

Changing perspective of carnitine function and the need for exogenous carnitine of patients treated with hemodialysis^{1,2}


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Carnitine was discovered in the first decade of this century, its role in transporting long-chain fatty acids across the mitochondrial membrane to facilitate β -oxidation was identified in the seventh decade, and the spectrum of metabolic functions of carnitine is beginning to be understood as this century comes to a close (1). Our changing perspective of the role of carnitine in metabolism naturally alters the questions addressed concerning the potential need of patients for carnitine.

Soon after the role of carnitine in facilitating β -oxidation of long-chain fatty acids was identified, altered carnitine status of patients treated with hemodialysis compared with that of healthy individuals was interpreted by several investigators as a state of carnitine deficiency (2). Coupled with the large body of data showing hypertriglyceridemia in many patients treated with hemodialysis, these data suggested the working hypothesis that patients treated with hemodialysis are at risk for carnitine deficiency, which leads to elevated triacylglycerol concentrations in their plasma. The hypothesis seems plausible if the major function of carnitine is to facilitate β -oxidation of long-chain fatty acids.

A logical extension of this hypothesis is the administration of carnitine to hemodialysis patients with the expectation that their lipid disease will improve. Numerous and often problematic clinical studies of various experimental designs were based on this hypothesis and showed that the role of carnitine in the metabolism of patients treated with hemodialysis is not as simple as was assumed by the working hypothesis being tested. Carnitine administration to hemodialysis patients with hypertriglyceridemia was reported to decrease, have no effect, or increase plasma triacylglycerol (3). Many health care professionals concluded from the disappointing results of many of the clinical trials that carnitine administration does not benefit patients treated with hemodialysis. Fortunately, many investigators chose to pursue several unexpected positive results, such as an improvement in hematocrit after carnitine treatment (4). One multicenter, randomized, placebo-controlled clinical trial showed overall clinical improvement in the carnitine-treated patients compared with the placebo-treated patients (5). Carnitine appeared to have effects that were not directly related to fatty acid oxidation. The report by Jackson and Lee (6) in this issue is an example of recent studies that address questions based on functions of carnitine other than facilitation of β -oxidation of long-chain fatty acids.

Data from many basic science and clinical investigations during the past decade have shown that facilitating β -oxidation of long-chain fatty acids is only one of the functions of carnitine. We now know that carnitine has many functions that position it to influence more areas of metabolism than previously predicted. For example, carnitine has a role in the metabolism of fuel substrates, including but not limited to long-chain fatty acids, by transporting the acyl portion of acylcoenzyme A esters (along with their high metabolic energy) across membranes (1). Carnitine modulates the availability of free coenzyme A concentrations (7). Carnitine removes from the cell acyl compounds that accumulate to toxic concentrations (8). Carnitine stores activated acyl compounds (at an energy level similar to ATP) for later use in a wide variety of metabolic pathways (1, 9). A current working hypothesis suggests that this last listed function explains how carnitine treatment of hemodialysis patients increases the hematocrit (10).

More metabolic functions of carnitine may yet be found. Analytical techniques permitting the identification and quantification of individual acylcarnitines may become a routine part of assessing carnitine status, thereby improving both the specificity and sensitivity of procedures used to identify patients who may benefit from carnitine supplementation. A better understanding of how the above listed functions affect metabolism in healthy individuals and in patients with different diseases should lead to improved carnitine treatment modalities. Assessment of carnitine status, indexes monitored to detect possible beneficial effects of carnitine treatment, inclusion and exclusion criteria to select the patient population that may benefit from carnitine treatment, as well as dose and route of administration of carnitine are now approached from a very different perspective than when many of the clinical studies now in the literature were designed. 

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