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ORGINAL ARTICLE

Trimethylamine-N-oxide and heart-type fatty acid-binding protein 3 are risk markers of cardiotoxicity in L carnitine supplemented students in faculty of physical education, Zagazig university

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ABSTRACT

Backgroung: Levo-Carnitine is known L-carnitine that is generally used in medical and nutritional fields. Recent studies highlightened L-carnitine-induced cardiovascular toxic effects. Trimethylamine-N-oxide (TMAO) and heart-type fatty acid-binding protein 3 (HFABP3) are risk markers of its toxicity. **Aim of this study** was to elucidate the relationship between L-carnitine metabolites and cardiac damage biomarkers in L-carnitine supplemented students. **Patients and Methods:** This study was carried out on students at tennis section, faculty of physical education for girls, Zagazig University. These students were divided into 2 groups. Group I: Forty nine healthy individuals (age- and grade-matched), and group II: Forty nine L-carnitine supplemented students (1000mg/day in 2 or 3 divided doses orally). Clinical examination and electrocardiography (ECG) were done for all of them. These students have been investigated for L-carnitine, cardiac troponin I (cTn-I), H-FABP3, and TMAO levels. **Results:** All markers have been significantly elevated when compared with those of the control group. ECG findings were ST depression in 24 students (49%), and T wave inversion in 1 9 students (38.8%) where sinus tachycardia was the commonest finding (77.6%). Furthermore, L-carnitine showed a significant positive correlation with H-FABP3, TMAO, cTn-I, and heart rate. **Conclusion:** TMAO, HFABP3 seem to be the strongest predictors for long term L-carnitine supplementation's cardiovascular toxicity. Further studies to assess both the efficacy and long term safety of oral L-carnitine supplementation for atheletes that used for physical enhancement were recommended.

Key Words: Atheletes, Cardiotoxicity, L-carnitine, Marker, Trimethylamine oxide.

INTRODUCTION

L-carnitine plays an important role in enrichment of energy by using long-chain fatty acids into mitochondria for β-oxidation. Ninty eight percent of L-carnitine is remained in skeletal muscle, and plasma. Also, L-carnitine plays a major role in exercise among athletes. Atheletes use it to increase the oxidation of fat during exercise and spare muscle glycogen. One of the main rules is to enhance red blood cells' oxygen carrying capability especially in stressful situations **[1].**

Supplementation of L-carnitine is beneficial to increase energy used by muscles and enhance exercise performance. In contrary, in other study of healthy persons, no exercise performance's enhancement was recorded, despite reported increase in skeletal muscle L-carnitine concentration**[2].**

There aren't many studies on how oral L-carnitine supplements affect athletes. Oral L-carnitine was not listed as a helpful therapy in a recent significant statement from the Mitochondrial Medicine Society due to a lack of evidence for its efficacy. Nonetheless, in reality, a lot of athletes continue to take oral L-carnitine supplements [3].

An important component of red meat, L-carnitine, is broken down by intestinal bacteria to create trimethylamine (TMA), which is then broken down further by the hepatic enzyme flavin monooxygenase 3 to produce trimethylamine N-oxide (TMAO) (FMO3). Many studies have recently concentrated on a potential adverse effect of TMAO on cardiovascular effectiveness. Studies in 2011 found a link between TMAO and

cardiovascular disease in people, and other research found that TMAO can hasten atherosclerosis in animals [4]. Moreover, a significant number of clinical research discovered a connection between plasma L-carnitine levels and myocardial infarction (MI), stroke, and death [5].

Myoglobin, creatine kinase-MB, cardiac troponins I and T (cTn I, -T), and heart-type fatty acid-binding protein 3 (H-FABP3) are indicators of cardiac tissue injury. H-FABP3 is a quick and accurate indicator of myocardial infarction and acute ischemia [6,7].

Up to our knowledge, few previous studies investigated the relationship between cardiac damage biomarkers and L-carnitine metabolite in L-carnitine supplemented individuals. So, we aimed here to study the cardiac effects of L-carnitine in L-carnitine supplemented students through assessment of TMAO and cardiac damage biomarkers H-FABP3 and the relationship between them.

