINE POOL IN THE BODY

Physiological Compartments	Carnitine Concentrations	Estimated Carnitine Content	% of Listed Compartments
Plasma and Extracellular fluids	0.0064-0.0081 mg.mL ⁻¹	80.6 mg	≈ 0.4
Liver	0.081-0.161 mg.g ⁻¹	209 mg	≈ 1
Kidney	0.053-0.096 mg.g ⁻¹	32.2 mg	≈ 0.2
Skeletal muscle	up to 0.645 mg.g ⁻¹	20375 mg	> 98
Total of listed compartments		20697 mg	

MITOCHONDRIAL CARNITINE PATHWAY INTERPLAY between LIPID and GLUCOSE METABOLISM

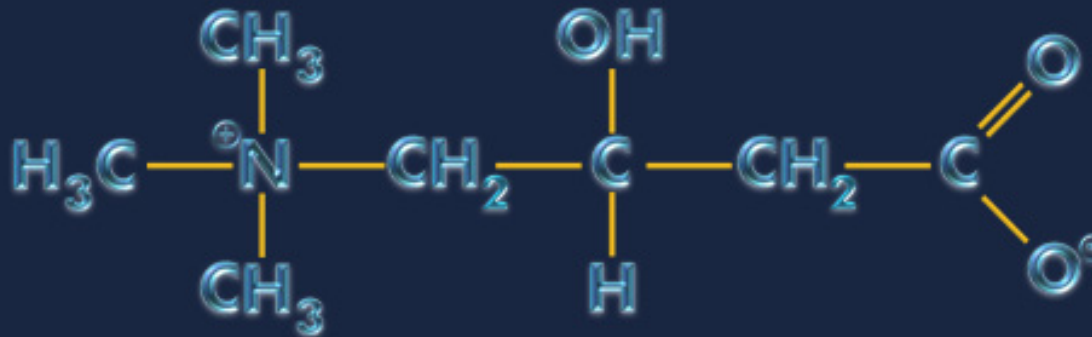
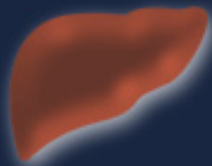
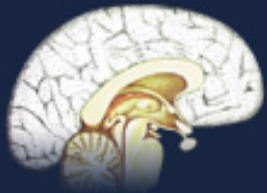
CPT-I= Carnitine Palmitoyl Transferase I CPT-II= Carnitine Palmitoyl Transferase II CT= Carnitine Translocase CAT= Carnitine Acetyl Transferase Scientific Department sigma-tau...



Molecular Biology of the Cell, 6th Edition, © 2008 W. H. Freeman & Co. All rights reserved.

CARNITINE SOURCES

Endogenous



Exogenous



DAILY CARNITINE KIDNEY DISPOSITION IN HEALTHY SUBJECTS AND UREMIC PATIENTS

Plasma conc mM	Glomerular Filtration Rate (ml/min)	Filtration Load mmoles	Reabsorption mmoles	Excretion mmoles
40	125	7.2	6.84	0.36
40	50	2.90	?	?
117	15	2.53	?	?

PLASMA CARNITINE IN UNDIALYSED UREMIC PATIENTS

TOTAL CARNITINE

OR

FREE CARNITINE

(DIRECTLY CORRELATED
WITH SERUM
CREATININE)



- From 84 to 117 mmol/L
- Short- and Long-chain acylcarnitines increase

INCREASE WITH
PROGRESSION OF
THE UREMIC
STATE

ASSOCIATED FINDING:

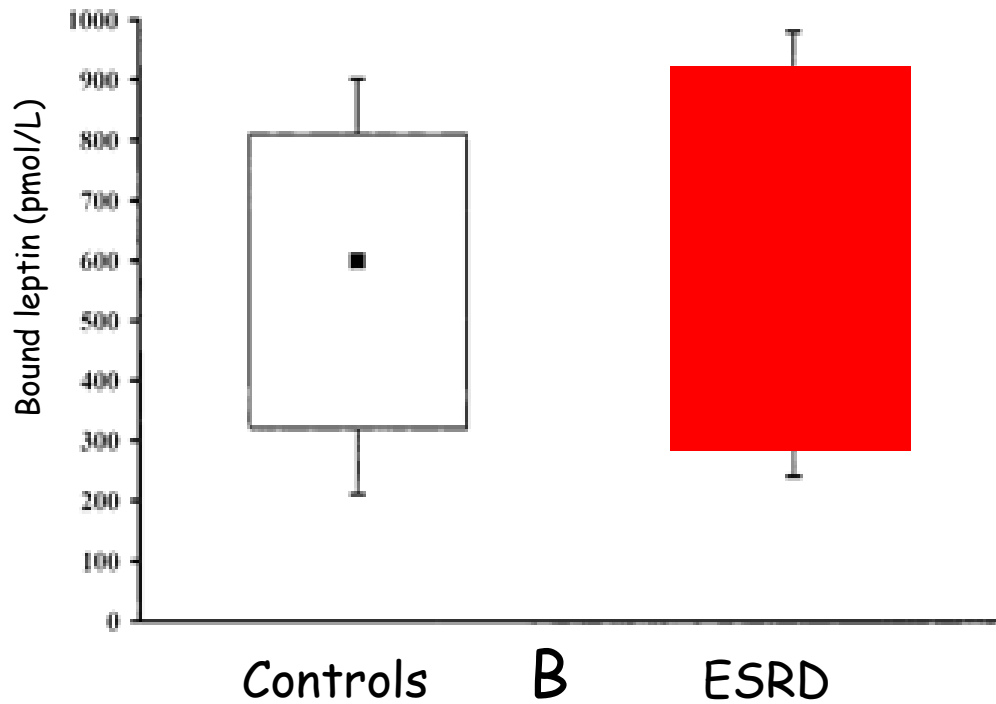
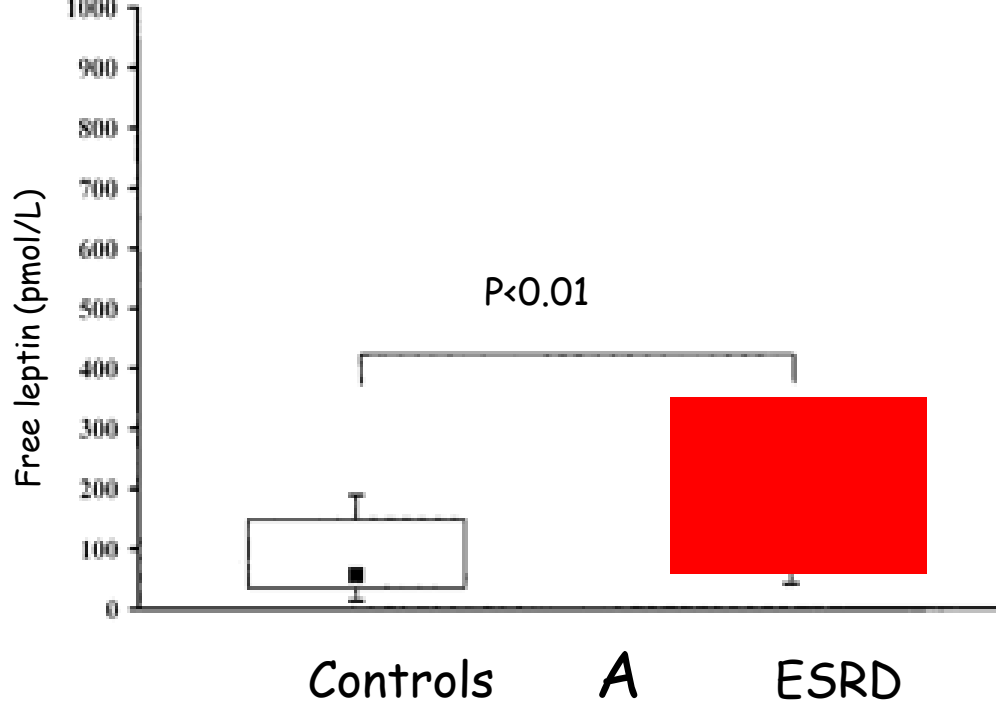
- MAJOR LIPID ABNORMALITIES

Novoa D et al., 1987
Wanner C et al., 1987
Bartel LL et al., 1981
Chen SH et al., 1977

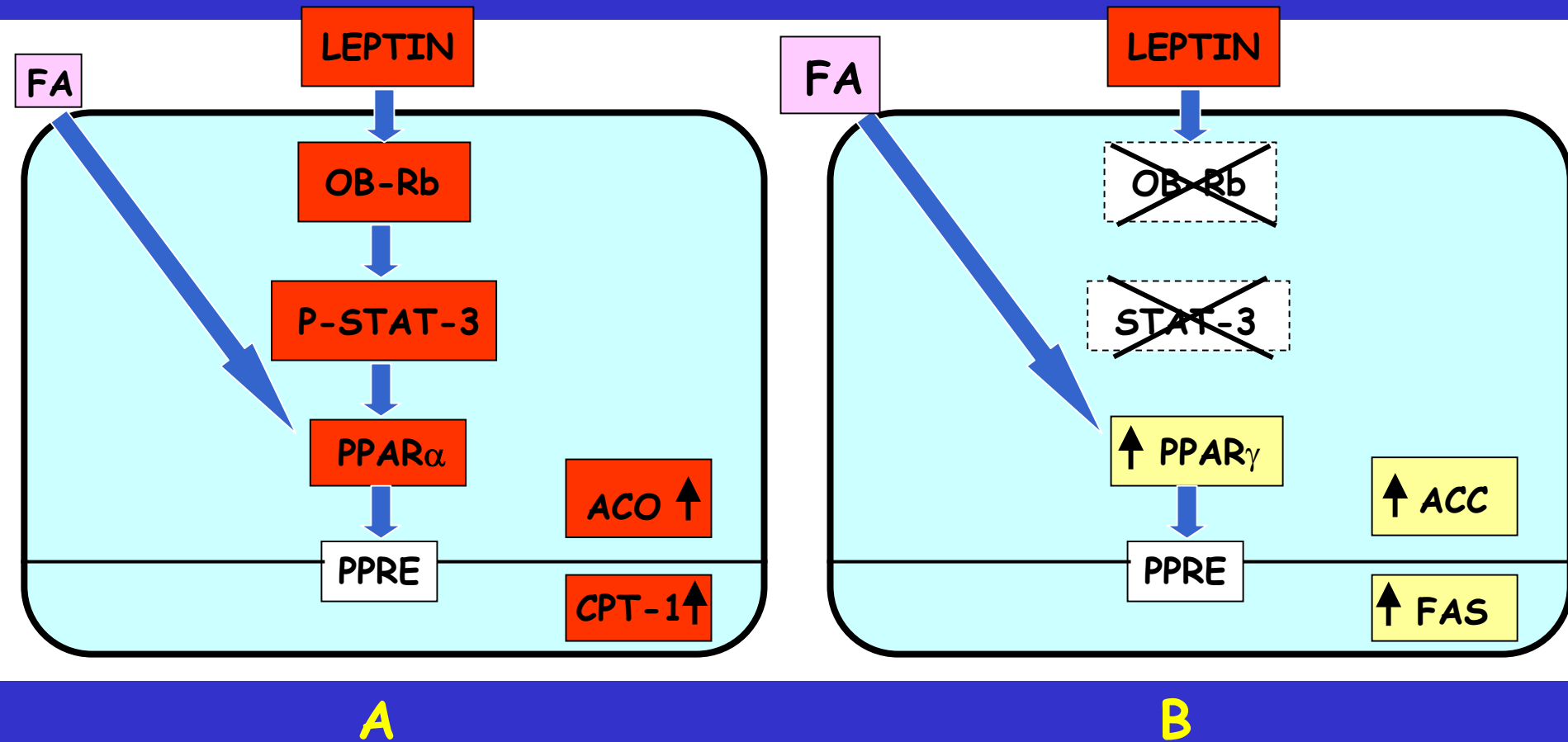
INSIGHT INTO THE ABNORMALITIES OF UREMIC PATIENTS

- LEAN MASS decreased
- FAT MASS increased
- LEPTIN increased
- CPT-1 decreased expression

