



Atorvastatin and carnitine combination versus atorvastatin alone impacts on the lipid profile of haemodialyzed patients: A randomised clinical trial

Hamid Noshad¹ , Davoud Mohammadi-Nejhad², Parastou Hoseini³, Majid Montazer⁴, Behnaz Ghamari⁵, Farid Karkon-Shayan*¹

¹ Chronic Kidney Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

² Department of Internal Medicine, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

³ Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

⁴ Department of Surgery, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁵ Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Article History:

Received: 18 Jan. 2018

Accepted: 12 May 2018

ePublished: 15 Dec. 2018

Keywords:

Carnitine,
Atorvastatin,
Hemodialysis,
Dyslipidemia

Abstract

Introduction: Dyslipidemia is one of the most common problems in hemodialysis patients and healthcare system. Some studies have suggested the use of carnitine in the treatment of dyslipidemia in hemodialysis patients. This study was carried out aiming to evaluate the effect of atorvastatin and carnitine combination versus atorvastatin alone on the lipid profile of hemodialyzed patients.

Methods: In this clinical trial, 50 hemodialysis patients referred to the educational centres of Tabriz University of Medical Sciences, Tabriz, Iran, for haemodialysis were enrolled. Patients were randomly assigned into two groups. In the first group, patients were treated with carnitine (1000 mg three times daily) and atorvastatin (10-80 mg/day based on the baseline lipid profile of the patients) and in the second group, the patients were treated with atorvastatin alone for six months. The levels of triglyceride (TG), cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and haemoglobin before and after intervention were compared. The side effects of carnitine administration were also evaluated.

Results: Results showed that TG, cholesterol, and LDL levels were significantly lower in the carnitine group compared to those in the other group at the end of study ($P < 0.050$). In addition, HDL and haemoglobin levels were significantly higher in the carnitine group in comparison to the other group ($P < 0.050$). No major side effects of carnitine were observed among the patients.

Conclusion: The use of carnitine plus atorvastatin combination is an effective and safe method in the treatment of dyslipidemia in patients undergoing hemodialysis without imposing significant side effects.

Citation: Noshad H, Mohammadi-Nejhad D, Hoseini P, Montazer M, Ghamari B, Karkon-Shayan F. **Atorvastatin and carnitine combination versus atorvastatin alone impacts on the lipid profile of haemodialyzed patients: A randomised clinical trial.** J Anal Res Clin Med 2018; 6(4): 165-71. Doi: 10.15171/jarcm.2018.027

Introduction

The incidence of chronic kidney disease (CKD) is rising in the world and Iran, becoming a threat to the global health.^{1,2} Although the improvement of dialysis techniques in recent years has been shown to

increase the life expectancy of these patients, in the long run, dialysis causes complications that reduce the quality of life (QOL).³

Dyslipidemia is one of the common problems in dialysis patients resulting in atherosclerosis progression.^{4,5} It manifests

* Corresponding Author: Farid Karkon Shayan, Email: faridkarkonshayan@yahoo.com



with an increase in the serum triglyceride (TG) levels and a decrease in the high-density lipoprotein (HDL) plasma levels.⁶ It has been shown that cardiovascular disorders (CVDs) due to advanced atherosclerosis are one of the major causes of death among patients with renal insufficiency, and dyslipidemia is the most critical risk factor for these events due to vascular calcification and atherosclerotic plaque formation.^{7,8} It is important to note that mortality rate from heart diseases in these patients is 30 times higher than that of healthy subjects.⁹

About 40% of patients undergoing hemodialysis suffer from dyslipidemia and prevalence of metabolic syndrome, and hypertension plus dyslipidemia have been reported to be as high as 77% in these patients.⁷ Given that there are approximately 35000 dialysis and transplantation patients in Iran,¹⁰ paying attention to the problems of these patients is essential.

L-carnitine is quaternary ammonium found in milk and meat. The liver is also one of the main sources of endogenous carnitine producing it from lysine, methionine, ascorbate, niacin, pyridoxine, and iron. Carnitine is used in a variety of metabolic processes, including the regulation of Ketogenesis as well as mitochondrial processes, and the transfer of free fatty acids.¹¹ Studies have shown that carnitine supplementation among patients undergoing dialysis decreases inflammatory responses and also improves their metabolic status.¹² Moreover, carnitine has lipid-lowering effects and improves lipid metabolism, and is effective in preventing hypotension during hemodialysis.¹³ On the other hand, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, such as atorvastatin, have been long known to possess remarkable lipid-lowering effects.⁷

Although both statins and carnitine are effective in reducing the level of plasma lipids, the effects of their combination on the lipid profile of patients undergoing dialysis are unclear. The purpose in this study was to investigate and compare the effect of

atorvastatin plus carnitine combination therapy with atorvastatin alone on blood lipid profile of patients undergoing dialysis.

