® Postepy Hig Med Dosw (online), 2013; 67: 548-552
e-ISSN 1732-2693

www.phmd.pl
Original Article

**Received:** 2012.10.09
**Accepted:** 2013.03.04
**Published:** 2013.05.31

# Plasma carnitine concentrations after chronic alcohol intoxication*

## Stężenie karnityny w osoczu po przewlekłym zatruciu alkoholem

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## Summary

**Background:** Carnitine transports fatty acids from the cytoplasm to the mitochondrial matrix, where the fatty acids are oxidized. Chronic alcohol consumption reduces the concentration of carnitine and interferes with oxidative processes occurring in the cell.

**Aim:** The assessment of carnitine concentrations in plasma of chronically intoxicated alcohol dependent persons in a 49-day abstinence period.

**Material/Methods:** The study included 31 patients (5 women and 27 men) aged from 26 to 60 years (44.6± 8.9) and 32 healthy subjects (15 women and 17 men) aged 22-60 years (39.8± 9.4). The patients' alcohol dependence ranged from 2 to 30 years (13.6± 7.5). Examined subjects consumed 75-700 g of ethanol/day (226.9± 151.5). Plasma concentrations of free and total carnitine were measured three times: at the first (T0), 30th (T30) and 49th (T49) day of hospital detoxification. Free (FC) and total (TC) carnitine were determined by the spectrophotometric method. Plasma acylcarnitine (AC) concentration was calculated from the difference between TC and FC; then the AC/FC ratio was calculated. To determine statistically significant differences for related variables, Student's t-test was used.

**Results:** At T0, alcoholics had significantly lower concentration of FC and TC ($p < 0.05$) in plasma, as compared to the control group. In comparison to controls, at T30, plasma TC and FC ($p < 0.01$) as well as AC ($p < 0.001$) were reduced. The lowest concentration of TC, FC and AC ($p < 0.001$) was found at T49. The ratio of AC/FC at T0 had a tendency to be higher in alcoholics than in the control group ($p = 0.05$), whereas at T49 it was significantly lower in alcoholics as compared to the control subjects ($p < 0.05$).

**Conclusions:** Chronic alcohol intoxication causes a plasma deficiency of carnitine. Forty-nine days of abstinence showed a significant decrease in the concentration of TC, FC and AC. Further research is

*The study was performed as part of project no. POIG.02.01.00-14-059/09-00 co-financed by the European Union under the European Regional Development Fund.

necessary to clarify whether a low level of plasma carnitine after chronic alcohol intoxication is caused by the uptake of blood carnitine by tissues such as liver or muscles. In alcoholics the supplementation of carnitine is recommended in the case of a low level of plasma carnitine.

**Keywords:** carnitine • plasma • alcohol

**Full-text PDF:** http://www.phmd.pl/fulltxt.php?ICID=1051649

**Word count:** 2195
**Tables:** –
**Figures:** 2
**References:** 38

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## Introduction

Carnitine (3-hydroxy-4-N-trimethylammoniobutyrate) is a transporter of fatty acids from the cytoplasm to the mitochondrial matrix for their oxidation to $CO_2$ and $H_2O$ [21]. As acyl-CoA molecules with long chains of fatty acids do not pass easily through the inner mitochondrial membrane, they need a special transport mechanism in which carnitine plays a central role. This mechanism is called a carnitine "bridge" or "shuttle". Carnitine is also involved in the transfer of β-oxidation products from the peroxisomes to the mitochondria, where shortened fatty acids are then oxidized. Acylcarnitine affects stability of the cell membranes, mainly of erythrocytes, by increasing activity of glutathione reductase and arginase, which minimizes depletion of reduced glutathione (cells that contain an insufficient amount of reduced glutathione are readily hemolyzed) [10]. Carnitine is also necessary for proper function of the central nervous system as acetylcarnitine is a donor of acetyl groups in the biosynthesis of the neurotransmitter acetylcholine. It appears that fatty acid ethyl esters (FAEEs) play a key role in the organ damage induced by ethanol [34,37,38]. Even short-term administration of ethanol causes a significant increase in FAEE concentrations, particularly in the brain and heart, but also in the kidneys and liver. Administration of acetyl-L-carnitine significantly reduces levels of FAEEs and prevents metabolic problems in the cell, induced by alcohol [9].