SUBJECTS AND METHODS

Study population

Girls from the Faculty of Physical Education at Zagazig University who had been registered in the Tennis department with L-carnitine supplementation were the subjects of this cross-sectional comparative study. At the time of study recruitment, students aged 19 to 22 who had been taking L-carnitine supplements orally for at least three months were enrolled in our study. Students who used multiple supplements, were treated for chronic drug use, or had taken L-carnitine for less than three months were not included. In accordance with these exclusion criteria, our study only included 49 pupils, informed consent from every participant was signed. The Zagazig University Faculty of Medicine's Ethics Committee for Research (Institutional Review Board, or "IRB") provided an approval letter (ZU-IRB # 10378-24-1-2023).

METHODS

To evaluate the improvement in physical performance, all pupils must engage in physical activities' exercises. L carnitine, TMAO, H-FABP3, and circulating troponin I (cTn I) levels were measured in blood samples that were taken from the subjects. In Zagazig University Hospitals, electrocardiograms were performed. Every student had her 12-lead ECG analysis collected at a pace of 25 millimeters per second in Zagazig hospital's cardiology departments. According to Apple et al., VIDAS1 Troponin I Ultra (TNU, BioMerieux Inc., France) used the enzyme linked fluorescence assay technology using immunoassay sandwich technique to measure the levels of circulating cTn-I in serum. [8]. Myocardial injury was identified as occurring at levels higher than 1.3 ng/mL [9]. According to Wodzig et al., the serum concentration of H-FABP3 was measured using the ELISA method [10], kits, (Oxis International Inc., Foster City, California, USA). 1.6–19 ng/mL is its normal range [11] Using a triple quadrupole mass spectrometer and the stable isotope dilution tandem mass spectrometry approach, plasma TMAO was analyzed by ELISA [12]. Whole blood was used for the sandwich enzyme-linked immunosorbent assay (ELISA) method to analyze L-carnitine [13], kits (Bioassay Technology Laboratory, China).

Statistics

SPSS (Statistical Program for the Social Sciences) version 26 was used for data analysis. When necessary, the chi square test was used to compare categorical variables and describe them using their absolute frequencies. To validate the assumptions employed in parametric tests, the Shapiro-Wilk test was applied. Depending on the type of data, the means, standard deviations, or median and interquartile range of quantitative variables were used to characterize them. Independent sample t tests (for normally distributed data) and Mann Whitney tests (for not normally distributed data) were used to compare quantitative data between two groups. For properly distributed data, the Pearson correlation coefficients were utilized to determine the degree and direction of the link between two continuous variables. The beast cutoff of a specific quantitative parameter in diagnosis was determined using ROC curve. The best cutoff value for a particular quantitative measure was determined using the ROC curve to diagnose a particular medical condition. Using binary logistic regression, it was possible to pinpoint independent risk variables linked to certain health issues. To quantify the associated independent components for the dependent factor, linear regression analysis was done. The level statistical significance was set at $P<0.05$. Highly significant difference was present if $p\leq0.001$.

RESULTS

Regarding the age, there was no significant difference between the L-carnitine supplemented pupils and the controls **(Table 1).**

Laboratory findings of L-carnitine, TMAO, H-FABP3, and cTn-I in group II compared to controls are presented in (**Table 2).** There is statistically significant difference between two groups **(Table. 2).**

Between the tested groups, there is a statistically significant difference in terms of cardiovascular symptoms and ECG abnormalities. Heart rate was

the most frequent cardiovascular symptom (significantly higher in group II). In group II, ST segment depressions were found in 24 students (49%) and inverted T waves in 19 individuals (38.8%), as well as short PR intervals in 38 students (77.6% of whom were in group II) (Figure 2). For the control group, there were no ECG alterations and a normal ECG (Figure 1). Based on sinus tachycardia and a short PR interval, early clinical indicators of cardiotoxicity, 38 students met these requirements with a frequency of 77.6%. (Table 2). L-carnitine, TMAO, H-FABP3, and cTn-I laboratory results in group II compared to co ntrols are shown in (Table 2). Two groups diff er significantly from one another (Table. 2).

Higher levels of L carnitine and HFABP3 indepen dently enhance cardiotoxicity by 1.344 and 1.617 times, respectively, according to multivariate regr ession analysis of predictors of cardiotoxicity (Ta ble. 3).