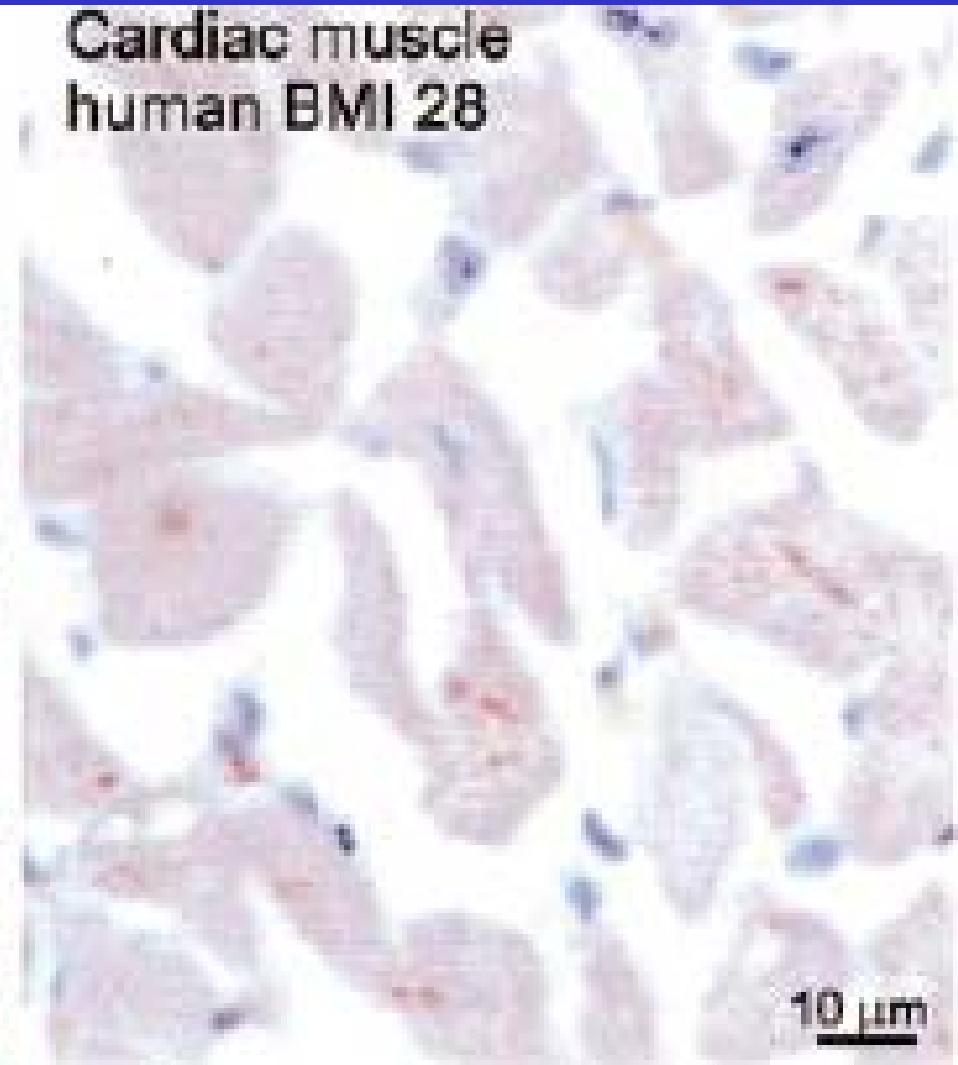
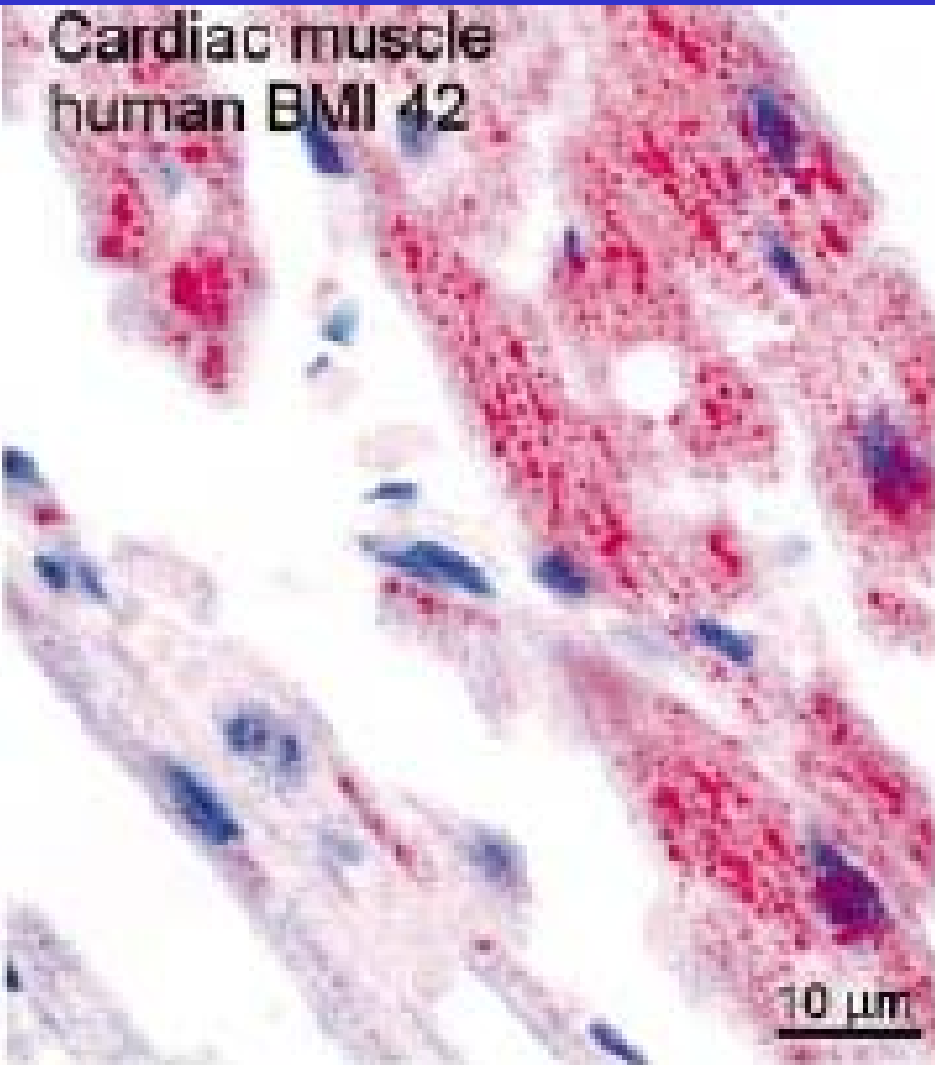
SERUM-FREE (A) AND BOUND LEPTIN LEVELS (B) IN CONTROLS AND PATIENTS WITH ESRD.



HOMEOSTATIC SYSTEM IN NORMAL (A) AND LEPTIN-RESISTANT (B) ISLETS IN ZDF (fa/fa) RATS



HUMAN CARDIAC MUSCLE FROM OBESE (A) AND LEAN MALE (B)



