CARNITINE REPLACEMENT IN END-STAGE RENAL DISEASE AND HEMODIALYSIS

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BETHESDA, MARYLAND
CARNITINE HOMEOSTASIS IN NORMAL SUBJECTS

Diet
100-400 mg/day

OCTN2+

Fecal Excretion

Microbial Degradation in Large Intestine

Secretion in bile
1.9-66 mg/day

Absorption
65-75%

10 mg/L Carnitine

EXTRACELLULAR FLUID

Synthesis
14 mg/day

OCTN2+

Urinary Excretion
16-64 mg/day

Reabsorption
98-99%

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

Rebouche CJ et al., 1998
CARNITINE/ACETYLCARNITINE RATIO IN FLUIDS

**CSF**
- **CAR**: 5.4 nmol/ml
- **ACAR**: 3.5 nmol/ml

**BLOOD**
- **CAR**: 40.90 nmol/ml
- **ACAR**: 5-18 nmol/ml

**URINE**
- **TOTAL CAR**: 125 μmol/day

**CAR** = CARNITINE  \quad **ACAR** = ACETYLCARNITINE  \quad **CSF** = CEREBROSPINAL FLUID

References:

Scientific Department
## DISTRIBUTION OF THE CARNITINE POOL IN THE BODY

<table>
<thead>
<tr>
<th>Physiological Compartments</th>
<th>Carnitine Concentrations</th>
<th>Estimated Carnitine Content</th>
<th>% of Listed Compartments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma and Extracellular fluids</td>
<td>0.0064-0.0081 mg.mL$^{-1}$</td>
<td>80.6 mg</td>
<td>≈ 0.4</td>
</tr>
<tr>
<td>Liver</td>
<td>0.081-0.161 mg.g$^{-1}$</td>
<td>209 mg</td>
<td>≈ 1</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.053-0.096 mg.g$^{-1}$</td>
<td>32.2 mg</td>
<td>≈ 0.2</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>up to 0.645 mg.g$^{-1}$</td>
<td>20375 mg</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>Total of listed compartments</td>
<td></td>
<td>20697 mg</td>
<td></td>
</tr>
</tbody>
</table>

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...
CARNITINE SOURCES

Endogenous

Exogenous

$\text{CH}_3\text{CH}_2\text{CCH}_2\text{N}^+\text{CH}_3$

$\text{H}_2\text{O}$

$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$

25%

75%

Scientific Department
<table>
<thead>
<tr>
<th>Plasma conc mM</th>
<th>Glomerular Filtration Rate (ml/min)</th>
<th>Filtration Load mmoles</th>
<th>Reabsorption mmoles</th>
<th>Excretion mmoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>125</td>
<td>7.2</td>
<td>6.84</td>
<td>0.36</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>2.90</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>117</td>
<td>15</td>
<td>2.53</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
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

ASSOCIATED FINDING:
• MAJOR LIPID ABNORMALITIES

INCREASE WITH PROGRESSION OF THE UREMIC STATE

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

Unger RH, PNAS 1999; 96:2327-2332
HUMAN CARDIAC MUSCLE FROM OBESE (A) AND LEAN MALE (B)

Cardiac muscle human BMI 42

Cardiac muscle human BMI 28

A B

Unger RH, FASEB J, 2001
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)
PLASMA CONCENTRATIONS OF ENDOGENOUS L-CARNITINE DURING HEMODIALYSIS

![Graph showing plasma concentrations of endogenous L-carnitine during hemodialysis.](image)

- Pre-dialysis time
- Post-dialysis time

**Normal Levels:**

Concentration (µM)

Time (Hours)

Evans A, Clin Pharmacol Ther 2000
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 ± 7.9 microM (Suzuki 1982)
- 28 ± 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 ± 7 microM (Van Es 1992) (A/f=.98)
- 19.2 ± 6.5 microM (Sakurabayashi 1999) (A/f=.87)
- 19.5 ± 5.6 microM (Evans 2000) (A/f=.77)

(Normal Control Value 40 → 50 microM) (A/f<.4)
## ABNORMAL BLOOD CARNITINE LEVELS (microM) IN CAPD PATIENTS

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

\(^a\) Males: 35 ± 9; females: 26 ± 10

\(^b\) For more than 5 years on CAPD, the FC level was 27
HEALTHY SUBJECTS

PLASMA CONCENTRATIONS (mg/L)

HEMODIALYZED PATIENTS

PLASMA CONCENTRATIONS (mg/L)