Every parameter was noticeably greater than what the control group had. L carnitine positively correlates with all other aberrant measures, including heart rate, TMAO, CNT-1, and H-FABP-3, in a statistically significant manner (Table. 4).

L carnitine and TMAO both independently correlated with H-FABP3 (unstandardized p=0.011 and p=0.001, respectively) (Table. 5). L carnitine level was independently linked with TMAO (unstandardized =1.276, p0.001) (Table. 6).

L-carnitine, TMAO, and H-FABP3 are statistically significantly correlated with T wave inversion and are statistically considerably higher in individuals with T wave inversion. While the relationship between cTn-I and T wave inversion is insignificant (Table. 7). A statistically significant correlation exists between ST depression and TMAO, as well as H-FABP3, which is statistically significantly greater in ST segment depression patients. Although there isA statistically significant correlation exists between ST depression and TMAO, as well as H-FABP3, which is statistically significantly greater in ST segment depression patients. Although L carnitine or cTn-I have no statistically significant relationship with ST segment depression (Table. 7).

The optimal L-carnitine cutoff for detecting L-carnitine-induced cardiotoxicity is 99.43 with an area under the curve of 0.952, a sensitivity of 94.7%, and a specificity of 81.8%. The optimal TMAO cutoff for detecting L-carnitine-induced cardiotoxicity is 95.9, with an area under the curve of 1, a sensitivity of 78.9%, and a specificity of 90.9%. With an area under the curve of 1, sensitivity of 78.9%, and specificity of 72.7%, 0.315 is the optimal CNT-1 cutoff for the diagnosis of L-carnitine-induced cardiotoxicity. The area under curve cutoff for H-FABP3 in the diagnosis of L-carnitine-induced cardiotoxicity is 43.645.

The best cutoff of L carnitine in diagnosis of L-carnitine induced cardiotoxicity is ≥99.43 with area under curve 0.952, sensitivity 94.7% and specificity 81.8%. The best cutoff of TMAO in diagnosis of L-carnitine induced cardiotoxicity is ≥95.9 with area under curve 1, sensitivity 78.9% and specificity 90.9%. The best cutoff of CNT-1 in diagnosis of L-carnitine induced cardiotoxicity is ≥0.315 with area under curve 1, sensitivity 78.9% and specificity 72.7%. The best cutoff of H-FABP3 in diagnosis of L-carnitine induced cardiotoxicity is ≥ 43.645 with area under curve 1, sensitivity 89.5% and specificity 72.7% **(Table. 8) (Figure. 3).**

Table (1) Age among the studied groups.

	Group I (n=49)	Group II (n=49)	T	P
	Mean ± SD	**Mean ± SD**		
Age (years)	19.5 ± 2.2	20.02 ± 1.14	0.63	NS

Table (2) Comparison between the studied groups regarding the studied parameters.

	Group I (n=49) **Mean ± SD**	Group II (n=49) **Mean ± SD**	χ^2	P
ST depression	0 (0%)	24 (49%)	31.784	<0.001**
T wave inversion	0 (0%)	19 (38.8%)	23.57	<0.001**
Short PR interval	0 (0%)	38 (77.6%)	12.391	<0.001**
	Mean ± SD	**Mean ± SD**	T	P
Heart rate	78.86 ± 7.06	111.37 ± 15.75	-23.411	<0.001**
L carnitine	44.95 ± 5.27	112.85 ± 15.14	-29.638	<0.001**
TMAO	4.92 ± 0.82	99.72 ± 9.52	-69.471	<0.001**
H-FABP3	1.71 ± 0.28	48.24 ± 2.87	-112.823	<0.001**

	Group I (n=49) **Mean ± SD**	Group II (n=49) **Mean ± SD**	χ^2	P
	Median (IQR)	**Median (IQR)**	Z	P
CNT-1	0.01 (0.01 – 0.02)	0.39(0.27 – 0.52)	-8.663	<0.001**

t independent sample t test Z Mann Whitney test χ^2Chi square test IQR interquartile range **p≤0.001 is statistically highly significant