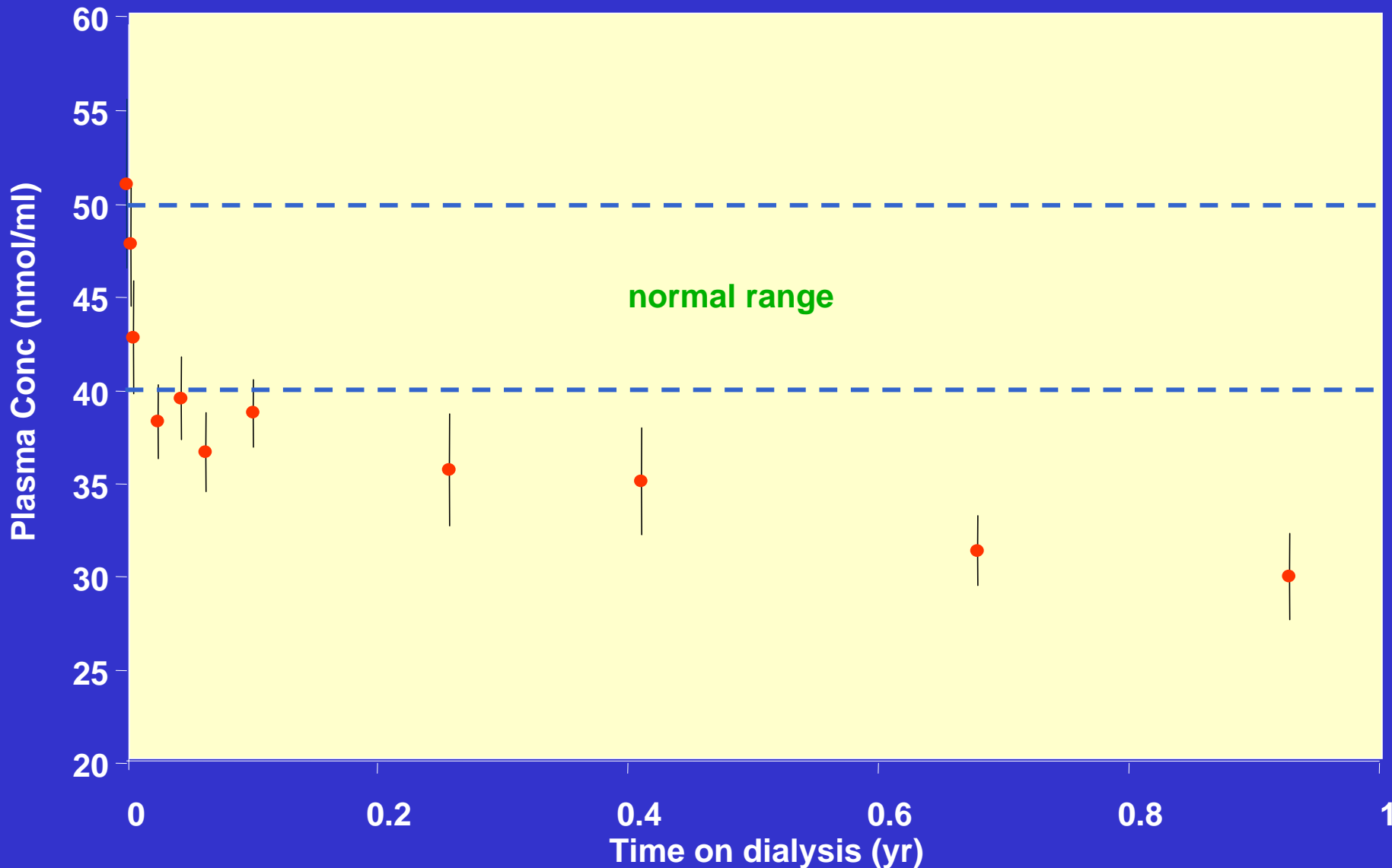
A

B

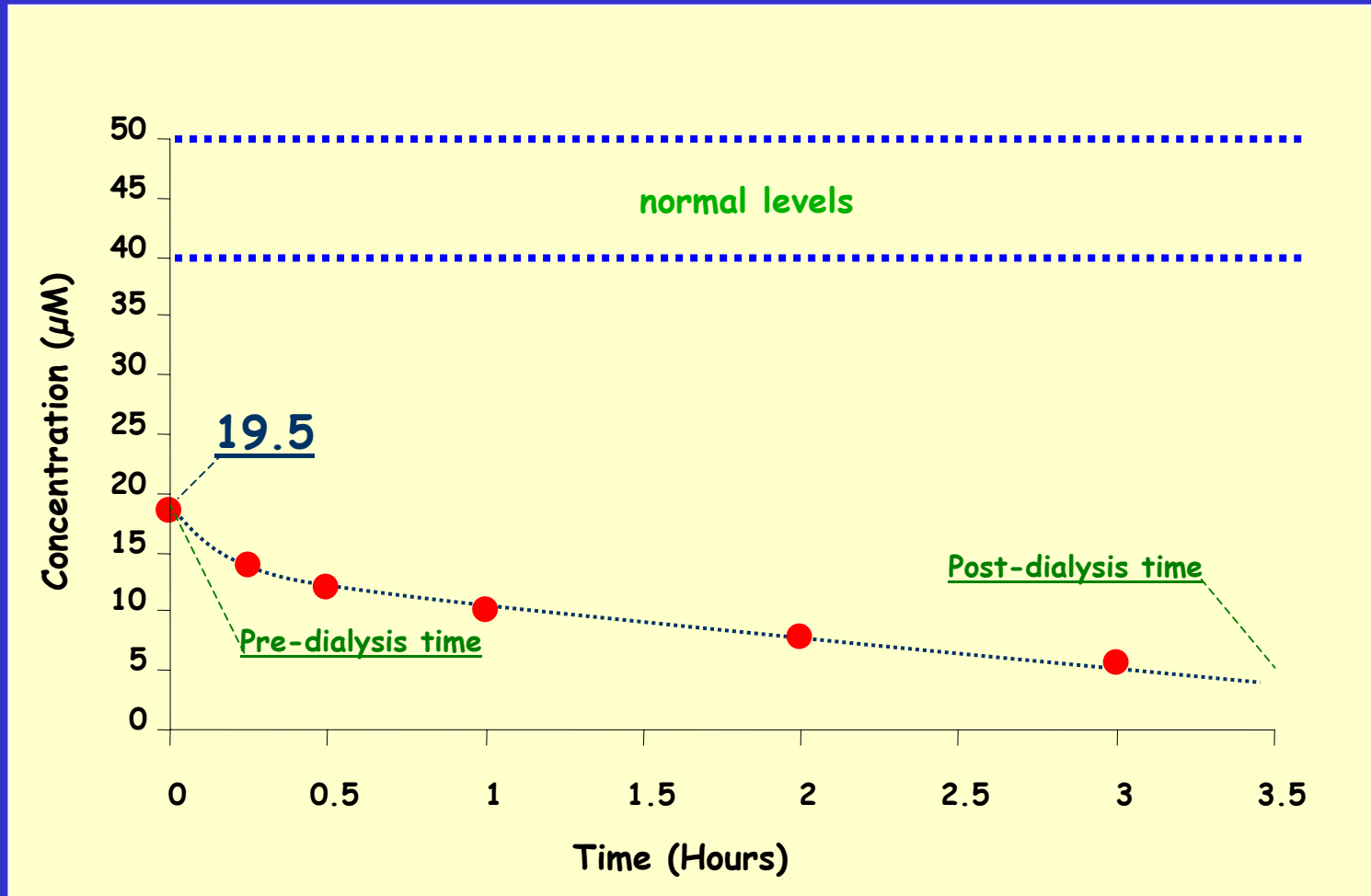
DOCUMENTED FATTY ACID ABNORMALITIES IN ESRD PATIENTS

- Increased Plasma Free Fatty Acids (FFA)
 - Four-fold increase with dialysis (Bartel 1982)
 - Six-fold increase with dialysis (Maeda 1989)
 - Five-fold increase with dialysis (Suzuki 1982)
- Abnormalities of Myocardial Fatty Acids
 - Increased FFA level in myocardium (Sakurabayashi 1999)
 - Deficient metabolism of FFA in myocardium (Sakurabayashi 1999)
- Abnormality of Skeletal Muscle Fatty Acid Metabolism
 - Fatty acid oxidation control = 1487 ± 267 dpm/mg (Savica 1983)
 - Fatty acid oxidation hemodialysis patients = 638 ± 285 dpm/mg
($p < 0.003$ control vs HD) (Savica 1983)

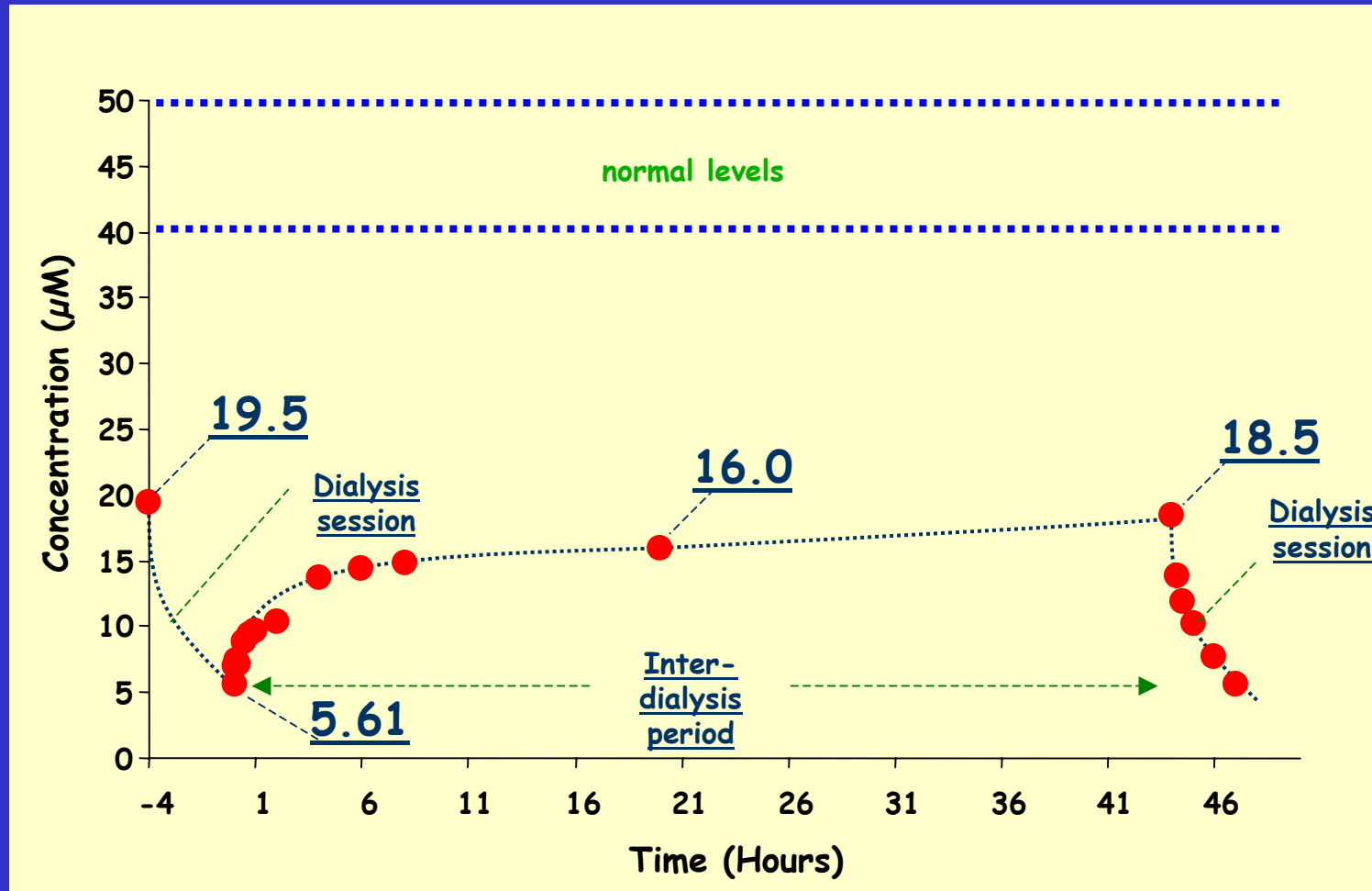
L-CARNITINE PLASMA CONCENTRATIONS IN ESRD PATIENTS DURING THE FIRST YEAR OF DIALYSIS TREATMENT



PLASMA CONCENTRATIONS OF ENDOGENOUS L-CARNITINE DURING HEMODIALYSIS



PLASMA CONCENTRATIONS OF ENDOGENOUS CARNITINE DURING TWO CONSECUTIVE DIALYSIS SESSIONS (INTER-DIALYSIS PERIOD)



DECREASED PLASMA FREE CARNITINE LEVELS IN HEMODIALYSIS PATIENTS

Value (\pm SD) pre-hemodialysis session

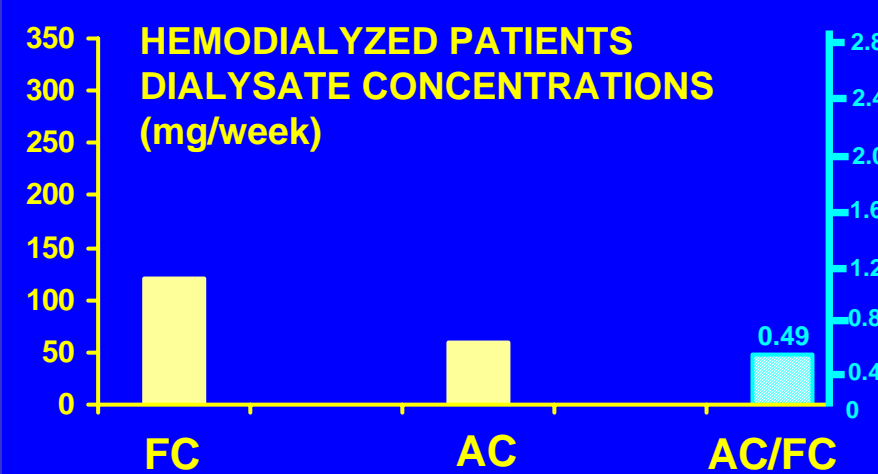
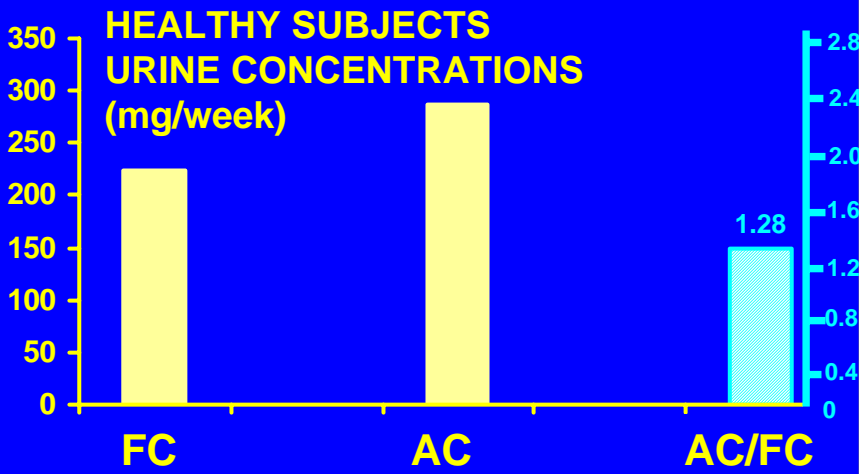
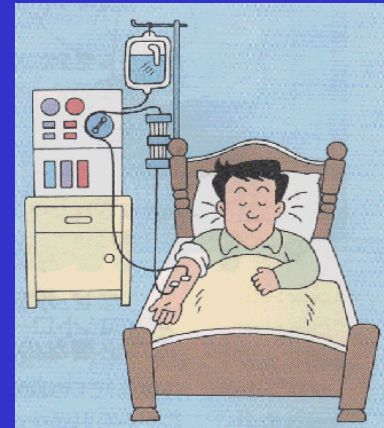
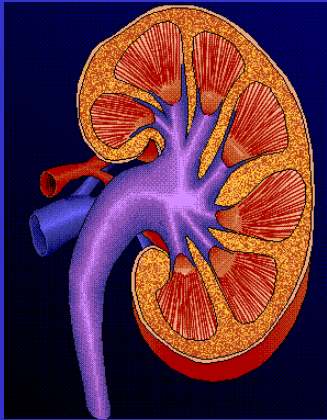
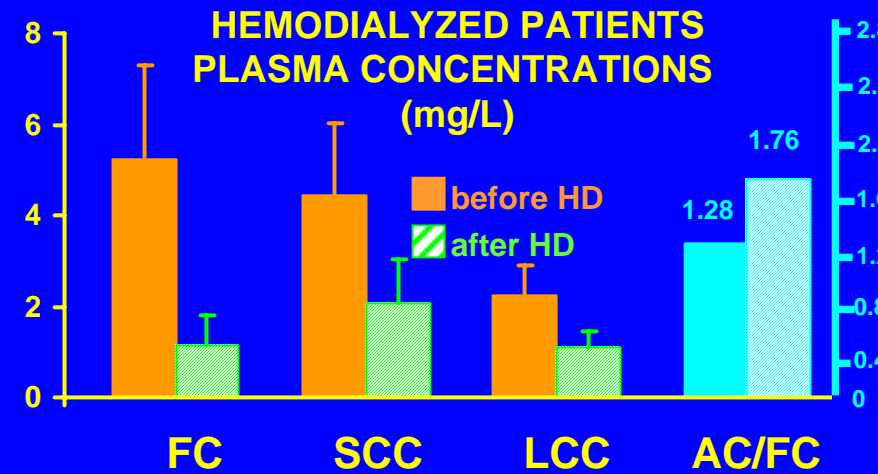
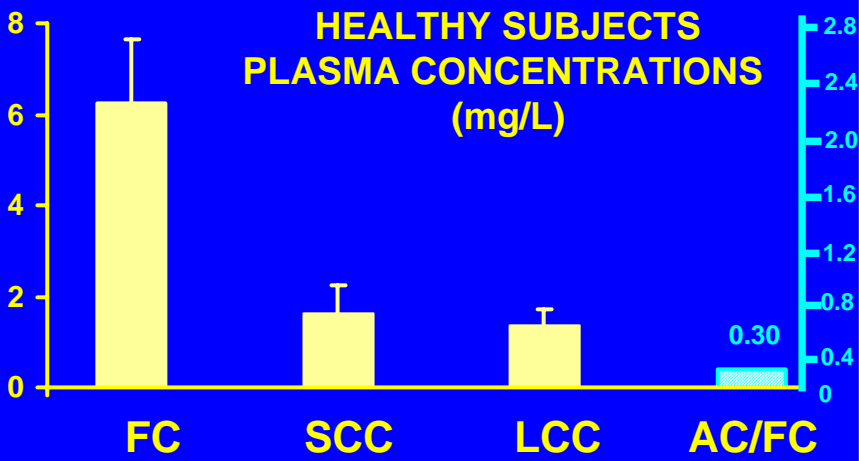
- 24.8 \pm 7.9 microM (Suzuki 1982)
 - 28 \pm 6.0 microM (Bellinghieri 1983)
 - 30.4 microM (Savica 1983)
 - 32.4 microM (Rossle 1985)
 - 25.9 microM (Lennon 1986) (A/f=.96)
 - 21.5 \pm 7 microM (Van Es 1992) (A/f=.98)
 - 19.2 \pm 6.5 microM (Sakurabayashi 1999) (A/f=.87)
 - 19.5 \pm 5.6 microM (Evans 2000) (A/f=.77)
- (Normal Control Value 40 \rightarrow 50 microM) (A/f<.4)

