



# Association of Abnormal Serum L-Carnitine Levels with Idiopathic Changes in Left Ventricular Geometry in Pediatric and Adolescent Patients

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## Abstract

**Background:** There is no compelling evidence to prove an association between serum free L-carnitine levels and changes in left ventricular (LV) geometry. The present study aimed to evaluate a possible association between these parameters.

**Methods:** In a cross-sectional study, 504 outpatients were randomly selected among those registered at Sanandaj Pediatric Heart Clinic (Sanandaj, Iran) during 2014-2020. The patients aged one to 25 years and were presented with cardiac complaints. The serum L-carnitine levels of all patients were evaluated and associated with changes in LV geometry measured by echocardiography. The association was assessed using the Chi squared test, Fisher's exact test, and one-way ANOVA with *post hoc* Tukey test. Data were analyzed using SPSS software (version 22.0).  $P \leq 0.05$  was considered statistically significant.

**Results:** The mean serum L-carnitine levels in the normal, low, and high serum groups were 52.69, 14.16, and 178.67 nmol/dL, respectively. There was a significant statistical association between abnormal serum levels of free L-carnitine and changes in LV geometry ( $P < 0.001$ ).

**Conclusion:** Our findings are indicative of an association between abnormal serum L-carnitine levels and changes in LV geometry in pediatric and adolescent patients.

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## What's Known

- Clinical symptoms of L-carnitine deficiency are progressive muscle weakness and cardiomyopathy, especially the dilated type.
- There is no compelling evidence to prove an association between abnormal serum L-carnitine levels and changes in left ventricular geometry.

## What's New

- Abnormal serum levels of free L-carnitine are relatively common findings among patients with changes in cardiac geometry.

## Introduction

Changes in left ventricular (LV) geometry are categorized into three types, namely eccentric remodeling, concentric hypertrophy, and eccentric hypertrophy.<sup>1-5</sup> Evidently, it starts as early as childhood or adolescence and may progress into old age.<sup>6-10</sup> Prognostic significance of early changes in LV geometry due to various etiologic factors has been reported.<sup>9, 11</sup> Abnormal changes in LV geometry commonly occur in older adults with or without established clinical cardiovascular diseases that increase the risk of mortality.<sup>12</sup>

Up till now, we have frequently treated patients with mild to moderate LV dilatation or hypertrophy without cardiac or extra-cardiac etiology, which we call idiopathic changes in LV geometry. Most of these early cardiac changes are not an

immediate medical problem, however, they could, later on, become an issue because of their potential to develop into cardiac remodeling and dysfunction.<sup>6, 13</sup> Since laboratory results indicated that our patients commonly have low or high serum L-carnitine levels, an association between echocardiographic and laboratory findings was suspected. As reported in some studies, L-carnitine has a positive influence on cardiac function and myocardial protection.<sup>14-16</sup>

Symptomatic dilated cardiomyopathy has been reported in patients with L-carnitine deficiency caused by genetic disorders.<sup>17-19</sup> Besides, administration of L-carnitine has been reported as an effective treatment for both diastolic and systolic dysfunction.<sup>20, 21</sup> Carnitine is involved in  $\beta$ -oxidation and plays an important role in the metabolism of fatty acids by transferring long-chain fatty acids into mitochondria.<sup>19, 22</sup> Clinical symptoms of L-carnitine deficiency include progressive muscle weakness, cardiomyopathy, hyperammonemia, and non-ketotic hypoglycemia.<sup>23, 24</sup>

L-carnitine hemostasis in the body is maintained by exogenous intestinal absorption or endogenous biosynthesis.<sup>25</sup> Genetic disorder of L-carnitine biosynthesis is the primary type of carnitine deficiency.<sup>26-28</sup> Defect in novel organic cation transporter-2 (OCTN2) is another primary type of L-carnitine deficiency. Increased renal depletion of carnitine, mediated by OCTN2 disorder, is an autosomal recessive carnitine deficiency. Carnitine is well deposited in the liver, heart, and muscle.<sup>29-31</sup> Secondary carnitine deficiency may be due to inadequate intake in patients with protein-energy malnutrition, chronic diarrhea, prematurity and those under total parenteral nutrition.<sup>25</sup> Urinary depletion of carnitine occurs in patients with organic aciduria, fatty acid oxidation disorder, diabetes type I, Fanconi syndrome, and hemodialysis. L-carnitine deficiency may also be observed in patients with severe liver disease.<sup>25</sup>

Given the above, in the present study, we evaluated a possible association between abnormal serum levels of free L-carnitine and echocardiographic findings of early changes in LV geometry.