Table (3) Multivariate analysis of factors

	B	P	AOR	95% C.I.	
				Lower	Upper
L_ carnitine	0.295	0.026*	1.344	1.035	1.744
H-FABP3 (ng/mL)	0.481	0.099	1.617	.913	2.865

AOR adjusted odds ratio CI Confidence interval *p<0.05 is statistically significant

Table (4) Correlation between L-carnitine and the studied parameters:

	R	P
TMAO	0.956	<0.001**
H-FABP3	0.943	<0.001**
CNT-1	0.904	<0.001**

**p≤0.001 is statistically highly significant r Pearson correlation coefficient

Table (5) Linear stepwise regression analysis of factors associated with H-FABP3

	Unstandardized Coefficients		Standardized Coefficients	t	P	95.0% Confidence Interval	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-.740	1.732		-.427	0.670	-4.179	2.699
TMAO	.469	.030	0.968	15.777	<0.001**	.410	.528
L-Carnitine	.011	.040	0.017	.280	0.780	-.068	.090

**p≤0.001 is statistically highly significant

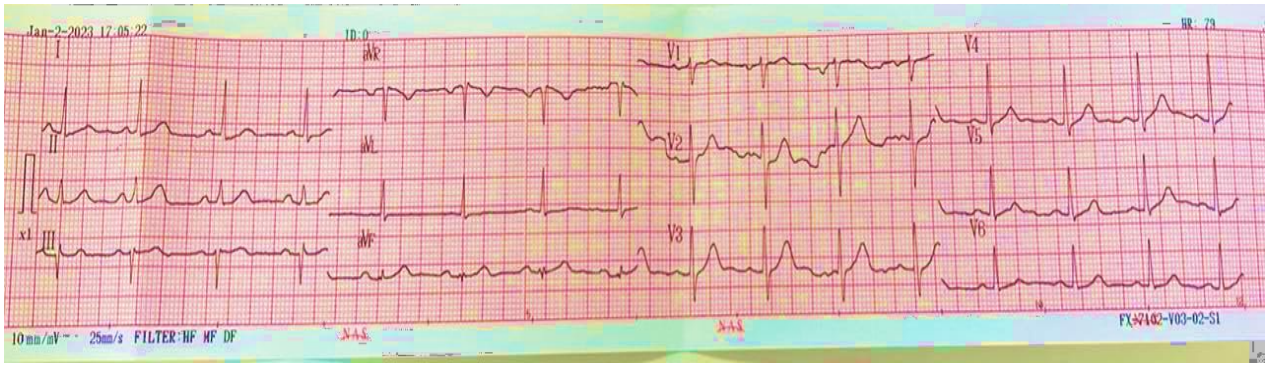
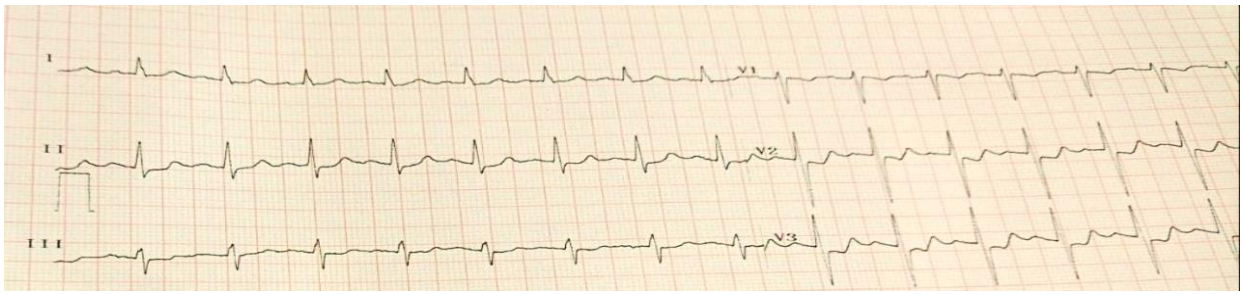


Figure 1. Normal ECG in control students. ECG: electrocardiography.