Methods

This study was a randomized clinical trial (RCT) performed in educational hospitals of Tabriz University of Medical Sciences on 50 patients undergoing hemodialysis between February 2016 and February 2017 for one year. The RCT was registered at Iranian Registry of Clinical Trials (IRCT) under IRCT201604273742N3 code.

All patients who were over 18 years of age and under hemodialysis were included in this study. Moreover, all patients who took any other medication to control his/her lipid profile were excluded from the study. Furthermore, if the patients did not fill in the informed consent form to participate in the study, they would be excluded.

50 patients who were over 18 years old, under hemodialysis and referred to the educational hospitals of TUOMS were enrolled into the study. The patients were randomly selected using convenient sampling method. All patients were randomly assigned to two equal groups (n = 25 each) using a random number table. In both groups, the haemoglobin and level of lipid profiles of patients including total cholesterol, TG, low-density lipoprotein (LDL), and HDL were measured in an academic laboratory at the beginning of the study and six months after treatment. One group of patients (n = 25) were treated with atorvastatin at a 10 to 80 mg daily dose (according to the baseline level of lipid profile in patients). The second group (n = 25) was treated with atorvastatin at a dose of 10 to 80 mg daily and carnitine 1000 mg three times daily with food for six months. The lipid profile of the patients in the first and third months was used to adjust the dosage of atorvastatin, as needed. During the study, all possible side effects of carnitine were also recorded (side effects of carnitine are rare, and in case of some complications, patients would be examined by their physician, who

would take necessary measures such as discontinuation of the drug).

For all statistical analyses, the SPSS (version 20, IBM Corporation, Armonk, NY, USA) was used. Data were expressed as mean \pm standard deviation (SD), frequency, and percentage. The normal distribution of data was evaluated using Kolmogorov-Smirnov (K-S) test. Chi-square test was used to compare the qualitative variables. In addition, the quantitative variables were compared between two groups using independent t-test or Mann Whitney U test. The sample size of the study was determined based on the previous studies and online at <http://www.parsmodir.com/db/research/ochran.php> website using the Cochran formula. The power of the study ($1-\beta$) and α were considered to be 80% and 0.05, respectively. In all comparisons, $P < 0.050$ was considered as statistically significant.

The purpose and manner of conduction of the study, potential benefits, and potential side effects of carnitine (based on previous studies, the incidence of severe side effects is unlikely) were utterly explained to the patients. It was also stated that all of their information would be kept confidential, and their personal information would not be mentioned anywhere. Informed written consent of the patients was also obtained from the patients.

Throughout the study, except for the administration of atorvastatin alone or atorvastatin with carnitine, no additional intervention was performed on the patients. In addition, the cost of the drugs used in the study and the relevant tests was provided by the project implementer and supported by the vice chancellor of TUOMS, and no additional charges were received from patients and their families.

Results

General study characteristics: In the atorvastatin group, 10 (40.0%) and 15 (60.0%) of the patients were men and women, respectively. Moreover, in the atorvastatin plus carnitine group, 15 (60.0%) and 10

(40.0%) of the patients were men and women, respectively. There was no significant difference regarding gender between the two groups ($P = 0.258$).

The mean age of the patients was 50.08 ± 12.90 and 47.12 ± 13.18 years in the atorvastatin group and in the atorvastatin plus carnitine group, respectively. The two groups did not have a significant difference in terms of their mean age ($P = 0.426$).

Lipid profile of the patients: The mean of TG level in the two groups was not significantly different at the beginning of the study ($P = 0.780$). After intervention for six months, the level of TG in the atorvastatin plus carnitine group was considerably lower than that of atorvastatin group ($P = 0.002$) (Figure 1). Furthermore, the mean total cholesterol level in the two groups was not significantly different at the beginning of the study ($P = 0.371$).

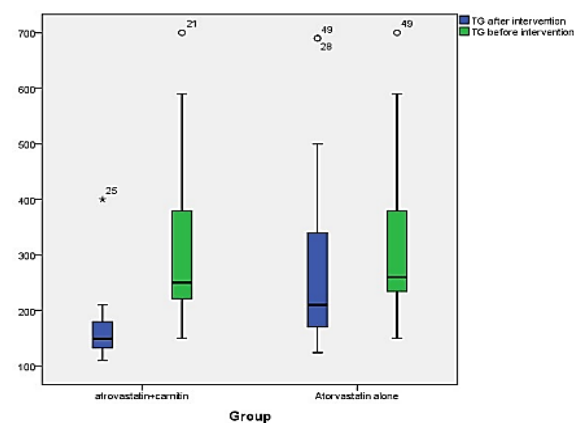


Figure 1. Comparison of triglyceride (TG) level before and after intervention

However, after treatment, total cholesterol level was significantly lower in the atorvastatin plus carnitine group compared to that of the atorvastatin group ($P = 0.024$) (Figure 2).