## Materials and Methods

In a cross-sectional study, 504 outpatients were randomly selected among those registered at Sanandaj Pediatric Heart Clinic (Sanandaj, Iran) during 2014-2020. The patients aged one to 25 years and were presented with cardiac complaints, including chest pain, respiratory distress, and palpitation. The exclusion criteria were known cases of congenital heart disease,

congenital or genetic cardiomyopathy, and myocarditis. Written informed consent was obtained from the participants aged  $\geq 18$  years and the parents of underage patients. The study protocol was assessed and approved by the Ethics Committee of Kurdistan University of Medical Sciences, Sanandaj, Iran (code: IR.MUK.REC.1399.244).

### Laboratory Tests

All patients were evaluated for serum L-carnitine and other routine laboratory tests such as calcium, magnesium, zinc, vitamin D3, and iron. Serum levels of free L-carnitine were measured using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) (Bioassay Technology Laboratory, China).<sup>32</sup> For accuracy, the serum L-carnitine level was independently measured by two reference laboratory centers at an interval of at least one week. The obtained levels were then categorized into normal, low, and high serum groups using cutoff points at 24 and 86 nmol/mL for the low and high serum levels, respectively.<sup>33</sup> The quantitative and categorized serum L-carnitine levels were then compared with echocardiographic LV measurements.

### Echocardiographic Assessment

In addition to the usual sequential echocardiographic assessment, a standardized assessment of changes in LV geometry was conducted.<sup>34</sup> LV end-diastolic diameter (LVEDD) was determined using two-dimensional images by measuring its diameter in short-axis view at the level of the papillary muscles. LV mass was determined using the area-length method by measuring the cross-sectional mass per unit area at the level of the papillary muscles.<sup>34</sup> The Samsung HS70 ultrasound system (Samsung, South Korea) was used for the assessments.

### Data Categorization

All geometric measurements were indexed by body surface area ( $m^2$ ) and categorized based on the referenced values set by the American Society of Echocardiography.<sup>35</sup> Accordingly, indexed LV mass ( $g/m^2$ ) and indexed LVEDD ( $mm/m^2$ ) were categorized into four geometric groups, namely normal, trivial, mild, and moderate.<sup>35</sup>

### Statistical Analysis

Data were analyzed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive and analytical methods were used for statistical analyses. Data were expressed as mean $\pm$ SD, frequency, and relative frequency

(percentage). Association between variables was assessed using the chi-squared test, Fisher's exact test, and one-way ANOVA with *post hoc* Tukey test.

## Results

Of the 504 patients, 296 (58.7%) were men with a mean age of 9.5 years and 208 (41.3%) women with a mean age of 8.5 years. There was no statistical association between the sex of patients and serum L-carnitine levels ( $P=0.706$ ) nor changes in LV geometry ( $P>0.050$ ). The prominent mean discrete serum L-carnitine levels in the normal, low, and high serum groups were 52.69, 14.16, and 178.67 nmol/dL, respectively (table 1). Moreover, there was a relatively close frequency distribution (from 31% to 37.5%) between the serum groups.

The indexed LVEDD ( $\text{mm}/\text{m}^2$ ) and LV mass ( $\text{g}/\text{m}^2$ ) for each geometric group were statistically compared with the L-carnitine levels

of each serum group (tables 2 and 3). There was a significant statistical association between the geometric groups of indexed LVEDD and LV mass with the L-carnitine levels of the serum groups ( $P<0.001$ ) (table 2). Approximately half of the patients with high serum L-carnitine levels had mild and moderate LV dilatation. However, this ratio was prominently lower (31.5%) in those with low serum L-carnitine levels. Furthermore, mild or moderate LV hypertrophy was indicated in 25.4% of cases with high serum L-carnitine levels, but only in 12.8% of those with low levels.