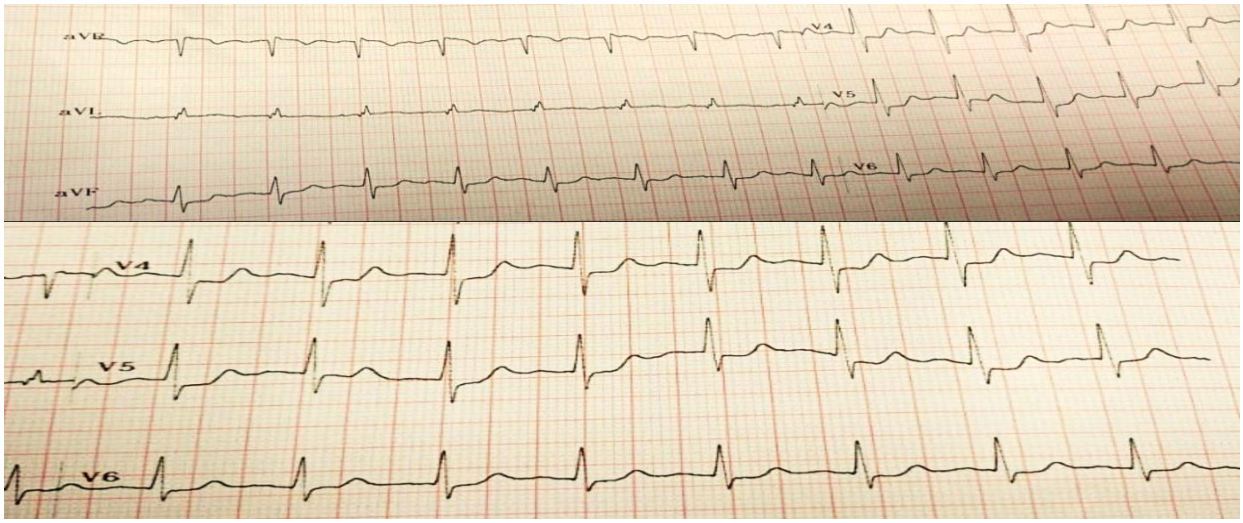


Figure 2. Some examples of ECG changes (short PR interval, ST segment depression) in L-carnitine supplemented students. ECG: electrocardiography.

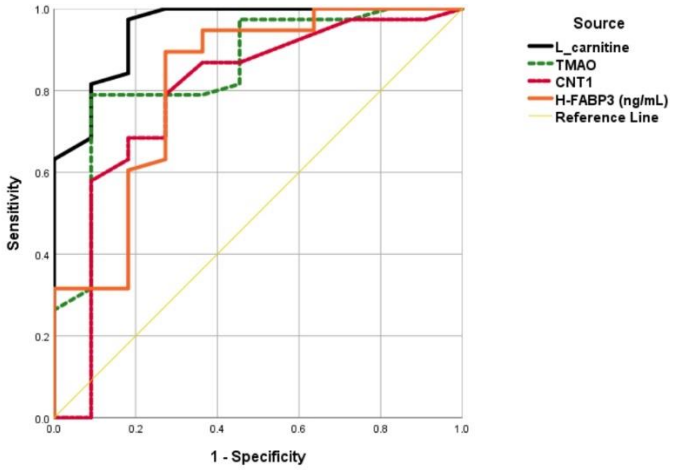


Figure (3) ROC curve showing Performance of L carnitine, TMAO, CNT-1 and H-FABP3 in diagnosis of cardiotoxicity among students receiving L carnitine

DISCUSSION

This study's major goal was to analyze the available data and assess the effects of L-carnitine supplementation on cardiac performance while assessing its impacts on exercise performance. The initial oral L-carnitine supplementation studies were unable to increase performance during moderate-intensity exercise. Studies on the long-term effectiveness and safety of L-carnitine supplementation have not been conducted but have recently been advised [14].

In our research, an aberrant ECG analysis revealed short PR intervals, ST segment depressions, and T wave inversions. No ECG alterations were seen in the control group. These results are consistent with those reported by Skagen et al. [15], who claimed that L-carnitine supplemented individuals had diagnostic ischemic changes recorded in the ECG that were in the form of T-wave changes (a "flat or inverted T-wave") and non-specific ST-changes, either elevation or depression of the segment.

In our investigation, group II had significantly higher blood levels of L-carnitine than the control group, and this finding was consistent with those of Arazi and Mehrtash [16].