ABNORMAL BLOOD CARNITINE LEVELS (microM) IN CAPD PATIENTS

	Free carnitine (FC)	Acylcarnitine (AC)	AC:FC ratio	Total carnitine (TC)
NORMAL VALUES	48 ± 11.2	6 ± 3	< 0.4	57 ± 11
PLIAKOIANNIS <i>et al</i>	30 ± 11 ^a	14 ± 8	0.5 ± 0.3	44 ± 4
CONSTANTIN-TEODOSIU <i>et al</i>	28 ± 1	9 ± 2	0.5 ± 0.1	43 ± 2
MORIWAKA <i>et al</i>	29 ^b	15	0.5	43
BUONCRISTIANI <i>et al</i>	28			

^a Males : 35 ± 9; females: 26 ± 10

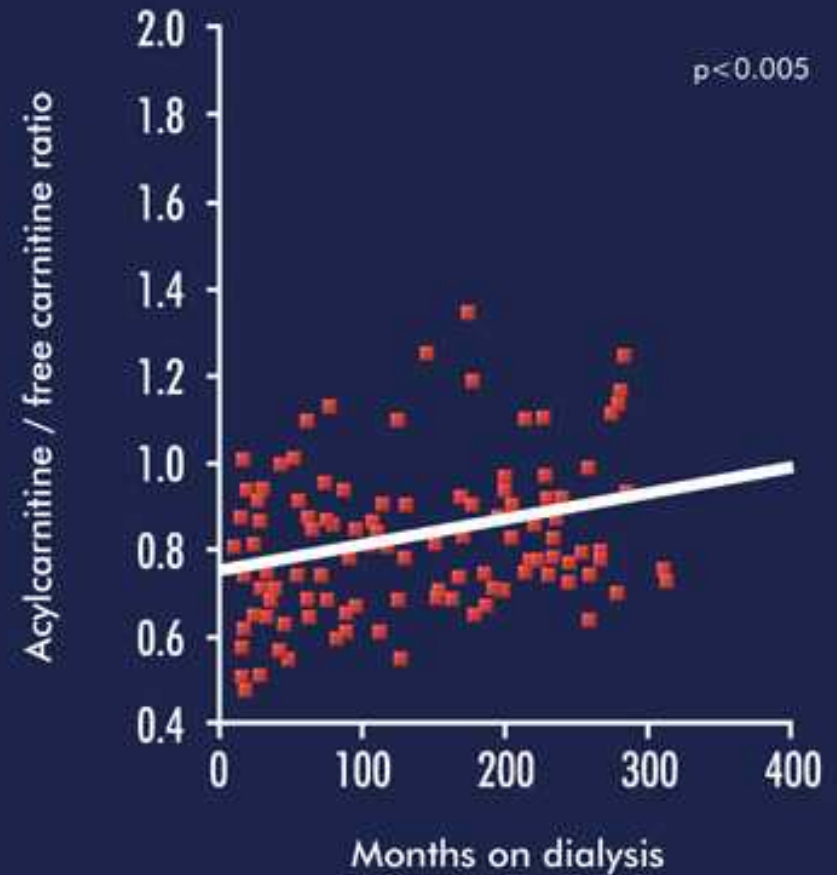
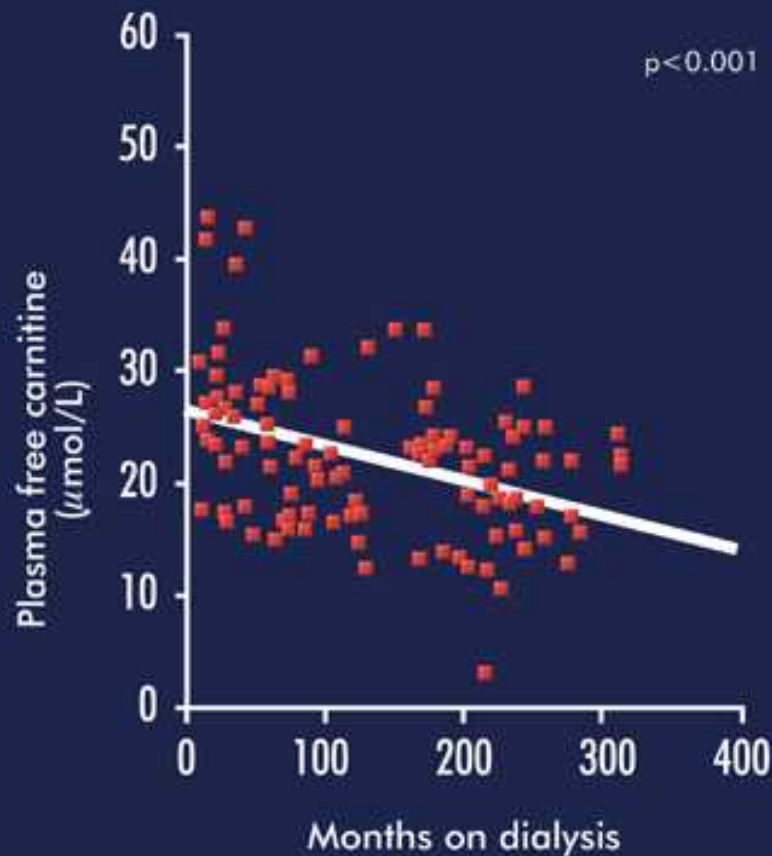
^b For more than 5 years on CAPD, the FC level was 27



L-CARNITINE IN HEMODIALYSED PATIENTS

CORRELATION BETWEEN DIALYTIC AGE AND PLASMA CARNITINE LEVELS

Scientific Department 



MUSCLE FREE CARNITINE LEVELS (MICROMOLES/G/NCP)

HEMODIALYSIS PATIENTS

9.88 (SAVICA 1983)

10.3 (BELLINGHERI 1983)

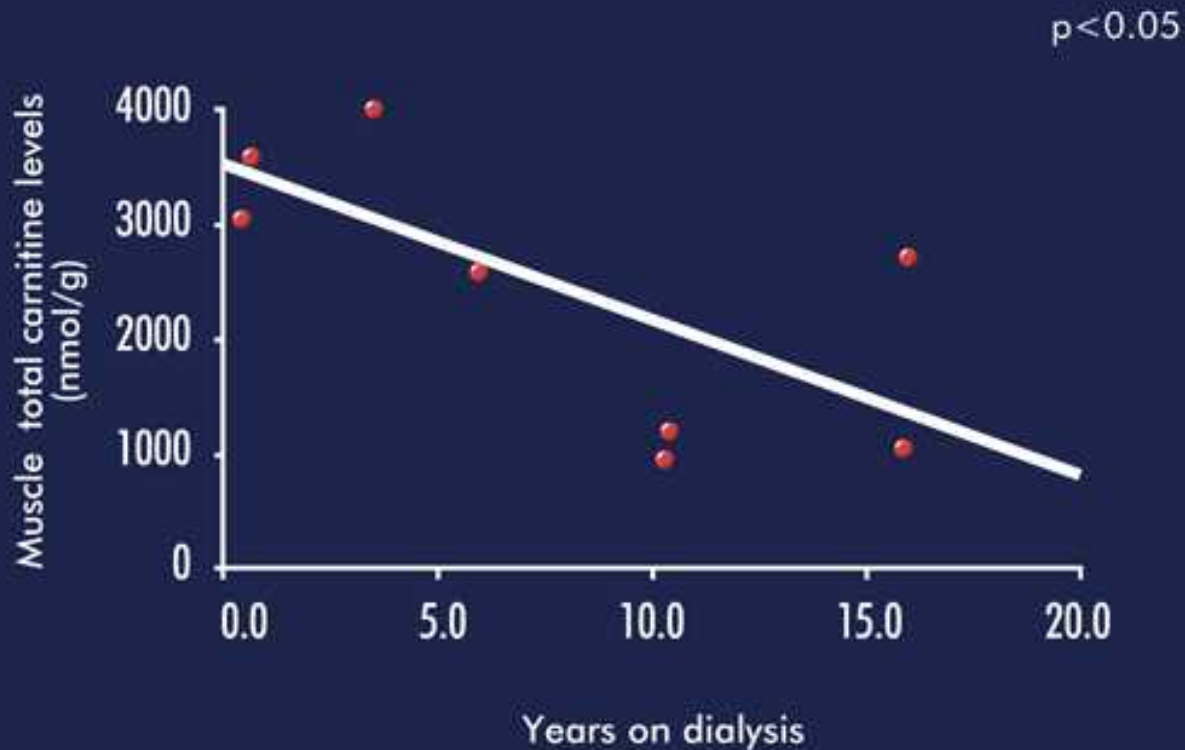
12.9 (FAGHER 1985)

