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Serum Carnitine Levels in Patients with Coronary Artery Disease

Abstract: Carnitine is an essential molecule for the transfer of long chain fatty acids through the inner mitochondrial membrane, for beta-oxidation (1). The long chain fatty acids provide a large proportion of the energy requirement of the myocardium. Thus, adequate amounts of tissue carnitine are required to maintain the normal function of the myocardium (2). Experimental studies on acute myocardial ischemia and clinical investigations of patients with congestive cardiac failure have indicated that the myocardial carnitine content was significantly lowered in both conditions, in contrast to raised or normal blood carnitine (3-5).

In the present study, alterations in serum carnitine levels were assessed in patients with atherosclerotic coronary artery disease (CAD) who did not exhibit any signs of cardiac failure. The possibility of a correlation between serum carnitine levels and the severity of the disease was also investigated in these patients. The subjects were assessed angiographically, and grouped according to the severity of the coronary artery disease (CAD) as control (n=15) and patients having mild (n=15), moderate (n=15), and severe (n=20) CAD. Serum free L-carnitine levels were measured in all of these groups by an enzymatic spectrophotometric method. There were no significant differences between the serum carnitine levels of the controls and mild and moderate CAD patients. On the other hand, a marked difference was observed between controls and the severe CAD patients (P< 0.01).These results imply that serum carnitine measurements cannot be used to define the presence of CAD, but they can be markers of advanced atherosclerotic lesions.

Key Words: Carnitine, Coronary artery Disease (CAD).

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Introduction

Prior to β-oxidation, long chain fatty acids form CoA esters in the outer mitochondrial membrane. However, the mitochondrial membrane is not permeable to these esters or free CoA. These substances are transported to the matrix, following their binding to carnitine (6, 7). Carnitine is widely distributed in mammalian tissues, principally in the cardiac and skeletal muscle (1). Since the muscle tissue comprises a large proportion of the body mass, it is a major site of fatty acid oxidation. This process is extremely important in the cardiac tissue, which supplies approximately 60% of its energy requirement from the oxidation of fatty acids (2).

Experimental studies revealed that one third of the myocardial carnitine content was lost within the first 10 minutes of acute myocardial ischemia, and half the amount in 30 minutes. An elevation in the levels of acetyl and long chain acylcarnitine esters was also detected during this period (3). In addition, postmortem examination of tissues with myocardial infarction disclosed a depression in the myocardial carnitine content (8). In a study in which carnitine levels in serum and endomyocardial biopsy tissues in patients with congestive cardiac failure due to various causes were measured, Regitz et al. noticed decreased tissue carnitine and increased serum carnitine (4). Another study, conducted by Pierpont et al. on patients with congestive cardiac failure, revealed diverse results in myocardial tissue carnitine levels, and a significant rise in plasma carnitine concentrations (5). Matsui et al. showed that acylcarnitine release was high in patients with more severe cardiac failure and concluded that there was a possible carnitine deficiency in these patients (9).

Carnitine loss from the myocardium as a result of any of the causal conditions, causes some metabolic alterations. In particular, the inhibition of adenine

nucleotide translocase in the mitochondrial membrane due to the accumulation of acyl-CoA in the sarcoplasma has a negative effect on the contraction of the myocardium (3, 8). To our knowledge, carnitine levels in coronary heart disease patients without cardiac failure had not been assessed previously. Hence, demonstration of changes in serum carnitine concentrations and investigation of the existence of a correlation between serum carnitine and the severity of coronary heart disease were the aims of the present study.

Materials and Methods

The study group comprised 65 subjects who attended and were diagnosed in the Department of Cardiology in Ege University, Faculty of Medicine. Serum samples were obtained from the patients before angiography. Following angiography, the subjects were grouped as control (n=15), and mild (n=15), moderate (n=15), and severe (n=20) CAD patients according to the severity of their disease. The control group consisted of fifteen patients (5 women, 10 men) who attended the Cardiology Outpatient Clinic of the same hospital due to various types of heart disease, and who had had an angiographic assessment. According to the angiographical examination results, the coronary arteries of all these patients were normal.

