Blood carnitine status after orthotopic liver transplantation in patients with end-stage liver disease 1-3

John D Palombo, Peggy R Borum, Roger L Jenkins, Charles Trey, and Bruce R Bistrian

ABSTRACT We determined the effects of orthotopic liver transplantation on plasma and red cell carnitine concentrations in patients with end-stage liver disease. Before transplantation, plasma and red cell carnitine were significantly elevated above normal. The partitioning factor (ratio of red cell carnitine to plasma carnitine) was four times greater than that observed in our reference population. After hepatic replacement, plasma and red cell carnitine approached normal levels within 6 mo. The partitioning factor, however, remained elevated at that time. These results indicate that 1) there is no evidence for carnitine deficiency in severe liver disease on the basis of carnitine concentrations in the plasma and red cell compartments and 2) altered partitioning of carnitine between plasma and red cells persists for >6 mo after hepatic replacement. Am J Clin Nutr 1989;50:504–7.

KEY WORDS Plasma carnitine, red cell carnitine, liver disease, liver transplantation

Introduction

Carnitine is required by most mammalian cells for the transport of long-chain fatty acids into mitochondria for subsequent oxidation and energy production. Because carnitine is synthesized by the liver, severe liver disease produces profound disturbances in whole-body carnitine metabolism. However, studies conducted to determine the plasma carnitine status of liver-disease patients yielded conflicting results (1–3). This in part may be due to the varying severity and etiology of liver disease in the patients studied.

Recent studies (4–6) revealed that red blood cells contain a carnitine pool that is metabolically distinct from that found in plasma. Our objective was to better characterize the carnitine status of patients with severe liver disease before and after transplantation.

Subjects and methods

Twenty-eight patients with end-stage liver disease were included in this study. Verbal consent was obtained from each patient and a protocol was approved by the New England Deaconess Hospital's Human Use Committee. The clinical status and selection criteria for these patients were delineated in an earlier report (7). Because the bulk of carnitine excretion occurs by kidney filtration, patients exhibiting severe renal dysfunction (serum BUN >36 mmol/L or creatinine >310 μmol/L) were excluded. Only those patients who had good posttransplant outcome, ie, those exhibiting satisfactory liver function without severe rejection, were used in this study. For purposes of comparison, the plasma and red cell carnitine concentrations of one to two age- and sex-matched control subjects were obtained for each transplant patient from a reference population. This reference population was described previously (4), and selection of the subset of control subjects for this study was done randomly.

Venous blood specimens were collected in evacuated tubes containing EDTA at the time of evaluation for hepatic replacement and at 3 and 6 mo after orthotopic liver transplantation. Each blood specimen was kept on ice and processed within 2 h of being drawn. Aliquots for hemoglobin and hematocrit were obtained before centrifugation. The blood was separated into plasma and red cell fractions in a refrigerated centrifuge (IEC Centra 7R, Needham Heights, MA) at 2000 × g for 10 min. The plasma was removed and stored at −20 °C until analysis. The buffy coat was removed from the red cells, which were then washed twice with saline and frozen until analysis.

Total carnitine was determined for all specimens as described previously (5). Hemoglobin was determined by a Coulter counter (S+6, Coulter Electronics, Inc, Hialeah, FL) and hematocrits were measured with a microcapillary centrifuge and reader (IEC). Indices used to describe the plasma and red cell carnitine compartments were defined in an earlier report (4).

Food-intake records were kept on a subset of patients for a 3-d period before transplantation and between 3 and 6 mo after
transplantation. The intake data were normalized per 1000 kcal.

Data were analyzed using the RS/1 Integrated Data Analysis System for the Digital Professional 350 Computer (Digital Equipment Corp, Maynard, MA). Data from populations were subjected to the Wilk-Shapiro test of normality. Normal populations were tested for equal or unequal variances with an F test for variance ratio. A t test for either equal or unequal variances was then performed. For nonnormal populations the Ansari-Bradley test for equal dispersions was used and then the Mann-Whitney test for unpaired samples with equal dispersions was applied.

Results

Of the 28 patients with end-stage liver disease selected for inclusion in this study, 16 were female. The age of the study population was 48 ± 11 (x ± SD). Approximately 50% of the patients were diagnosed as having chronic or acute hepatitis and another 25% had primary biliary cirrhosis (7).

Table 1 contains the dietary intake of carnitine and its metabolic precursors, lysine and methionine, for a subset (n = 7) of these patients. There were no significant differences between intakes before and after liver transplantation.

The plasma carnitine concentration of the patients before transplantation, these levels remained significantly above that of the reference population. Although they decreased after transplantation, these levels remained significantly higher than the reference levels through the sixth postoperative month. There were no significant differences observed in mean corpuscular hemoglobin concentrations between the patients and the reference population.

Figure 3 depicts the changes in the calculated whole-blood carnitine expressed as nmol/mL for the patients and the reference population. The mean pretransplant concentration was more than double the corresponding reference population level. By the third month after transplantation, whole-blood carnitine was normalized in these patients relative to reference levels. This normalization reflected a combination of the depressed plasma level (Fig 1) with the concomitantly elevated red cell level (Table 2).