HEALTHY CONTROLS

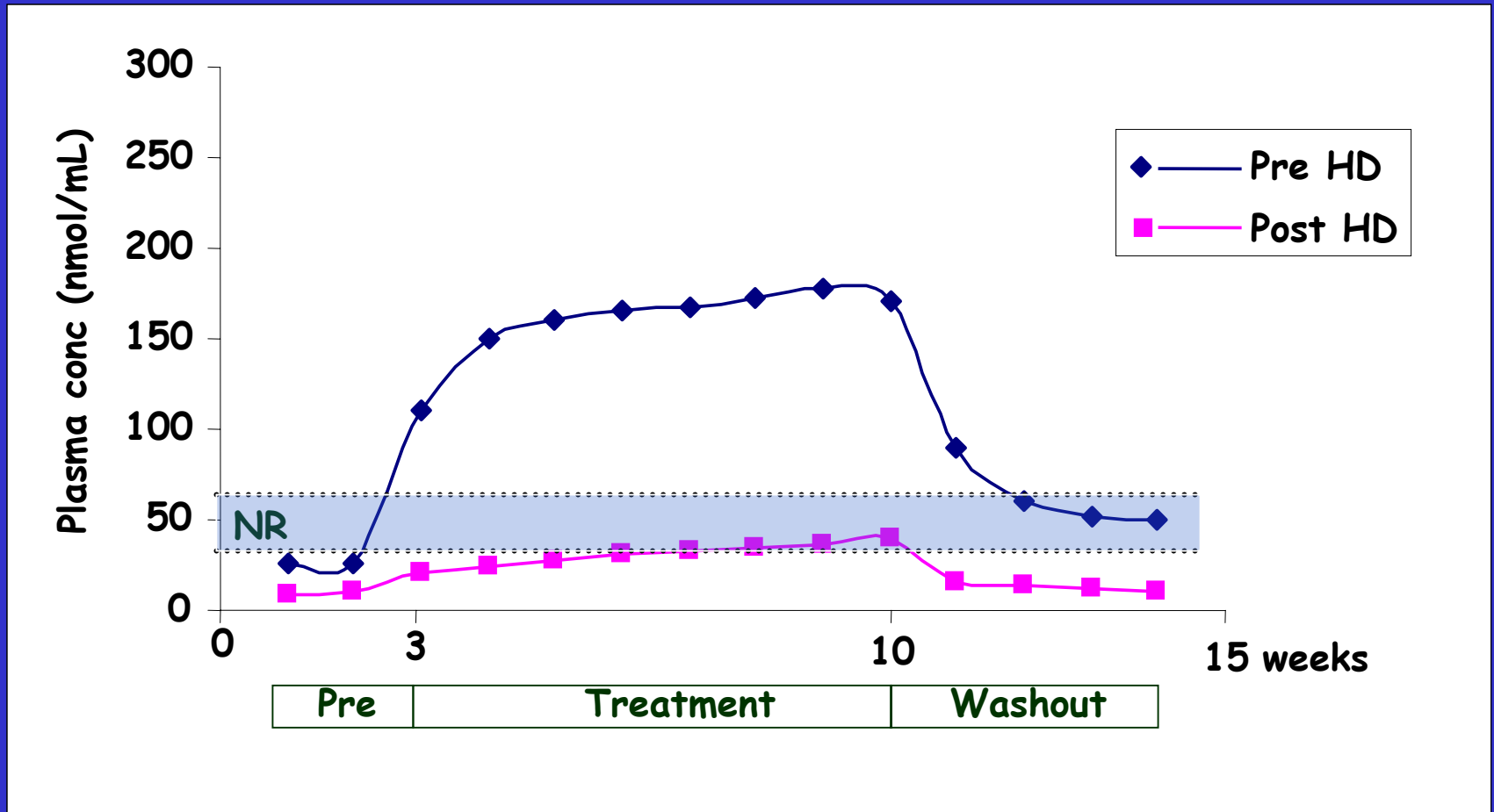
19.34-27.7

L-CARNITINE IN HEMODIALYSED PATIENTS

CORRELATION BETWEEN DIALYTIC AND MUSCLE CARNITINE LEVELS



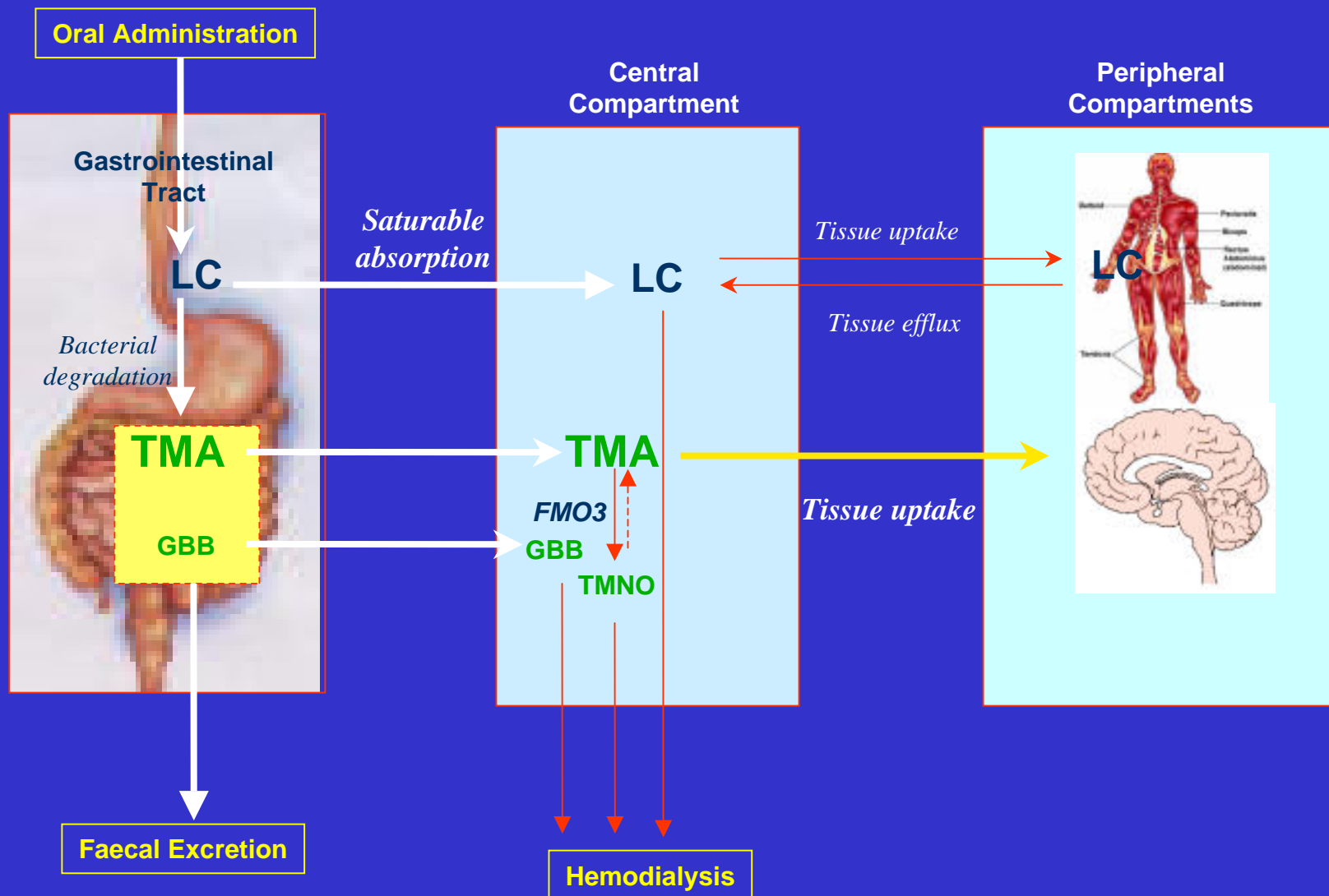
PLASMA CONCENTRATIONS OF L-CARNITINE DURING INTERDIALYTIC SESSIONS



L-Carnitine Administration in Hemodialysis Patients

Increase of body content	% Dose reaching tissue compartment	Dose administered	Time to double carnitine pool	
			No. Doses	Months
10 to 20g	50	2 mg/kg i.v after each dialysis session	130	12
10 to 20g	50	20 mg/kg i.v. after each dialysis session	13	1.2
10 to 20g	7.5	2 g os/die	?	?

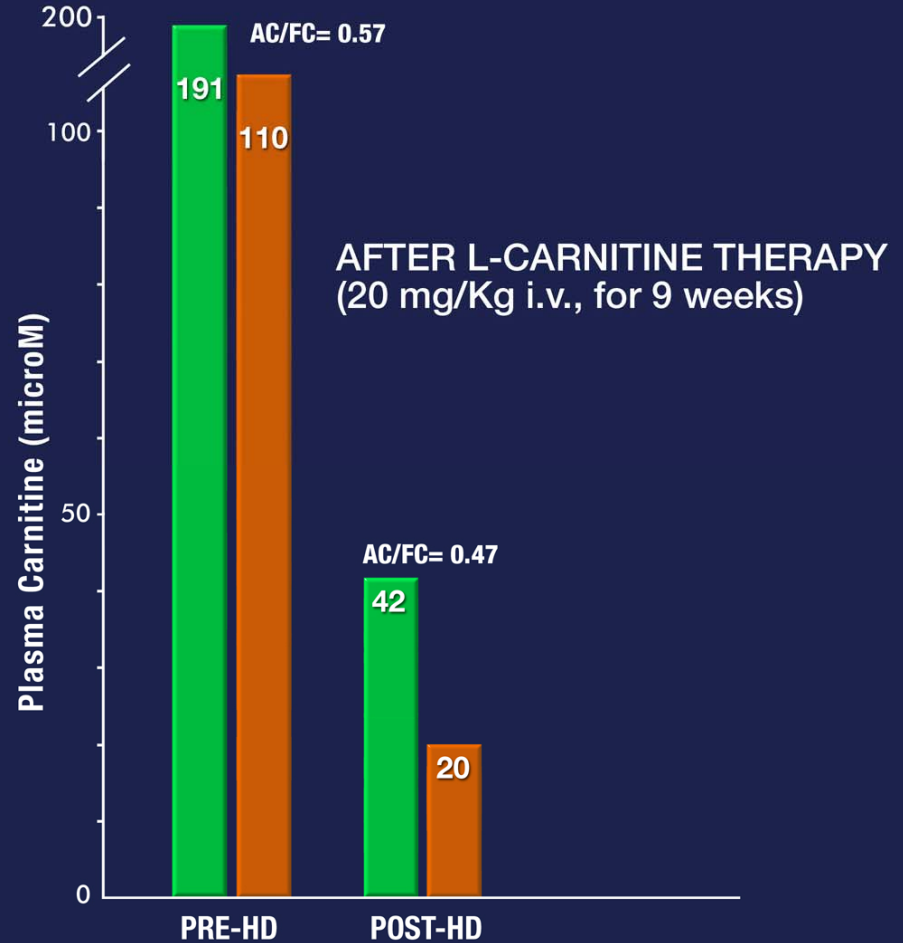
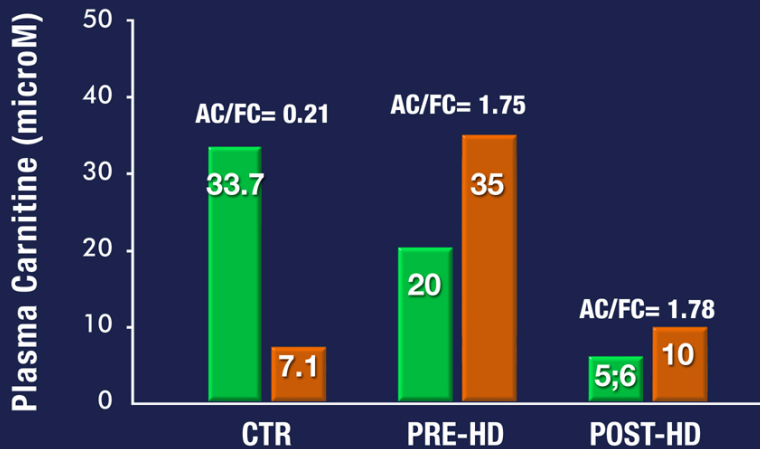
Disposition of L-carnitine in the body following oral administration of Levocarnitine



CARNITINE LEVELS IN HEMODIALYSED PATIENTS

- free carnitine (FC)
- acylcarnitines (AC)