Electrocardiographic evaluation in our work showed abnormal ECG findings including short PR interval, ST segment depression, and T wave inversion. In the control group, no ECG changes were found. These findings agree with Skagen et al. [17] who reported that L-carnitine supplemented individual had diagnostic ischemic changes recorded in the ECG which were in the form of T-wave changes ‘flat or inverted T-wave, and non-specific ST-changes, either elevation or depression of the segment.

In our study, blood L-carnitine was highly increased in group II compared to the control group, and this result was in agreement with Arazi and Mehrtash [18].

In our investigation, there was no correlation between T wave inversion and other ECG

abnormalities, but there was a statistically significant relationship between T wave inversion and L-carnitine, which is statistically higher in those with T wave inversion. Nonetheless, numerous writers hypothesized that myocardial shocking could cause L-carnitine-induced myocardial impairment to occur even when there are no ECG alterations [19].

Heart damage and L-carnitine levels are strongly connected. Additionally, ECG results do not always reflect L-carnitine-induced heart injury. A suitable diagnostic method is needed to assess the degree of heart injury caused by L-carnitine. It is crucial to look for additional indicators as a result, such as biochemical markers [20].

In our investigation, group II participants' TMAO levels were much greater than those of the control group, and there was a statistically significant correlation between ST depression and TMAO, which is markedly higher in ST segment depression pupils. Their findings concurred with those of Senthong et al. [20].

The earlier reviews of Liu et al. [21] and Tang et al. [22] and their links between TMAO and the increased risk of major adverse cardiovascular events are available online.

Koeth et al. demonstrated that adding choline or L-carnitine to mice's diets increased TMAO levels and accelerated the development of atherosclerosis. According to reports, flavin monooxygenase 3 plays a critical role in integrating hepatic inflammation, lipid metabolism, and cholesterol levels. The metabolism of sterols and cholesterol was found to be modulated by TMAO, which would, at contribute, to the rising risk of cardiovascular illnesses [23].

Plasma TMAO has recently been labeled as a cardiovascular morbidity and mortality risk biomarker by a number of meta-analyses. According to studies using animal models, TMAO increases the expression of inflammatory gene pathways and encourages the proliferation of aortic endothelial cells. Moreover, TMAO has been demonstrated to directly interact with platelets, potentiating them quickly to engage with thrombin, ADP, and collagen, disrupting intracellular calcium channel signaling, and enhancing in vivo thrombus development [24].

In our investigation, group II had significantly higher levels of H-FABP3 than the control group. We identified its level elevation as an early heart risk biomarker in the analyzed group since few experimental and clinical research have examined H-FABP3 levels in L-carnitine supplementation.

The smallest molecule among the cardiac injury biomarkers, heart-type fatty acid-binding protein 3 is able to leave injured cardiomyocytes earlier [25]. Serum H-FABP3 levels were measured in a rat model research by Sayed-Ahmed et al. [26] following a month of L-carnitine administration. Rats treated with L-carnitine had higher levels than the untreated rats. According to their findings, rats treated with L-carnitine may exhibit early cardiotoxicity depending on H-FABP3 levels. The findings of Valle et al. [27], who said that H-FABP3 is a helpful and sensitive sign in the early assessment of acute coronary syndrome, validated our findings. Due to its strong affinity for and ability to interact with long-chain fatty acid oxidative stress products, FABP is thought to be a potent antioxidant. The amount of total methionine residues in FABP is high. Amino acids methionine and cysteine are thought to be scavengers of cellular oxidative damage brought on by xenobiotics [28].

In our investigation, group II's cTn-I level was significantly higher than that of the control group. This outcome is consistent with Emran et al's findings [29].

Not just in acute myocardial infarction, cardiac troponins are sensitive indicators of heart muscle injury (AMI). Troponin levels can also rise under a variety of circumstances that either directly or indirectly cause heart muscle dysfunction. They start to show up in the serum four to eight hours after the commencement of the symptoms, reach their peak concentration, and continue to do so for seven to ten days following myocardial infarction [30].