In humans, carnitine is synthesized from lysine and methionine with the participation of ascorbic acid, niacin, pyridoxine and $Fe^{2+}$ [17]. Alcohol decreases synthesis of carnitine *de novo* in the liver, brain and kidneys, by inhibiting active transport of certain amino acids, e.g. methionine [18]. Humans synthesize daily 100-200 μmoles of carnitine (25% of demand) and provide with the diet 300-400 μmol of carnitine (75% of demand) [22]. In a vegetarian diet there is a low level of carnitine, as compared to a meat diet [7]. Whole-body carnitine turnover time is 39-119 h (300-500 micromol/day) [23,29], In the bloodstream, there is about 75% of free carnitine, 15% of acetylcarnitine (principal acylcarnitine ester) and the remaining 10% is found in other carnitine derivatives [4]. Carnitine, taken with the food, passes through the membrane of enterocytes by active (sodium-dependent) and passive transport. Under the influence of alcohol, there is an imbalance in the carnitine profile, which results from the metabolism of alcohol. Chronic alcohol abuse impairs digestion and absorption of nutrients by causing functional changes in the mucosa of the gastrointestinal tract such as gastritis, gastrointestinal bleeding, impaired digestion in the intestinal brush border, impaired gastrointestinal motility and absorption, increased intestinal permeability (called "leaky gut syndrome") [5] and impaired bacterial colonization. Alcohol often damages the pancreas (acutely and chronically), which leads to impaired secretion of pancreatic enzymes and thus to abnormal food digestion. In consequence the amount of carnitine supplied with food is insufficient. In addition, endogenous synthesis of carnitine in alcoholics is impaired due to the toxic effects of alcohol on liver cells (steatosis, inflammation, cirrhosis) and the endocrine system (impaired synthesis, release and transport of hormones). The probability of alcoholic hepatitis increases proportionally to the amount of ethanol consumed and duration of alcohol abuse. Another important factor in impairment of carnitine supply is the neuropathy caused by toxic effects of alcohol on the central, peripheral, and autonomic nervous system.

Ethanol is predominantly metabolized in the liver. The liver cell has three major metabolic pathways of ethanol oxidation: the cytosolic alcohol dehydrogenase pathway, the microsomal ethanol oxidizing system (MEOS) located in the endoplasmic reticulum, and peroxisomal catalase [19]. Chronic ethanol intoxication leads to changes in the mitochondrial ultrastructure and integrity of its membranes, as well as to the excessive production of ke-

tones [25,35]. Not only chronic alcohol abuse but also a single heavy drinking session leads to disturbance in β-oxidation of fatty acids in the mitochondria and inhibits the activity of the Krebs cycle, interfering with normal activity of various enzymes including β-hexosaminidase [20,32,35,36]. The effect of alcohol on carnitine homeostasis is a result of alcohol metabolism, which inhibits mitochondrial oxidation of fatty acids. It is known that the oxidation of ethanol to acetate uses $NAD^+$ and gives rise to an excess of NADH [33,36], which leads to the inhibition of $NAD^+$-dependent oxidations such as β-oxidation of fatty acids [35]. Products of alcohol metabolism inhibit the tricarboxylic acid cycle [1,12] which increases amounts of acetyl-CoA available for the biosynthesis of fatty acids. Increased biosynthesis and reduced β-oxidation of fatty acids lead to their accumulation and, consequently, to increased biosynthesis of triacylglycerols, lipids, cholesterol, and phospholipids, and their increased transport to the fatty liver [21,24]. It has been proven that increased levels of propionic and methylmalonic acids under the influence of alcohol are associated with reduced levels of carnitine in plasma and increased urinary excretion of acylcarnitine [7,8].

Secondary deficiency of carnitine in the body is associated with: a reduced amount of carnitine in the diet, impaired carnitine absorption and transport, increased carnitine excretion in urine, liver and kidney disease, increased carnitine demand during e.g. strenuous physical exercise and alcohol toxicity [15]. Generally, the longer is the exposure to alcohol, the lower the concentration of carnitine in plasma [25].

This study evaluates the plasma concentration of FC and TC, as well as AC and the AC/FC ratio, during 49 days after chronic alcohol intoxication.

## Material and methods

### Material

The concentrations of FC and TC in plasma were determined in:

a) 32 healthy social drinkers (15 women and 17 men) aged from 22 to 60 years (39± 9.4 years), staying on a general diet, not taking any drugs. Social drinkers did not consume alcohol one week prior to the blood sampling.

b) 31 patients (5 women and 27 men) hospitalized in the Detoxification Unit and the Therapeutic Unit of Alcohol Dependence in Choroszcz Psychiatric Hospital, Poland, aged from 26 to 60 years (44.6± 8.9 years). The alcohol dependence ranged from 2 to 30 years (mean 13 years). The amount of alcohol consumed by the individuals ranged from 75 to 700 g/day.

