L-Carnitine and Endothelial Function

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Introduction

Endothelium participates in the regulation of vascular tone, thrombosis, and VSMC proliferation and migration.

Increased rates of cardiovascular mortality and morbidity in obesity and type 2 DM.

Endothelial function is impaired in obesity and type 2 diabetes.

Impaired endothelial function is a predictor of CVD.
Acetylcholine-Induced Vasoreactivity as a Predictor of Cardiovascular Events

Proportion without cardiovascular event (%) vs. Months exposed to risk:

Vasodilation: 50 39 37 36 24 17 7
Vasoconstriction: 95 83 70 64 50 35 12

p = 0.022 (log rank)

Introduction cont.

FFA levels are elevated in obesity and DM
Carnitine levels have been reported to be decreased in DM
Carnitine supplementation has been reported to improve vascular function
Endothelial nitric oxide system

Acetylcholine
Methacholine

Insulin
Shear stress
Bradykinin
Thrombin

Nitroprusside
Nitroglycerin

L-arginine
L-NMMA
ADMA

Endothelial cell

Endothelin ?

Vascular smooth muscle

↑cGMP → VASODILATION

Adapted from Baron, AJC 1999
Protocol 1
Effect of L-Carnitine on FFA induced endothelial dysfunction

L-CARNITINE
INTRALIPIDS + HEPARIN

<table>
<thead>
<tr>
<th></th>
<th>-30</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>320</th>
<th>min</th>
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<tbody>
<tr>
<td>LBF</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mch</td>
<td>X</td>
<td>X</td>
<td>X</td>
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### Demographic, Metabolic, and Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>32±5</td>
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<tr>
<td>Body Mass Index</td>
<td>22±2</td>
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<tr>
<td>% body fat</td>
<td>17±3</td>
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<tr>
<td>Glucose (mg/dl)</td>
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<tr>
<td>Total Cholesterol (mg/dl)</td>
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<td>Triglycerides (mg/dl)</td>
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<td>HDL-Cholesterol (mg/dl)</td>
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<td>LDL-Cholesterol (mg/dl)</td>
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<tr>
<td>MAP (mmHg)</td>
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<tr>
<td>Heart Rate (bpm)</td>
<td>62±3</td>
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Carnitine Levels

![Bar chart showing carnitine levels with different categories: Total Carnitine, Free Carnitine, and Acyl Carnitine. The chart compares basal, FFA, and L-Carnitine + FFA conditions.](image)
LBF in response to Methacholine

**Graph:**
- **Y-axis:** L/min
- **X-axis:** Basal, 5 µg/min, 10 µg/min, 15 µg/min
- Three lines:
  - **Blue dot line:** basal
  - **Red triangle line:** FFA
  - **Green square line:** L-carnitine + FFA

**Legend:**
- basal
- FFA
- L-carnitine + FFA
Maximal change in LBF in response to Methacholine
Effect of Body Fat and Type 2 Diabetes on Endothelial Dependent Vasodilation (Endothelial Function)

![Graph showing the effect of body fat and Type 2 Diabetes on endothelial dependent vasodilation. The graph compares the responses of females with obesity, lean, and Type 2 Diabetes under varying Methacholine Infusion Rate (µg/min). The y-axis represents 2% Leg Blood Flow, while the x-axis represents the Methacholine Infusion Rate (µg/min). The graph shows a trend where the blood flow increases with higher Methacholine Infusion Rate, with differences observed between the groups.](image-url)
Protocol 2
Effect of L-Carnitine on endothelial function in obese subjects

L-CARNITINE

<table>
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<tr>
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<th>-30</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Mch</td>
<td>X</td>
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<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Body Mass Index</td>
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<tr>
<td>% body fat</td>
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<tr>
<td>Glucose (mg/dl)</td>
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<td>Total Cholesterol (mg/dl)</td>
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<td>Triglycerides (mg/dl)</td>
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<tr>
<td>MAP (mmHg)</td>
<td>100±5</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>65±4</td>
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</table>
Carnitine Levels

![Bar chart showing carnitine levels: Total Carnitine, Free Carnitine, and Acyl Carnitine. The chart compares basal and plus carnitine conditions.](image-url)
LBF in response to Methacholine

![Graph showing LBF in response to Methacholine with basal and plus carnitine lines.](image-url)
Maximal change in LBF in response to Methacholine
Summary and Conclusion

In the lean group FFA elevation caused a fall in Acyl-carnitine levels and blunting of LBF responses to Mch. Administration of L-carnitine restored both, acyl-carnitine levels and the normal LBF response to Mch.

In the obese group, LBF responses to Mch were blunted under basal conditions. 4 hour infusion of L-carnitine increased acyl-L-carnitine levels and improved the LBF response to Mch.

Our data suggest that short term elevation of FFA depletes the systemic acyl-carnitine pool. This could be due to a direct effect of FFA, a decreased production, or a shift of acyl-carnitine into cells.

The results of our studies indicate that administration of L-carnitine may exert protective effects on the vasculature. This effect appears to be mediated at least in part via the improved release or action of nitric oxide. Further work is necessary to characterize the mechanism(s) by which L-carnitine improves vascular function.
Further Research

• Define cellular mechanism of L-carnitine action on endothelial function.

• Assess effect of oral L-carnitine supplements on vascular function in type 2 DM and obesity.
These Studies would not be possible without

• Collaborators:
  Sudha S. Shankar, M.D.
  Bahram Mirzamohammadi, M.D.
  James P. Walsh, M.D.

• Research volunteers

• GCRC support