A comparison of the mean serum L-carnitine levels for each geometric group is presented in table 3. There was a significant progression of indexed LVEDD and LV hypertrophy (LVH) mass toward mild and moderate categories with the highest L-carnitine level. On the other hand, comparing the quantitative mean of indexed LVEDD and LVH mass for each serum group showed significant changes in LV geometry in the high serum group (table 4). The results

**Table 1:** Frequency distribution of the patients and L-carnitine levels for each serum group

Serum group	Patients N (%)	L-carnitine level (nmol/dL) mean $\pm$ SD
Normal	159 (31.5%)	52.69 $\pm$ 23.71
Low	156 (31%)	14.16 $\pm$ 7.41
High	189 (37.5%)	178.67 $\pm$ 102.97
Total	504 (100%)	88.01 $\pm$ 96.59

**Table 2:** Association of serum L-carnitine levels with changes in LV geometry for both LVEDD and LV mass indexed by body surface area

Variable	Geometric group	L-carnitine serum group			P value
		Normal N (%)	Low N (%)	High N (%)	
Indexed LVEDD ( $\text{mm}/\text{m}^2$ )	Normal	80 (50.3)	62 (39.7)	57 (30.2)	<0.001*
	Trivial	34 (21.4)	45 (28.8)	29 (15.3)	
	Mild	27 (17)	33 (21.2)	49 (25.9)	
	Moderate	18 (11.3)	16 (10.3)	54 (28.6)	
Indexed LV mass ( $\text{g}/\text{m}^2$ )	Normal	134 (84.3)	105 (67.3)	116 (61.4)	<0.001**
	Trivial	13 (8.2)	31 (19.9)	25 (13.2)	
	Mild	10 (6.3)	17 (10.9)	30 (15.9)	
	Moderate	2 (1.3)	3 (1.9)	18 (9.5)	

\*Chi-squared test, \*\*Fisher's exact test; LVEDD: Left ventricular end-diastolic diameter; LV mass: Left ventricular mass

**Table 3:** The difference in the mean L-carnitine levels for each geometric group

Variable	Geometric group	L-carnitine level (nmol/dL) mean $\pm$ SD	P value
Indexed LVEDD ( $\text{mm}/\text{m}^2$ )	Normal	68.96 $\pm$ 8.89	<0.001*
	Trivial	71.34 $\pm$ 2.33	
	Mild	103.32 $\pm$ 104.20	
	Moderate	132.58 $\pm$ 111.11	
Indexed LVH mass ( $\text{g}/\text{m}^2$ )	Normal	82.08 $\pm$ 89.83	<0.001*
	Trivial	73.38 $\pm$ 86.40	
	Mild	115.22 $\pm$ 121.72	
	Moderate	155.88 $\pm$ 121.36	

\*One-way ANOVA; LVEDD: Left ventricular end-diastolic diameter, LVH: Left ventricular hypertrophy

**Table 4:** Comparison of the mean LV dilatation and LV hypertrophy levels for each serum group per age category

Age category	Serum group	LV dilatation		LV hypertrophy	
		Mean±SD	P value	Mean±SD	P value
≤8 years	Normal	55.26±10.43	0.01*	57.51±14.64	<0.001*
	Low	55.56±12.42		67.99±18.34	
	High	60.07±12.13		76.81±20.22	
>8 years	Normal	33.21±9.84	0.02*	63.19±13.99	<0.001*
	Low	37.15±9.67		70.63±16.73	
	High	34.96±9.51		73.59±16.01	
Total	Normal	41.52±14.68	<0.001*	61.05±14.46	<0.001*
	Low	44.11±13.99		69.64±17.35	
	High	51.04±16.50		75.65±18.83	

\*One-way ANOVA; LV: Left ventricular

of both categorized and quantitative analyses showed a significant statistical difference between changes in LV geometry and high serum levels of L-carnitine. Similar differences were also observed with a subgroup analysis of patients younger and older than eight years (table 4).

The result of *post hoc* Tukey test showed a reasonable discrepancy between normal and moderate indexed LV mass ( $P=0.031$ ). It also showed a statistical variation between normal and mild or moderate indexed LVEDD ( $P<0.001$ ). Similarly, a rational difference in indexed LVEDD between normal and high serum L-carnitine levels was observed ( $P=0.006$ ). Additionally, the results showed a statistical difference in indexed LV mass between normal and high serum L-carnitine levels ( $P=0.005$ ). There was a statistical relationship between diastolic dysfunction and L-carnitine levels ( $P=0.004$ ). However, this was not the case for the LV ejection fraction. Furthermore, there was no statistical difference between quantitative serum L-carnitine levels and diastolic ( $P=0.712$ ) or systolic ( $P=0.831$ ) function.

The results of other blood tests showed no statistical relationship between LV dilatation and the levels of zinc ( $P=0.781$ ), vitamin D3 ( $P=0.542$ ), iron ( $P=0.340$ ), and serum lipid profile ( $P=0.711$ ). Details of this analysis are not presented.