Under non-pathological conditions, H-FABP3 serum concentration in the blood is very low (5 mg/L)[31]. H-FABP3 secretion, however, is brought on by cardiac injury, which is connected to a rise in myocardial cell membrane permeability. Several reports have been made. showing H-FABP3 monitoring can accurately and without false-negative results predict myocardial infarction within 1 hour [32].

CONLUSION

The focus of this investigation is on the relation between long-term L-carnitine supplementation and its metabolites, TMAO, and the novel heart injury biomarker H-FABP3. H-FABP3 appears to be a marker for cardiovascular harm brought on by L-carnitine early on. To further understand the involvement of H-FABP3 and TMAO in L-carnitine-induced cardiotoxicity, larger clinical trials should be done in the future as this study only used a small sample size. Moreover, a thorough

trans-thoracic ECG examination of heart function would be beneficial.

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Conflict of Interests Statement

Conflicts of interest were not disclosed by the author(s).

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REFERENCES

1) Gnoni, A.; Longo, S.; Gnoni, G.V.; Giudetti, A.M. Carnitine in human muscle bioenergetics: Can carnitine supplementation improve physical exercise? *Molecules* **2020**, *25*, 182.

2) Burrus, B.M.; Moscicki, B.M.; Matthews, T.D.; Paolone, V.J. The Effect of Acute L-carnitine and Carbohydrate Intake on Cycling Performance. *Int. J. Exerc. Sci.* **2018**, *11*, 404–416.

3) Oliveira, C.; Sousa, M. The effects of L-carnitine supplementation in athletic performance. *Sci. Sport.* **2019**, *34*, 63–72.

4) Stephens, F.B.; Constantin-Teodosiu, D.; Laithwaite, D.; Simpson, E.J. Insulin stimulates L-carnitine accumulation in human skeletal muscle, FASEB J. 20 (2006) 377–379.

5) Shannon, R.; Ghasemi, P.L.; Greenhaffff, F.B. Increasing skeletal muscle carnitine availability does not alter the adaptations to high-intensity interval training, Scand J. Med. Sci. Sports 12885. 2017;00:1–9

6) Chen C.Y.; Hsu H.C.; Lee B.C. Exercise training improves cardiac function in infarcted rabbits: involvement of autophagic function and fatty acid utilization. Eur J Heart Fail 2010; 12(4): 323–330.

7) Viswanathan K.; Kilcullen N.; Morrell C. Heart-type fatty acid-binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative. J Am Coll Cardiol 2010; 55(23): 2590–2598.

8) Apple FS, Smith SW, Pearce LA, et al. Use of the bioMe´rieux VIDAS1 troponin I ultra assay for the diagnosis of myocardial infarction and detection of adverse events in patients presenting with symptoms of acute coronary syndrome. Clin Chem Acta 2008; 390(1-2): 72–75.

9) Bonnefoy E, Godon P, Kirkorian G, et al. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. Eur Heart J 2000; 21(10): 832–836.

10) Wodzig KW, Pelsers MM, van der Vusse GJ, et al. One-step enzyme-linked immunosorbent assay (ELISA) for plasma fatty acid binding protein. Ann Clin Biochem 1997; 34(Pt3): 263–268.

11) Kleine AH, Glatz JF, Van Nieuwenhoven FA, et al. Release of heart fatty acid-binding protein into plasma after acute myocardial infarction in man. Mol Cell Biochem 1992; 116(1-2): 155–162.

12) Z. Wang, B.S. Levison, J.E. Hazen, L. Donahue, X.M. Li, S.L. Hazen, Measurement of trimethylamine-N-oxide by stable isotope dilution liquid chromatography tandem mass spectrometry, Anal. Biochem. 455 (2014 Jun 15) (35–4).

13) El Mously S, Abdel Ghaffar H, Magdy R, Hamza S, Mansour M. Carnitine deficiency in epileptic children treated with a diver- sity of anti-epileptic regimens. Egypt J Neurol Psychiatr Neurosurg. 2018;54:37.

14) Garthe, I.; Maughan, R.J. Athletes and supplements: Prevalence and perspectives. *Int. J. Sport Nutr. Exerc. Metab.* **2018**, *28*, 126–138.