HEALTHY SUBJECTS

URINE CONCENTRATIONS (mg/week)

HEMODIALYZED PATIENTS

DIALYSATE CONCENTRATIONS (mg/week)
L-CARNITINE IN HEMODIALYSED PATIENTS
CORRELATION BETWEEN DIALYTIC AGE AND PLASMA CARNITINE LEVELS

Sakurauchi W et al., 1998
<table>
<thead>
<tr>
<th>HEMODIALYSIS PATIENTS</th>
<th>HEALTHY CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.88 (SAVICA 1983)</td>
<td>19.34–27.7</td>
</tr>
<tr>
<td>10.3 (BELLINGHIERI 1983)</td>
<td></td>
</tr>
<tr>
<td>12.9 (FAGHER 1985)</td>
<td></td>
</tr>
</tbody>
</table>
L-CARNITINE IN HEMODIALYSED PATIENTS
CORRELATION BETWEEN DIALYTIC AND MUSCLE CARNITINE LEVELS

Hiatt WR et al., 1992
PLASMA CONCENTRATIONS OF L-CARNITINE DURING INTERDIALYTIC SESSIONS

## L-Carnitine Administration in Hemodialysis Patients

<table>
<thead>
<tr>
<th>Increase of body content</th>
<th>% Dose reaching tissue compartment</th>
<th>Dose administered</th>
<th>Time to double carnitine pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 20g</td>
<td>50</td>
<td>2 mg/kg i.v after each dialysis session</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 months</td>
</tr>
<tr>
<td>10 to 20g</td>
<td>50</td>
<td>20 mg/kg i.v. after each dialysis session</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2 months</td>
</tr>
<tr>
<td>10 to 20g</td>
<td>7.5</td>
<td>2 g os/die</td>
<td>?</td>
</tr>
</tbody>
</table>

Adapted from Evans & Fornasini *Clin Pharmacokin* 2003; 42: 941-967
Disposition of L-carnitine in the body following oral administration of Levocarnitine

Oral Administration → Gastrointestinal Tract → LC → Saturable absorption → Central Compartment

Central Compartment → Tissue uptake → TMA → Tissue efflux → Peripheral Compartments

Hemodialysis → Faecal Excretion

Disulfiram, FMO3, GBB, TMNO

CARNITINE LEVELS IN HEMODIALYSED PATIENTS

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

AC/FC = 0.21
AC/FC = 1.75
AC/FC = 1.78

Plasma Carnitine (microM)

33.7 20 10
7.1

AC/FC = 0.57

AFTER L-CARNITINE THERAPY
(20 mg/Kg i.v., for 9 weeks)

191 110
42 20

Plasma Carnitine (microM)

Adapted from Evans AM et al., 2000
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 X 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

Romagnoli GF., 2002
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

Bazemore J, NKF Clinical Nephrology Meetings, 2003: A3
GROUP MEAN NUMBER OF HYPOTENSIVE EPISODES (MONTHLY VALUES)

Baseline: 12.2
After 6 mon LC: 4.5
After 6 mon washout: 14

IV L-carnitine

Bazemore J, NKF Clinical Nephrology Meetings, 2002: A3
### Decrease in Hospitalization with Levocarnitine Therapy in 1,038 Patients With History of Cardiac Disease

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

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

(micromoles/g of NCP)

1st biopsy (12-month i.v. LC)
2nd biopsy (4-month wash out)
3rd biopsy (4-month dialytic fluid LC)
L-CARNITINE (LC) EFFECTS ON SERUM CARNITINE LEVELS IN HEMODIALYZED PATIENTS

(micromoles/liter)

1st biopsy (12-month i.v. LC)
2nd biopsy (4-month wash out)
3rd biopsy (4-month dialytic fluid LC)
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

Spagnoli LG et al., Nephron 55:16-23, 1990
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)

<table>
<thead>
<tr>
<th></th>
<th>HUROT et al. (1998)</th>
<th>AMATO et al. (Unpublished)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Studies</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>No of Patients</td>
<td>121/118</td>
<td>61/60</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Epo Requirement</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Pre-HD</th>
<th>Post-HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without L-C</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>With L-C</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Controls</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Without L-C</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>With L-C</td>
<td>2.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

p<0.001

Agryannis B et al, Dialysis & Transplantation, 2002; 31: 106
EFFECT OF L-CARNITINE ON RED BLOOD CELL SURVIVAL

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

RBC Survival: $^{51}$Cr $T_{1/2}$

(Clutterbuck EJ, submitted)
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)

AMATO A, Unpublished