The concentration of FC and TC in plasma was determined at the point of admission to the hospital (T0), at the 30th day (T30), and at the 49th day (T49) of hospitalization.

## Methods

For obtaining ultrafiltrate, 500 µL of plasma was filtered through a Centricon YM-30 filter (Millipore, Bedford, MA, U.S.A.) by centrifugation at 2000g for 40 min (Eppendorf AG Centrifuge 5702R, Hamburg, Germany). FC was determined in the plasma ultrafiltrate, without hydrolysis. Plasma TC and FC were determined by the enzymatic method of Cederblad et al. [13]. The method of FC determination is based on the reaction of FC with acetyl-CoA, catalyzed by CAT (carnitine acetyltransferase). FC reacting with acetyl-CoA releases CoA-SH, determined by reaction with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB). Increase in absorbance at 412 nm was measured using a Hitachi UV/VIS spectrophotometer, Model U-2900 (Tokyo, Japan). For determination of the plasma TC, to 200 µL of the plasma ultrafiltrate was added 20 µL of 1 mol/L KOH solution, mixed and incubated at 56ºC for 1 h (for hydrolysis the carnitine esters) and finally neutralized to pH 6-7 with 4 µl of 5 mol/L HCl and checked with pH-indicator strips. Liberated FC was determined as described above. AC concentration was calculated by subtracting FC from the TC concentrations and the AC/FC ratio was calculated as TC minus FC/FC, according to the scheme proposed by Schmidt-Sommerfeld [26] and Seccombe [27].

## Statistical analysis

All data were expressed as mean ± SD and analyzed by a statistical analysis system (Statistica 7.0, StatSoft, Cracow, Poland) using Student's t-test for independent samples. The statistical significance of differences was regarded to be at $p < 0.05$.

## Results

In the control group (n = 32) the plasma concentration of FC was 40.5± 7.6 µmol/L, TC 54.0± 11.4 µmol/L and AC 13.5± 8.4 µmol/L, while the ratio of AC/FC was 0.34± 0.23. In the healthy subjects, plasma FC is approximately 75% of the TC pool [16]. In our control group plasma FC concentration was approximately 72% of TC. Plasma concentrations of FC and TC at T0 were significantly lower ($p < 0.05$) when compared to the controls. At T30, the concentrations of FC and TC in alcoholics' plasma were significantly lower as compared to the control group ($p < 0.01$ and $p < 0.001$, respectively) (Figure 1). At T0, there was a tendency of AC/FC ratio to be higher in the alcohol dependent group than in the control group ($p = 0.05$), while at T30 and T49 it was significantly lower in alcoholics as compared to the control group ($p < 0.001$) (Figure 2). At T49, we noted significant reduction in the AC/FC ratio in comparison to the control subject ($p < 0.05$) (Figure 2).

## Discussion

Our alcohol dependent patients without evidence of liver cirrhosis, had at T0 a tendency to reduction of FC and significant reduction in plasma AC and TC concentrations ($p < 0.05$) as compared to the healthy controls (Figure 1). Af-

ter a 30-day period of abstinence, we found a significantly decreased level of plasma FC and TC ($p < 0.01$) as well as AC ($p < 0.001$), compared to the control group (Figure 1). At T49 our patients had the lowest concentration of FC, TC and AC ($p < 0.001$) in the study, when compared to the control group (Figure 1). Decrease in the plasma FC and AC concentrations in our study during abstinence may be due to increased tissue availability of FC for transport of fatty acids to mitochondrial matrix and subsequent normalization of energy imbalance in the cells (Figure 1).

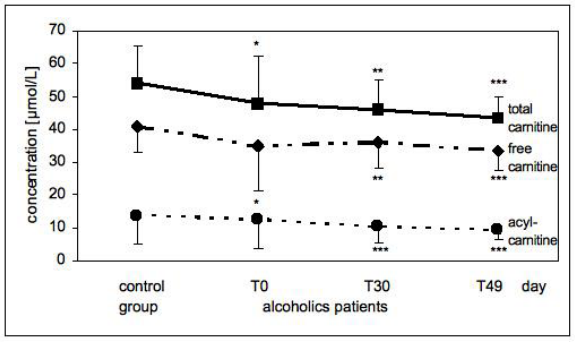


**Fig. 1. Plasma concentration of free(FC) and total(TC), as well as acylcarnitine(AC) after chronic alcohol intoxication at the first (T0), 30th (T30) and 49th (T49) day of abstinence; *p < 0.05; **p < 0.01; ***p < 0.001**