15) Skagen K, Troseid M, Ueland T, Holm S, Abbas A, Gregersen I, Kummen M, Bjerkeli V, Reier-Nilsen F, Russell D, Svardal A, Karlsen TH, Aukrust P, Berge RK, Hov JE, Halvorsen B, Skjelland M. The carnitine-butyrobetainetrimethylamine-N-oxide pathway and its association with cardiovascular mortality in patients with carotid atherosclerosis. Atherosclerosis. 2016;247:64–69.

16) Arazi, H.; Mehrtash, M. Effect of Acute L-Carnitine Supplementation on Blood Lactate, Glucose, Aerobic and Anaerobic Performance in Elite Male Artistic Gymnasts. *Balt. J. Sport Health Sci.* **2017**, *1*, 2–7.

17) Methley, A.M.; Campbell, S.; Chew-Graham, C.; McNally, R.; Cheraghi-Sohi, S. PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv. Res.* **2014**, *14*, 579.

18) Ottiger M, Nickler M, Steuer C, Odermatt J, Huber A, Christ-Crain M, Henzen C, Hoess C, Thomann R, Zimmerli W, Mueller B, Schuetz P. Trimethylamine-Noxide (TMAO) predicts fatal outcomes in community-acquired pneumonia patients without evident coronary artery disease. Eur J Intern Med. 2016;36:67–73.

19) Senthong V, Wang Z, Fan Y, Wu Y, Hazen SL, Tang WH. Trimethylamine N-oxide and mortality risk in patients with peripheral artery disease. J Am Heart Assoc. 2016;5:e004237. DOI: 10.1161/JAHA.116.004237.

20) Liu TX, Niu HT, Zhang SY. Intestinal microbiota metabolism and atherosclerosis. Chin Med J. 2015;128:2805–2811.

21) Tang WH, Hazen SL. Microbiome, trimethylamine N-oxide, and cardiometabolic disease. Transl Res. 2017;179:108–115.

22) Koeth RA, Levison BS, Culley MK, Buffa JA, Wang Z, Gregory JC, Org E, Wu Y, Li L, Smith JD, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. gamma-Butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO. Cell Metab. 2014;20:799–812.

23) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal

for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008–2012.

24) Gururajan P, Gurumurthy P, Nayar P, et al. Heart Fatty Acid Binding Protein (H-FABP) as a diagnostic biomarker in patients with acute coronary syndrome. Heart, Lung Circ 2010; 19(11): 660–664.

25) **Sayed-Ahmed M, Alrikabi A, Mashan L, Othman A, Al-Shabanah A.** Carnitine Supplementation Attenuates Sunitinib-Induced Inhibition of AMP-Activated Protein Kinase Downstream Signals in Cardiac Tissues Cardiovascular Toxicology (2019) 19:344–356

26) Valle HA, Riesgo LG, Bel MS, et al. Clinical assessment of heart-type fatty acid binding protein in early diagnosis of acute coronary syndrome. Eur J Emerg Med 2008; 15(3): 140–144.

27) Wang G, Gong Y, Anderson J, et al. Antioxidative function of L-FABP in L-FABP stably transfected chang liver cells. G Hepatology 2005; 42(4): 871–897.

28) Emran T, Chowdhury N, and Saker M. L-carnitine protects cardiac damage by reducing oxidative stress and inflammatory response via inhibition of tumor necrosis factor-alpha and interleukin-1beta against isoproterenol-induced myocardial infarctionSeptember Biomedicine and pharmacotherapy 2021,143(2):112-139.

29) Tsai SH, Chu SJ, Hsu CW, et al. Use and interpretation of cardiac troponins in the ED. Am J Emerg Med 2008; 26(3): 331–341.

30) Gerhardt W and Ljungdahl L. Detection of myocardial damage by serial measurements of cardiac troponin T, CK-MB mass, and TROPT rapid test. Cardiovasc Drug Ther 1997; 11(suppl 1): 227–240.

31) Arı H, Tokac¸ M, Alihanog lu Y, et al. Fatty acid-binding protein and exercise in CAD. Anadolu Kardiyol Derg 2011; 11(8): 685–691.

32) Chan CP, Wan TS, Watkins KL, et al. Rapid analysis of fatty acid-binding proteins with immunosensors and immunotests for early monitoring of tissue injury. Biosens Bioelectron 2005; 20(12): 2566–2580.

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