## Discussion

The results of our study showed that early changes in LV geometry in children and adolescents are relatively common cardiac manifestations, often with minimal clinical presentation. These primary changes in LV geometry during childhood are rarely addressed in previous studies, nonetheless, there are some reports of asymptomatic or low symptomatic cardiomyopathies associated with carnitine deficiency.<sup>4, 5</sup> Reddy and others reported

moderate cardiac hypertrophy and minimal cardiac dysfunction in uremic patients under dialysis with marked L-carnitine deficiency due to reduced renal biosynthesis or depletion by dialysis.<sup>36</sup> Likewise, Nishimura and others reported positive effects of L-carnitine on myocardial dysfunction in hemodialysis patients.<sup>3</sup>

L-carnitine deficiency, especially when caused by gene abnormality, is known as a relatively rare etiologic factor for dilated or hypertrophic cardiomyopathy (D-CMP, H-CMP).<sup>17, 37</sup> Autosomal recessive L-carnitine deficiency is a rare disease associated with very low serum L-carnitine level ( $<5$  nmol/dL) and usually presented with progressive dilated cardiomyopathy.<sup>17, 18, 30</sup> On the other hand, secondary L-carnitine deficiency is probably a more common condition with lower severity of both L-carnitine deficiency and cardiomyopathy.<sup>38</sup> In comparison with previous studies, we showed that both low and high serum levels of free L-carnitine are relatively common in patients with changes in cardiac geometry. Moreover, the relationship between changes in LV geometry and high serum L-carnitine level was even more prominent. In addition, our findings indicated that alteration in the serum level of free L-carnitine may be involved in mild to moderate changes in LV geometry, but not exclusively in D-CMP or H-CMP.

The association of high serum L-carnitine levels with different types of cardiomyopathies has been rarely mentioned in previous studies. Ueland and others reported that high serum levels of carnitine derivatives, especially palmitoyl-carnitine, were found in patients with chronic heart failure. They concluded that disturbed carnitine metabolism has a causative role in the pathogenesis of heart failure and proposed that some of its derivatives may provide prognostic information in these patients.<sup>37</sup> Some other studies have investigated the cause of high serum L-carnitine levels without considering its potential relationship with cardiac complications.

Carnitine homeostasis is related to intestinal absorption, cellular biosynthesis, tissue uptake, and renal reabsorption.<sup>26, 36</sup> Stanley and others reported that the hepatic form of Carnitine palmitoyltransferase I (CPT I) deficiency can be associated with high serum L-carnitine level.<sup>39</sup> Defect in L-carnitine transport into muscle or liver cells and its plasma accumulation is another etiologic factor of high L-carnitine plasma level.<sup>28, 38, 40</sup> Carnitine intestinal absorption and cellular uptake by hepatic and muscular tissues is mediated by OCTN2.<sup>27, 28</sup> Activation of peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) enhances carnitine biosynthesis and OCTN2-mediated tissue carnitine uptake.<sup>27, 41, 42</sup> Therefore, it can be suspected that any acquired or genetic defect in this cellular transporter system potentially prevents cellular carnitine uptake resulting in intracellular carnitine deficiency, but increased plasma accumulation. Further studies are required to substantiate these findings.

Although previous studies have reported an association between low serum L-carnitine levels and symptomatic cardiomyopathies,<sup>16-18</sup> there was a scarcity of information about the association of high serum L-carnitine levels with changes in LV geometry; hence instigating our study. The main limitation of the study is related to the methodology and design (cross-sectional) of our research, i.e., the temporal link between the outcome and exposure could not be determined since both are examined at the same time. Another limitation was the unavailability of plasma acylcarnitine to free carnitine ratio (AC/FC) as a marker of carnitine deficiency.<sup>21</sup> In addition, serum L-carnitine levels and echocardiographic LV measurements were conducted concurrently, which undermines strong evidence for a potential causative relationship. Moreover, we did not assess the relationship between other serum elements (iron, zinc, and vitamin D3) and changes in LV geometry.

## Conclusion

Our findings are indicative of an association between abnormal serum L-carnitine levels and changes in LV geometry. Although the etiology of these relatively common abnormal serum L-carnitine levels is not well-established, we recommend serum L-carnitine level monitoring in all patients with different degrees of changes in LV geometry. As a standard process, evaluation of LV geometry combined with routine sequential echocardiography in pediatric and adolescent patients is recommended. This may be followed

by laboratory assessment of L-carnitine in cases with suspected abnormal changes in LV geometry for appropriate management. Future studies should focus on a therapeutic approach for different types of change in ventricular geometry in relation to abnormal serum L-carnitine levels.

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**Conflict of Interest:** Not declared.

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