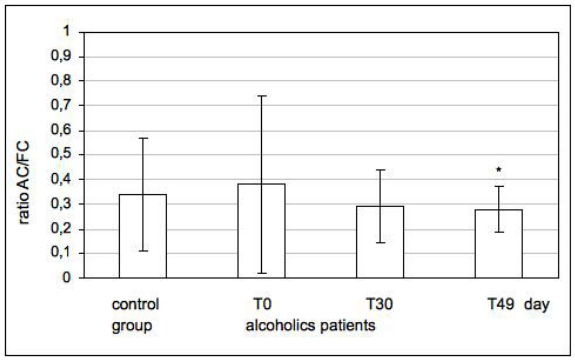


**Fig. 2. Acylcarnitine/free carnitine ratio (AC/FC) at the first (T0), 30th (T30) and 49th (T49) day of abstinence; *p < 0.05**

Carnitine imbalance can be detected by analyzing the relative levels of fatty acid carnitine esters (AC) to FC concentrations (the AC/FC ratio). Hypercatabolism of carnitine, carnitine deficit, and prolonged fasting are the cause of systemic ketoacidosis, which can lead to an abnormally high AC/FC ratio. Higher ratio of plasma AC/FC than 0.4 [11,30,31] or 0.6 [2] blocks key enzymes involved in energy production in the cell. In our alcohol dependent group at T0, there was a tendency of plasma AC/FC ratio to be higher than in the control group ($p = 0.05$). At T49 there was a significant reduction of the plasma AC/FC ratio relative to the control group ($p < 0.05$) (Figure 1b). A lower value of AC/FC ratio ($p < 0.05$) (Figure 1b) during abstinence indicates recovery to normal metabolic function of the cells and unlocking of key activity of the enzymes involved in energy production of the cell.

Our results are in agreement with animal experiments which proved alcohol's impairment of distribution and metabolism of carnitine. Sachan et al. [24] observed a decrease in the plasma total and unesterified (free) carnitine concentrations in rats on an ethanol diet. Supplementation with carnitine reduced fatty liver and inflammatory processes, inhibiting production of tumor necrosis factor (TNF-α) by Kupffer cells [6]. Sakvarelidze [25] observed a decrease in the plasma concentrations of carnitine in rats fed with 15% alcohol for about 3 weeks. It is difficult to compare our data to the equivocal results of human studies on free and acyl carnitine content in body fluids and tissues after alcohol intoxication. Ambiguities of human carnitine studies in alcoholics are probably due to ambiguous carnitine supply in the diet and carnitine metabolism disturbed by alcohol. In alcoholic hepatic steatosis De Sousa et al. [14] observed no change in the concentration of free, total and acylcarnitine in serum, urine and liver tissue, and increased levels of free and total carnitine in the muscles. Increased levels of acylcarnitine in serum were reported by Alonso de la Peña et al. [3] in patients with hepatic steatosis and Fuller and Hoppel [15] in patients addicted to alcohol but without evidence of cirrhosis. Discrepancies in carnitine concentration in alcoholics' plasma may also depend on time elapsed from the last alcohol consumption to blood collection. In our patients, alcohol abstinence before blood sampling for laboratory tests (T0) was very short (1.25± 0.8 days) as compared to Alonso de la Peña et al. (10-15 days) [3] and Fuller et al. (30 days) [15]. Time of biochemical parameters normalization in the abstinence period is different and depends on many factors, including time of exposure (intermittent, chronic), sex, and genetics. Traditional bioindicators of alcohol abuse have different normalization time. Sillanaukee et al. [28] found that the activity of aspartate aminotransferase (AST) returned to normal within 1 week and alanine aminotransferase (ALT) within 2-5 weeks, gamma-glutamyl transferase (GGT) within 2-6 weeks and carbohydrate-deficient transferrin (CDT) within 2-4 weeks. Kärkkäinen et al. [20] found that the activity of β-hexosaminidase normalized within 7-10 days of abstinence. The decrease in transaminases and other biomarkers indicates disappearance of bad effects of intoxication. Regarding carnitine, no literature data have been published concerning normalization of carnitine in people suffering from alcohol dependence.

In summary, our results suggest that chronic alcohol abuse leads to carnitine deficiency. During abstinence, the concentration of FC and TC in plasma is significantly reduced, and a 49-day period is insufficient to achieve the correct carnitine homeostasis in alcohol dependent patients. The low value of AC/FC during abstinence provides a return of normal metabolic function of the cells, and thus recovery of enzymes involved in energy production in the cell. In alcoholics, levels of plasma FC and AC should be checked and, in the case of low levels, carnitine supplementation should be prescribed.

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The authors have no potential conflicts of interest to declare.