The Gensini scoring system was used to establish the grouping of the subjects (10). According to this system, the patient groups were determined to be mild CAD (n=15, 5 women, 10 men, Gensini score: 1-10),

moderate CAD (n=15, 4 women, 11 men, Gensini score: 10-50) and severe CAD (n=20, 6 women, 14 men, Gensini score: > 50) patients. Cardiac and renal failure has been reported to have effects on the serum carnitine levels in various studies. Thus, the patients in the present study were selected from subjects without cardiac and renal failure. Subjects with a serum urea of less than 8.33 mmol/L and serum creatinine less than 88.4 mmol/L were included in the study. To exclude cardiac failure, patients were selected with regard to the following parameters: ejection fraction >55%, right ventricular end-diastolic pressure (RVEDP) 3-7 mm Hg, left ventricular end-diastolic pressure (LVEDP) 7-12 mm Hg, right ventricular end-systolic pressure (RVESP) 15-30 mm Hg, left ventricular end-systolic pressure (LVESP) 100-140 mm Hg. Serum samples obtained from the patients were centrifuged at 3000g for 15 minutes, transferred to plastic basins and kept at -20°C until analysis. Samples were conserved for a maximum period of four months before analysis. Serum free L-carnitine levels were measured by an enzymatic UV kit (Boehringer Mannheim GMBH, Mannheim, Germany) in which the amount of L-carnitine was quantitated by the amount of NADH consumed. Results are expressed as mean ± SD and statistical analyses were performed by Student's t-test. A p value of < 0.05 was considered significant.

Results

Subject data and cardiac hemodynamic parameters are shown in Table 1. Serum urea, creatinine and free L-

Table 1.   Subject data and cardiac hemodynamic parameter values of controls and patients (mean ± SD).

Subject groups	Control	Mild CAD	Moderate CAD	Severe CAD	P
n	15	15	15	20	-
Sex : Male	10	10	11	14	-
Female	5	5	4	6	-
Age (years)	54.13±11.26	53.47±10.02	60.27±9.74	57.30±10.85	NS
EF (%)	64.67±6.11	66.33±6.93	65.00±7.32	63.25±5.68	NS
LVEDP (mm Hg)	10.14±1.35	9.53±1.68	8.2±1.97	9.7±1.56	NS
RVEDP (mm Hg)	5.53±1.12	5.33±1.23	5.33±1.17	5.15±1.18	NS
LVESP (mm Hg)	126.27±9.85	127.33±9.42	128.67±8.96	124.75±11.29	NS
RVESP (mm Hg)	23.73±4.78	22.33±4.57	24.00±5.07	23.25±4.67	NS

NS: not significant.

carnitine levels are presented in Table 2. Figure 1 represents the graphical evaluation of the free L-carnitine levels of the study groups. Serum free L-carnitine levels were found to be 40.32 ±8.9, 38.95 ± 10.6, 45.90 ± 9.4 and 63.15 ± 12.4 µmol/L in the control, mild, moderate, and severe CAD patient groups, respectively. No statistical significance could be detected between serum carnitine levels of the control group and the mild CAD patient group (p > 0.5). Similarly, although the serum carnitine concentrations were slightly higher in the moderate CAD patient group than in the control group, this difference was not statistically significant (p > 0.5). However, serum carnitine levels of the severe CAD patients were significantly higher than those of the control group (p < 0.01).

Discussion

In studies on carnitine levels in various pathologic conditions, severe cardiac and renal failure are considered among the major factors that contribute to the elevation of blood carnitine levels (11). Therefore, these pathologic conditions were excluded in the present study by evaluating the patients with regard to urea and creatinine concentrations and the hemodynamic criteria of cardiac failure. High concentrations of serum carnitine in severe coronary heart disease could be attributed to the loss of carnitine from the myocardial tissue. The reason for this loss may be the nonspecific injury of the membrane due to ischemia. Although carnitine principally functions in the mitochondria, a great proportion (90%) of this molecule is in the cytoplasm of the myocardium (4).

In addition to the direct loss of carnitine due to ischemic membrane injury, the uptake of carnitine by the myocardium may also be hindered by the disturbance of the carnitine-deoxycarnitine exchange mechanism in the membrane (4). Some authors indicate that the clearance of carnitine released from the ischemic cardiac tissue by the enhancement of the renal clearence mechanism, prevents the elevation of plasma carnitine levels (11, 12). The analysis of plasma carnitine levels in various diseases in these studies demonstrated that the levels increased only in patients with severe renal failure.