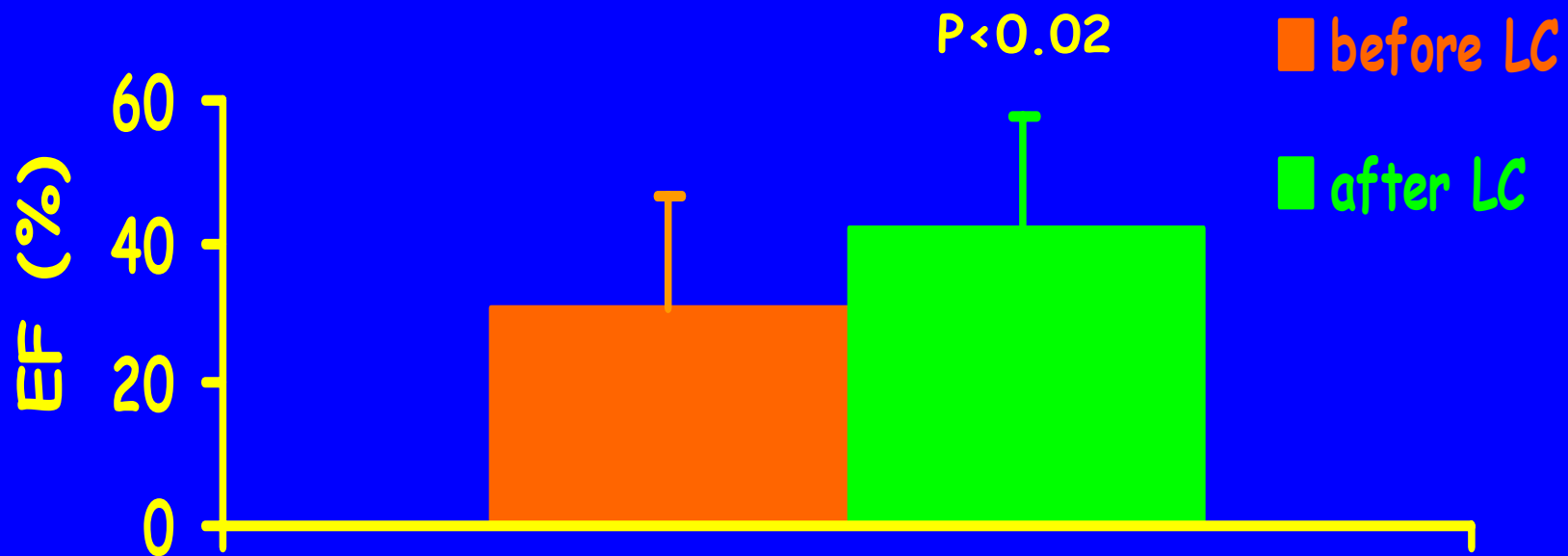
BEFORE L-CARNITINE THERAPY
At least 6 months of dialysis
(3 dialysis sessions/week)



CLINICAL CORRELATIONS TO LOW CARNITINE LEVELS IN HEMODIALYSIS PATIENTS (1)

- Kudoh 1983
 - Low plasma free carnitine levels corresponds to increased cardio thoracic ratio
- van Es 1992
 - Pearson's Correlation Coefficient of .60 ($p < 0.02$) between EF and plasma free carnitine; $EF = 1.65 \times FC + 7.02$
- Riley 1997
 - Low plasma free carnitine levels correspond to intradialytic hypotension and low Karnofsky Functional Activity Scale Score

AMELIORATION OF EJECTION FRACTION BY L-CARNITINE IN HEMODIALYZED PATIENTS

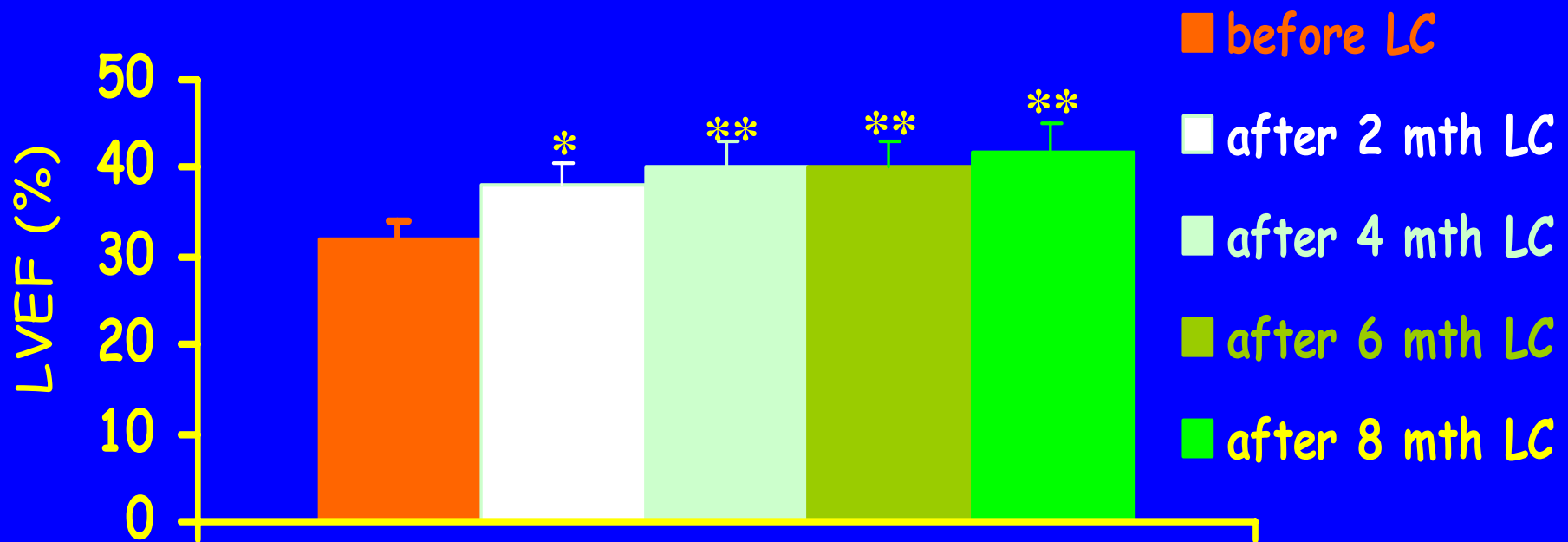


Treatment: LC 1g iv for 3 months

Van ES A., 1992

L-CARNITINE IMPROVES LEFT VENTRICULAR EJECTION FRACTION (LVEF) IN HD PATIENTS

L-Carnitine 1g iv for 8 months



* $p < 0.05$ vs before LC

** $p < 0.01$ vs before LC

GROUP MEAN EJECTION FRACTIONS

• Baseline

-17.5

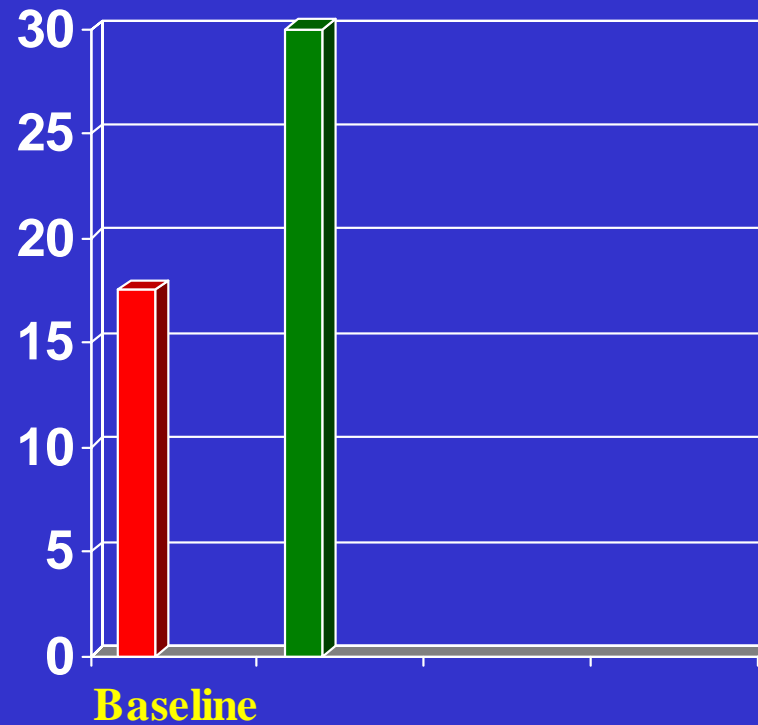
-SD 2.5

• After Six Months of IV
Levocarnitine Therapy

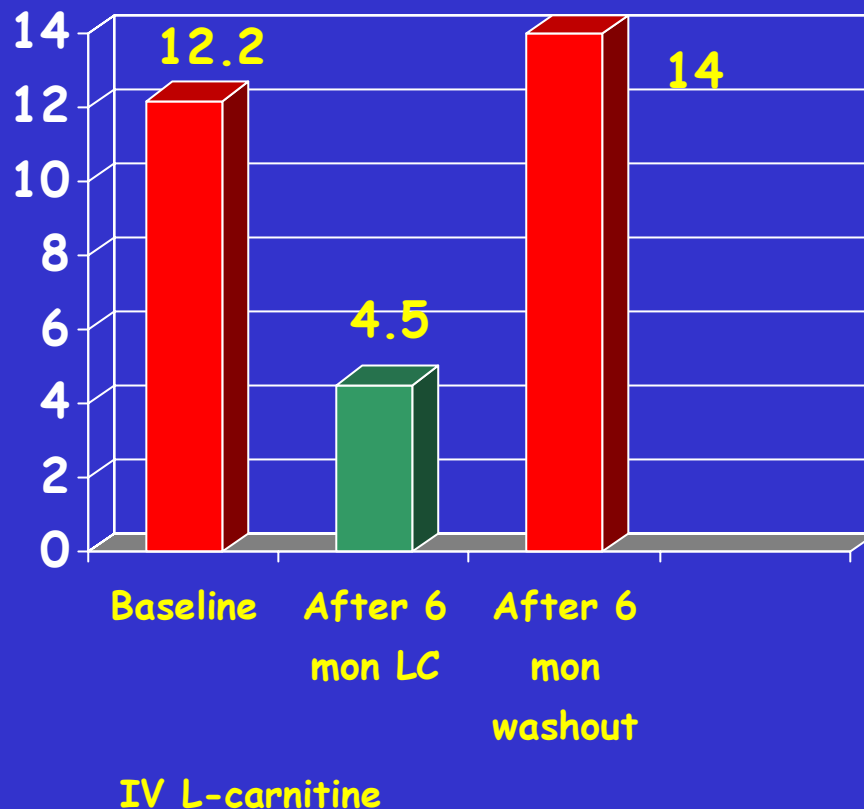
-30

-SD 4.0

-P Value <0.001



GROUP MEAN NUMBER OF HYPOTENSIVE EPISODES (MONTHLY VALUES)



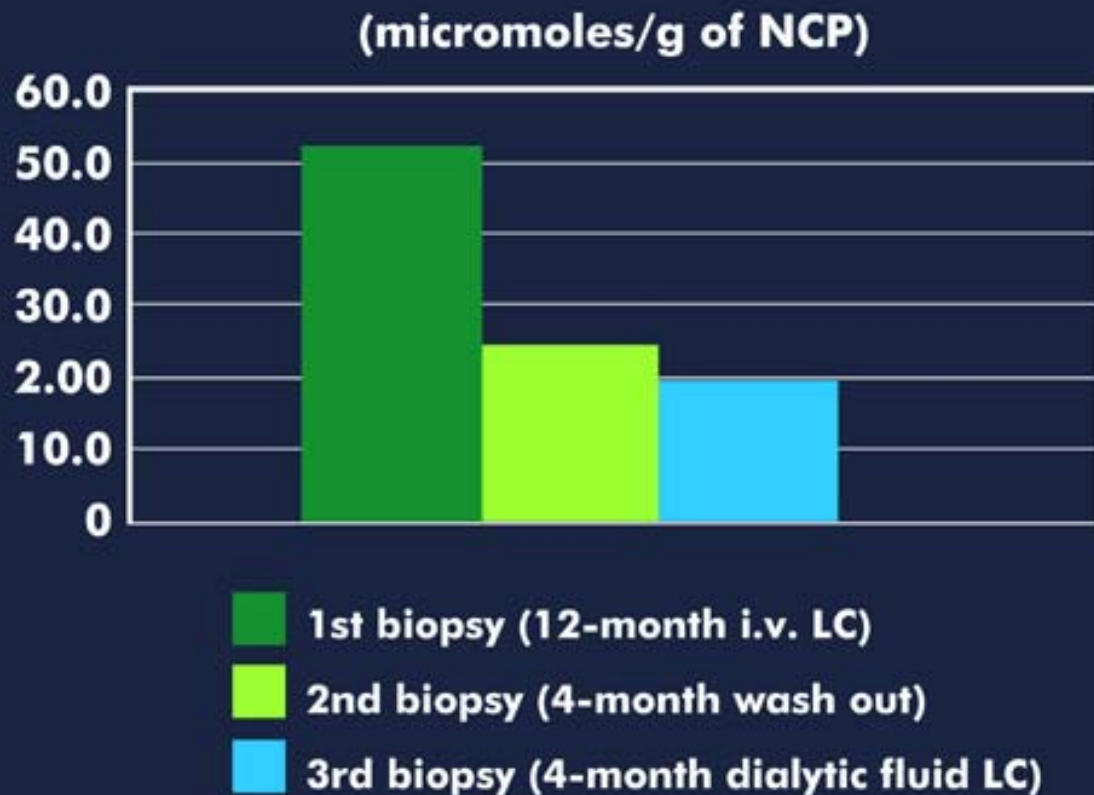
DECREASE IN HOSPITALIZATION WITH LEVOCARNITINE THERAPY IN 1,038 PATIENTS WITH HISTORY OF CARDIAC DISEASE