Despite the previous observation the actual partitioning of carnitine between plasma and red cell compartments remained abnormal during the posttransplant pe-
period. The percentage of whole-blood carnitine in red cells and the partitioning factor (red cell carnitine [µmol/L] divided by plasma carnitine [µmol/L]) are listed in Table 2. The patients' values for these two indices were significantly elevated both before and after transplantation in comparison with the reference population and decreased between the third and sixth postoperative months.

### Discussion

Our findings demonstrate that patients with end-stage liver disease have elevated plasma and red cell carnitine levels relative to an age- and sex-matched reference population. Elevated plasma carnitine concentrations were reported in cirrhotic patients (1). By the third month after hepatic replacement, the plasma carnitine concentration was significantly lower than that of the reference population. We also observed that after transplantation normalization of carnitine within the red cell compartment was slower to respond than that in the plasma compartment. After 6 postoperative months the partitioning of carnitine favored red cells 2.3 times over plasma (Table 2). In comparison, the partitioning factor for the reference population was 1.2. This slower equilibration suggests that the red cell may serve as a temporary sink for excess carnitine appearing in the plasma compartment. The data also suggest that carnitine transport and metabolism in red cells is subject to different regulatory processes than those governing carnitine flux in the plasma pool. This effect is not limited to disease states but also appears to occur in healthy adults (4), albeit to a lesser degree.

Although this study elucidated the changes in whole-blood compartmentalization of carnitine before and after liver transplantation, we did not examine any possible mechanisms causing the apparent shift in carnitine concentration toward the red cell pool. Possible causes of elevated carnitine concentrations in blood from patients with severe liver disease include 1) increased biosynthesis, 2) decreased hepatic clearance, 3) decreased urinary excretion, and 4) increased release from tissues. Given the effects of severe liver disease on synthetic function (7), it is unlikely that excess quantities of carnitine would have been synthesized. Additionally, because we excluded patients with moderate or severe renal impairment, we discount any effect from impaired renal clearance. Thus, elevated blood levels of carnitine probably arose from either impaired hepatic uptake and/or excessive release from peripheral and hepatic tissues. Muscle contains a significant quantity of carnitine for fatty acid transport (8). Given the attending protein malnutrition commonly observed in these patients (3, 7), loss of muscle mass may promote carnitine release into the blood compartment with further partitioning into the red cell and plasma pools. Despite this potential source and the increased influx into the blood compartment, increased renal clearance of carnitine usually occurs when plasma carnitine levels increase (1, 9). For reasons explained below, compartmentalization of carnitine into red cells may serve as a protective mechanism to reduce carnitine losses by renal filtration in patients with severe liver disease.

![](https://example.com/carnitine.png)

**FIG 3.** Whole-blood carnitine concentrations ($\bar{x} \pm SD$) before and after liver transplantation. *t* test comparisons vs reference population: **$p < 0.001$.**

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Before transplant</th>
<th>3 mo</th>
<th>6 mo</th>
<th>Reference population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 11)</td>
<td>(n = 12)</td>
<td>(n = 13)</td>
<td>(n = 55)</td>
</tr>
<tr>
<td>Red cell carnitine (µmol/L)</td>
<td>305 ± 237†</td>
<td>131 ± 58†</td>
<td>89 ± 38‡</td>
<td>60 ± 23</td>
</tr>
<tr>
<td>MCHC (%)‡</td>
<td>35 ± 4</td>
<td>36 ± 2</td>
<td>35 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>RC/wbC (%)</td>
<td>55 ± 9†</td>
<td>58 ± 10†</td>
<td>49 ± 10†</td>
<td>36 ± 9</td>
</tr>
<tr>
<td>PF†</td>
<td>3.7 ± 1.6†</td>
<td>3.8 ± 1.6†</td>
<td>2.3 ± 1.3**</td>
<td>1.2 ± 0.5</td>
</tr>
</tbody>
</table>

* $\bar{x} \pm SD$.
† Significantly different from reference population, $p < 0.001$ (*t* test).
‡ Significantly different from reference population, $p < 0.05$ (*t* test).
§ Mean corpuscular hemoglobin concentration.
|| Percentage of whole blood carnitine in red blood cells.
† Partitioning factor, red cell carnitine (µmol/L) divided by plasma carnitine (µmol/L).
** Significantly different from reference population, $p < 0.01$ (*t* test).
Carnitine may also have an important role as a buffering agent by trapping toxic acyl CoA compounds and organic acids that are generated during catabolic stress (10). We (7) already showed that these patients with end-stage liver disease have significantly elevated serum levels of bile acids, which contribute to the plasma pool of organic acids. The formation of acylcarnitine provides a mechanism for the body to rid itself of these toxic compounds through renal clearance. Thus, the elevated plasma concentrations of carnitine in these patients may reflect the increased need to detoxify and excrete these metabolites present in higher-than-normal concentrations. After transplantation the rapid decrease in plasma carnitine may reflect this reduced requirement for detoxification as well as an increased hepatic uptake and/or reduced tissue loss during this anabolic phase.

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References