Carnitine is rapidly excreted from the kidneys, that is, 24 hours after the intravenous administration of carnitine, 83.5% was shown to be excreted in the urine (8). It is still controversial how a substance excreted so rapidly can remain elevated in blood. We propose two possible reasons for this. One reason could be that carnitine released from the ischemic muscle tissue exceeds the capacity of renal clearance, or the renal reabsorption increases secondary to the deficiency in the muscle. Another reason may be the increase in hepatic and renal synthesis of carnitine in response to the deficiency in the muscle (carnitine cannot be synthesized in the muscle), consequently, this acceleration of the carnitine cycle may cause an elevation in the plasma concentration. The relative stability of serum carnitine levels in the mild and moderate CAD patients may be attributed to the renal clearance of carnitine possibly released from the myocardium. In severe disease conditions however, released carnitine levels might exceed the renal threshold and plasma levels may rise. Simultaneous analyses of carnitine in blood and in biopsy specimens from ischemic myocardium of angiographically staged patients will certainly serve to enlighten these controversies.

In conclusion, loss of myocardial carnitine may augment destruction caused by ischemia and contribute to the development of irreversible cardiac failure. In this case administration of carnitine along with other treating agents might be beneficial for the performance of the myocardium. The high levels of carnitine may be considered an indication for carnitine therapy.

The statistically insignificant difference in serum carnitine levels of the mild and moderate CAD cases in

Subject groups	Control	Mild CAD	Moderate CAD	Severe CAD
Carnitine (µmol / L)	40.32±8.9	38.95±10.06	45.90±9.4	63.15±12.4**
Urea) (mmol / L)	12.87±1.84	14.16±1.92	13.96±2.07	13.94±2.47
Creatinine (mmol / L)	70.72±12.37	65.41±14.14	70.72±12.37	71.60±9.72

Table 2. Serum carnitine, urea and creatinine values of patients and controls (mean ± SD).
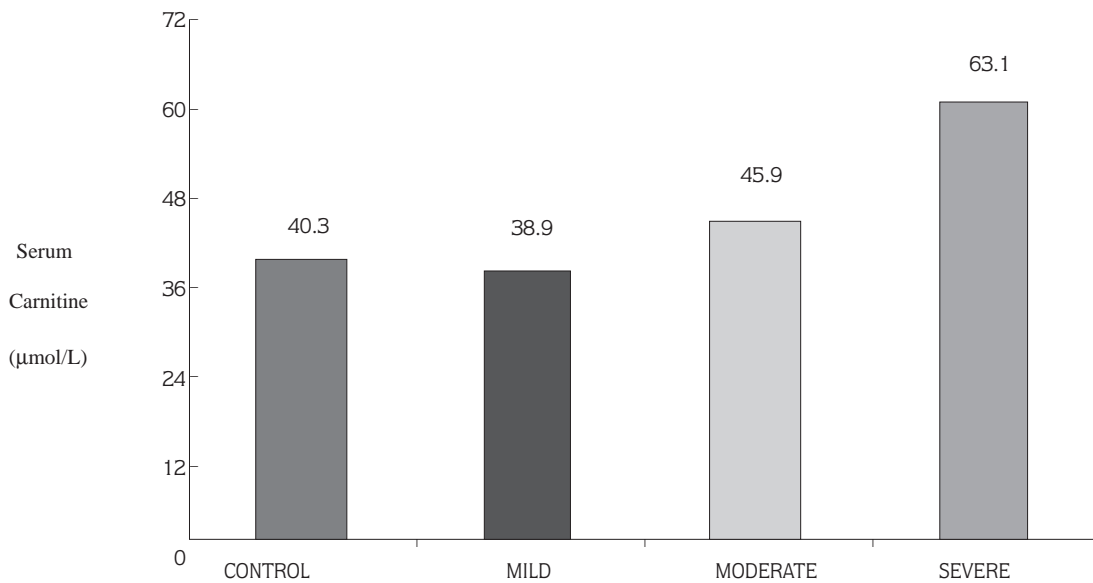
** p < 0.01.

Figure 1.   Serum carnitine levels in the four different groups of subjects.

comparison with the controls suggests that serum carnitine cannot be used as a marker for the presence of CAD, instead it can only be indicative of advanced atherosclerotic lesions.

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