Time (before and during carnitine)	Relative risk	95% CI
- 12 to - 9 months	0.72	(0.64, 0.82)
- 9 to - 6 months	0.76	(0.68, 0.86)
- 6 to - 3 months	0.81	(0.73, 0.91)
- 3 to 0 months	1.00	-
0 to + 3 months	0.76	(0.69, 0.85)
+ 3 to + 6 months	0.69	(0.62, 0.77)
+ 6 to + 9 months	0.66	(0.57, 0.76)
+ 9 to + 12 months	0.66	(0.56, 0.77)

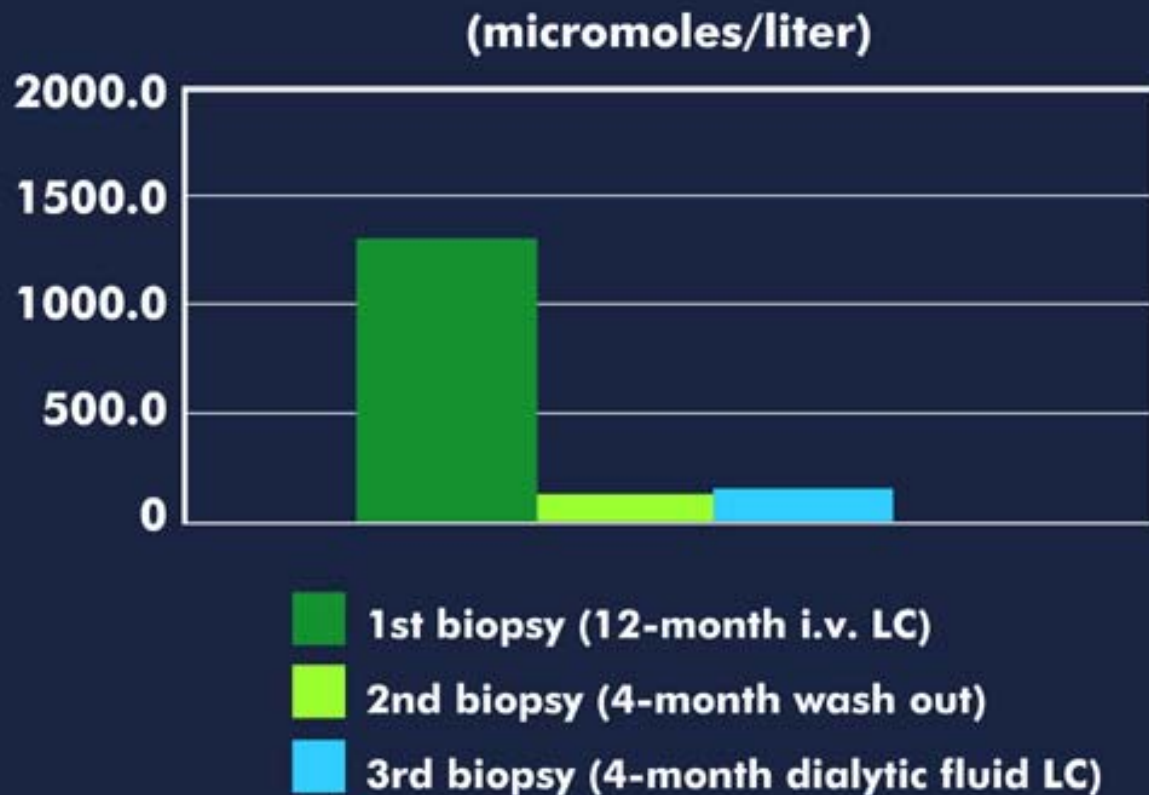
CLINICAL CORRELATIONS TO LOW CARNITINE LEVELS IN HEMODIALYSIS PATIENTS (2)

- Hiatt 1992
 - Positive correlation between muscle carnitine content and peak exercise performance

L-CARNITINE (LC) EFFECTS ON SKELETAL MUSCLE CARNITINE LEVELS IN HEMODIALYZED PATIENTS

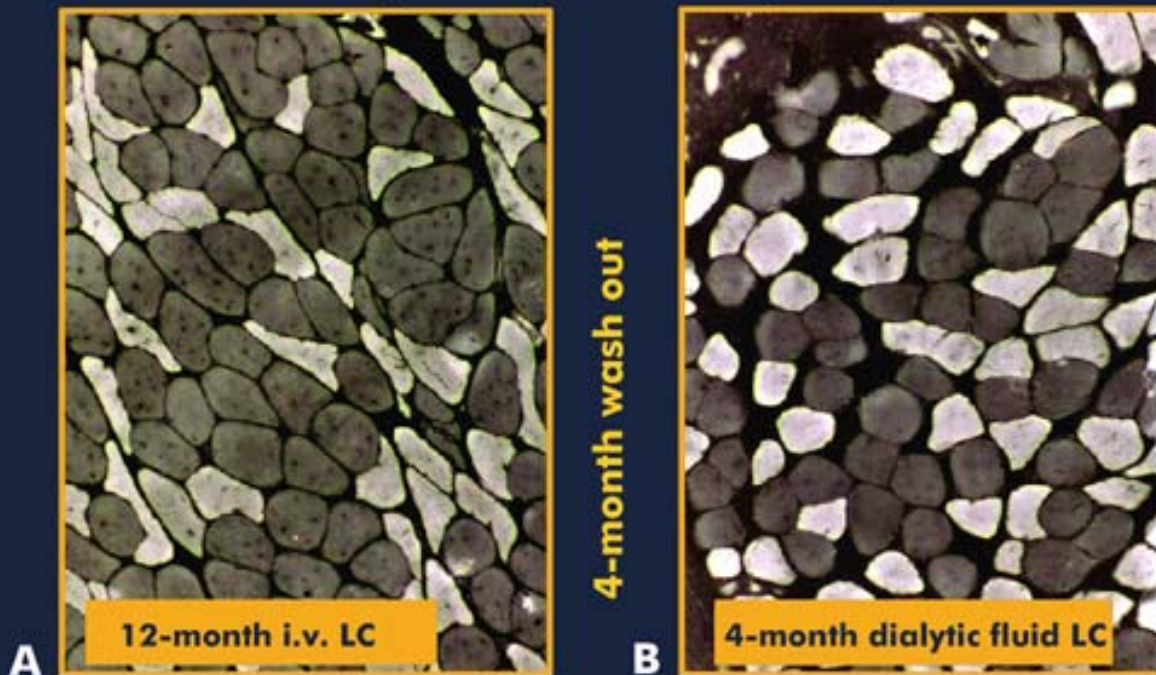


L-CARNITINE (LC) EFFECTS ON SERUM CARNITINE LEVELS IN HEMODIALYZED PATIENTS



L-CARNITINE (LC) EFFECTS ON SKELETAL MUSCLE IN HEMODIALYSED PATIENTS

Type I fibers (dark) of biopsy B are smaller in biopsy B than biopsy A.
(ATPase preincubated pH 9.4)



Changes in serum and muscle carnitine levels are related to
modification of both the enzymatic pattern of muscle and the
morphology of single fibers

CLINICAL CORRELATIONS TO LOW CARNITINE LEVELS IN HEMODIALYSIS PATIENTS (3)

- **Kooistra 1991**
 - Negative correlation between plasma total carnitine level and weekly maintenance rHuEPO dose
- **Matsumura 1996**
 - Negative correlation between plasma carnitine level and both erythrocyte fragility and weekly maintenance rHuEPO dose
- **Steiber 2004**
 - Positive correlation between plasma free carnitine level and hematocrit

EFFECT OF L-CARNITINE SUPPLEMENTATION ON HEMATOLOGICAL STATUS IN DIALYSIS

(SUMMARY OF LITERATURE REVIEWS)

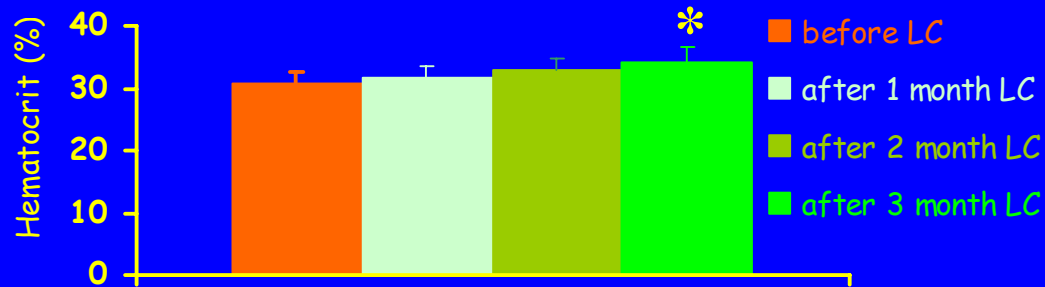
	HUROT et al. (1998)	AMATO et al. (Unpublished)
No OF STUDIES	9	4
No OF PATIENTS (treatment/control)	121/118	61/60
HEMATOCRIT	↑	↑
EPO REQUIREMENT	↓	↓

L-CARNITINE EFFECTS IN HD PATIENTS

Sotirakopoulos N., 2000

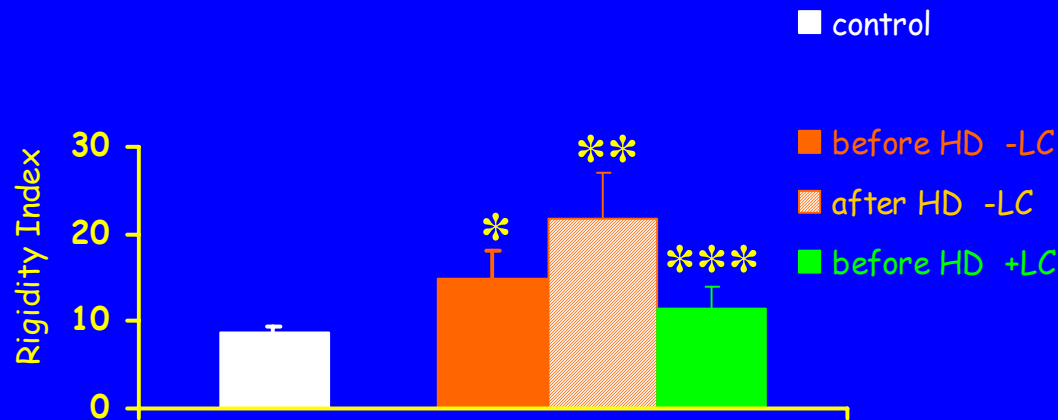
(30 mg/Kg iv for 3 months)

HEMATOCRIT LEVELS



* $p < 0.00001$ vs before LC

RIGIDITY INDEX

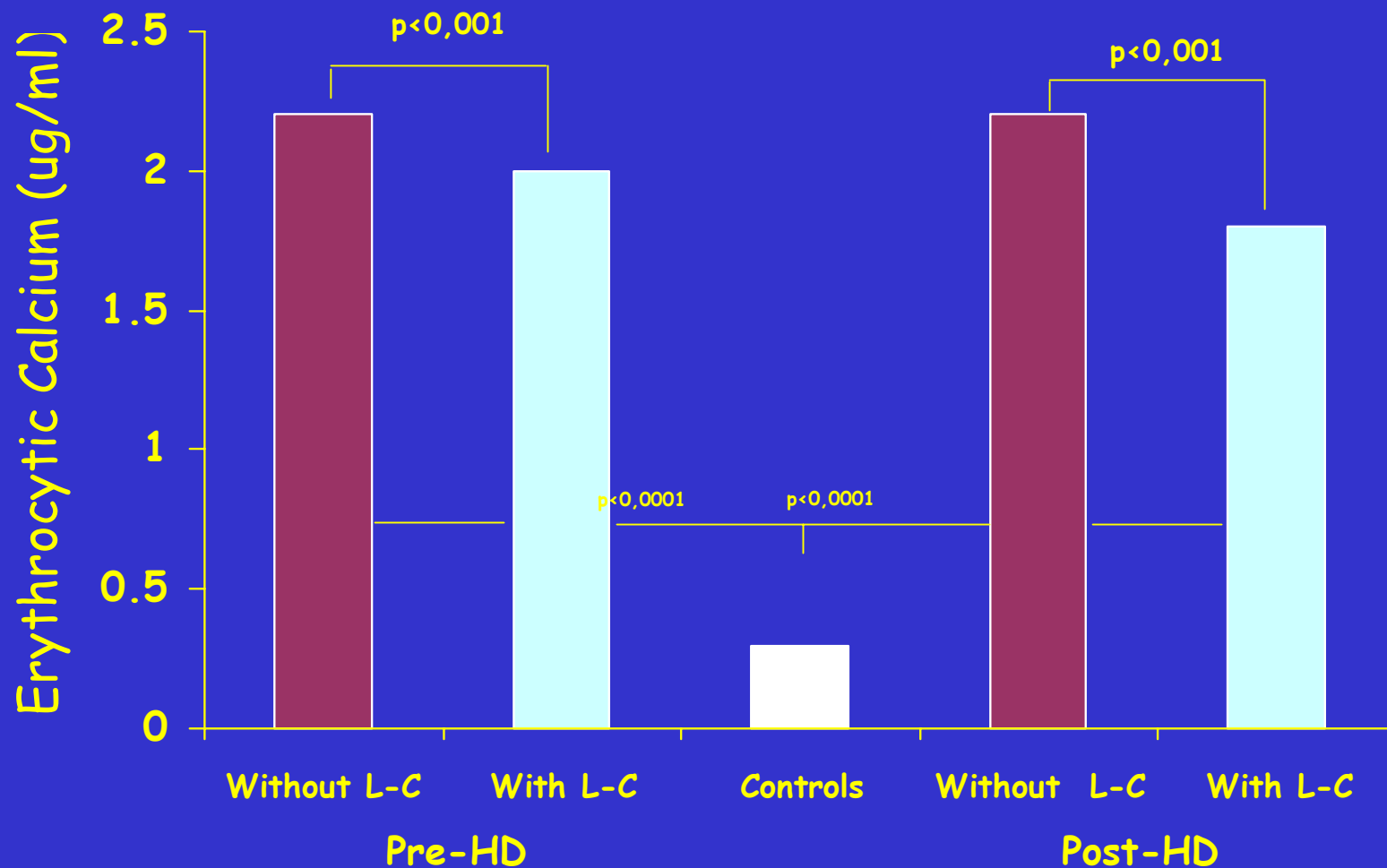


* $p < 0.00001$ vs control

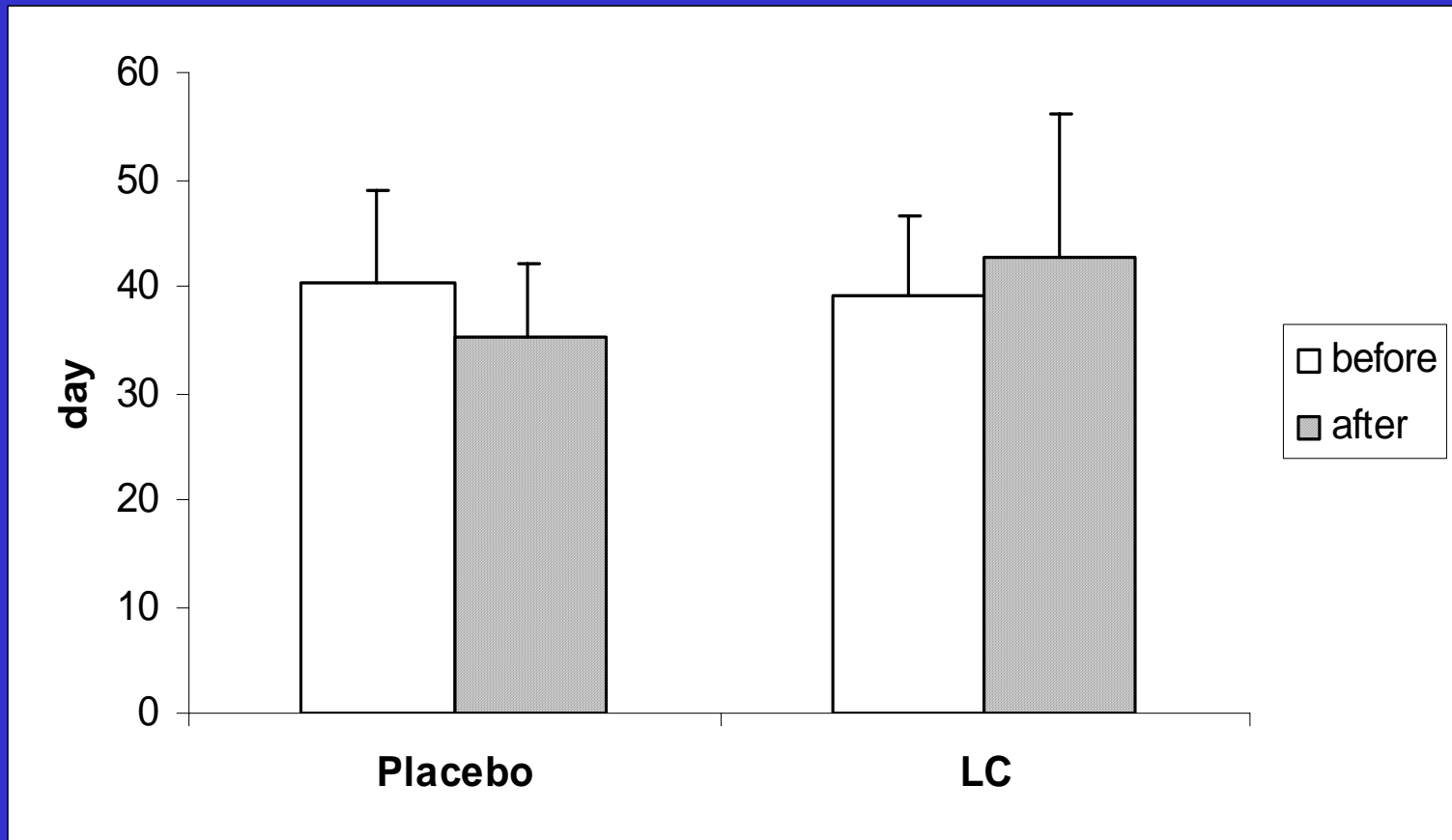
** $p < 0.00001$ vs before HD -LC

*** $p < 0.004$ vs before HD -LC

ERYTHROCYTIC CALCIUM & L-CARNITINE



EFFECT OF L-CARNITINE ON RED BLOOD CELL SURVIVAL



Treatment: LC (20mg/kg) or placebo iv post dialysis for 24 weeks

RBC Survival: $^{51}\text{Cr } T_{\frac{1}{2}}$

CLINICAL INDICATIONS FOR LEVOCARNITINE IN HEMODIALYSIS PATIENTS (FDA APPROVAL OF DEC 1999)

“For the prevention and treatment of carnitine deficiency in patients with End Stage Renal Disease who are undergoing dialysis”

CLINICAL INDICATIONS FOR LEVOCARNITINE IN HEMODIALYSIS PATIENTS (CONSENSUS CONFERENCE 2003)

Anemia

- Hgb <11-12 With >300 Unis/kg/wk IV or 200 S.C

Intradialytic Hypotension

- Sudden Drop to Systolic < 90, > 30 Point Drop in MAP or Systolic BP With Symptoms

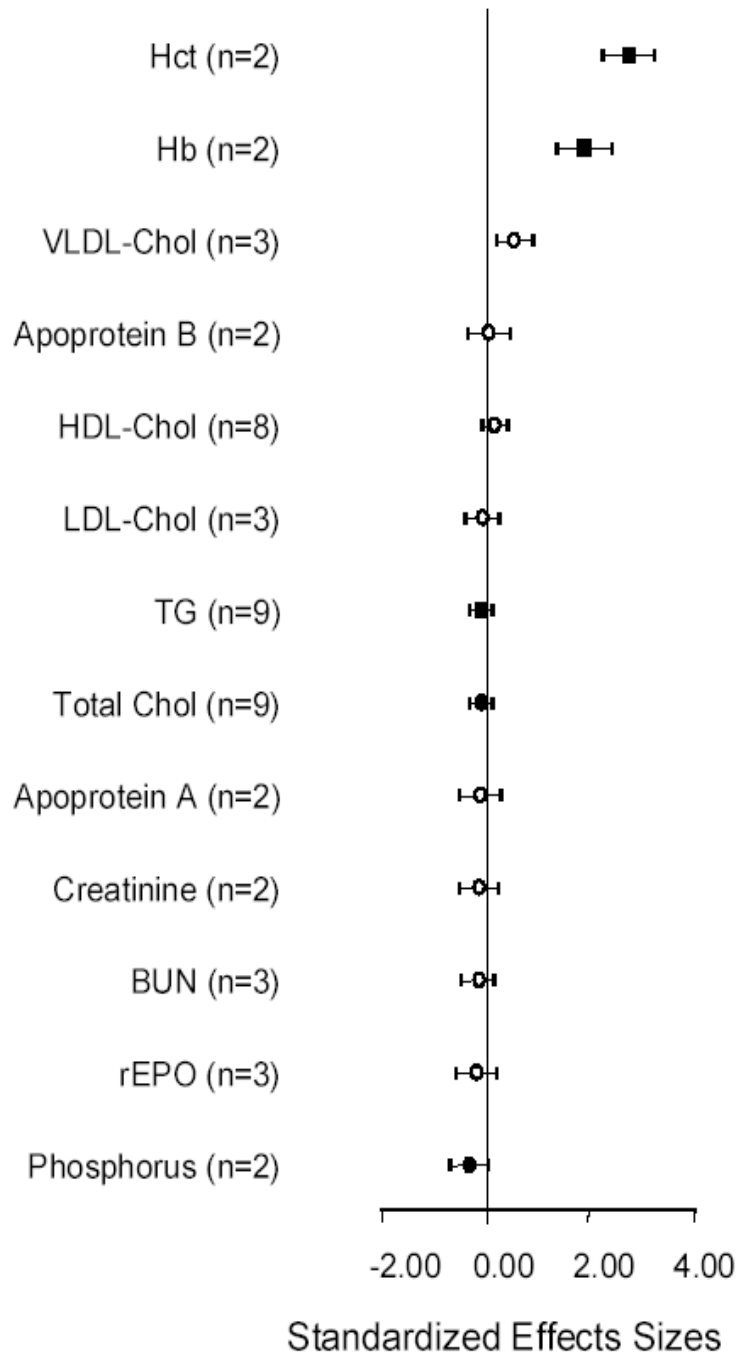
Cardiomyopathy

- NYHA Class III-IV or ACA/AHA Stage C-d; symptomatic Impairment of E.F

Muscle Weakness

L-CARNITINE THERAPY IN HD PATIENTS: A META-ANALYSIS BASED REVIEW

Primary meta-analysis
(24 prospective randomized
controlled studies)



L-CARNITINE THERAPY IN HD PATIENTS: A META-ANALYSIS BASED REVIEW

Secondary meta-analysis
(24 prospective uncontrolled studies)