In addition, the mean LDL and HDL levels in the two groups were not significantly different at the beginning of the study ($P = 0.183$ and $P = 0.296$, respectively). On the other hand, after intervention, the LDL and HDL levels were significantly lower in the atorvastatin plus carnitine-treated group in comparison to the other one ($P = 0.001$ and $P = 0.001$, respectively) (Figures 3 and 4).

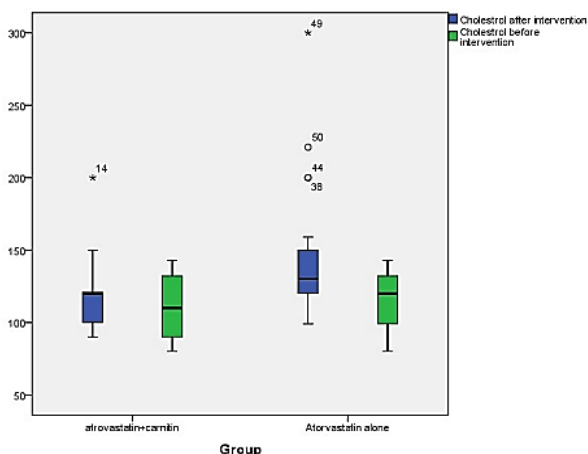


Figure 2. Comparison of patients' total cholesterol levels before and after intervention

Moreover, the mean of haemoglobin level in the two study groups was not significantly different at the beginning of the study ($P = 0.765$).

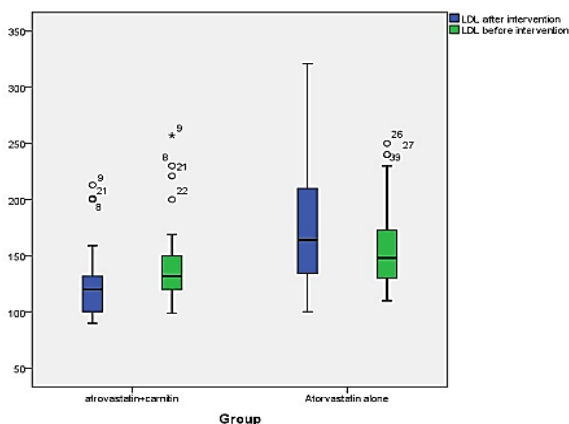


Figure 3. Comparison of low-density lipoprotein (LDL) level before and after intervention

However, after intervention for six months, haemoglobin levels were

significantly higher in the atorvastatin plus carnitine group compared to the atorvastatin alone group ($P = 0.032$). During the study, no significant side effect of carnitine or atorvastatin was reported (Table 1).

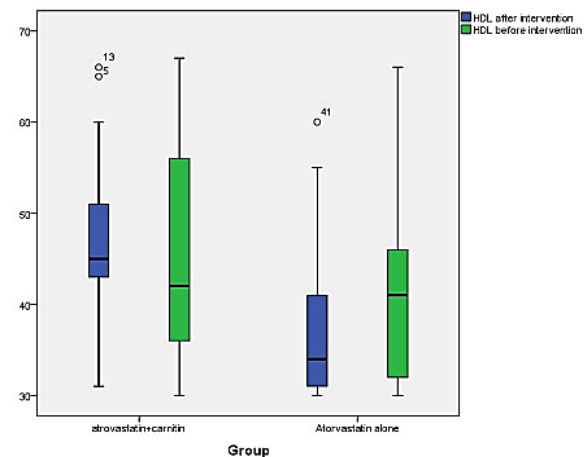


Figure 4. Comparison of high-density lipoprotein (HDL) level of patients before and after intervention

Discussion

The Global Burden of Disease Study (GBD) stated renal failure as one of the three leading causes of death in the world.¹⁴ Mortality in patients with CKD is associated with a combination of socioeconomic causes, related illnesses, modalities for renal replacement therapy, and kidney failure itself. Furthermore, CVDs are more common than the general population and are a common cause of death in these patients. CKD causes the impairment of production of many major enzymes and receptors involved in the metabolism of lipoproteins, especially HDL which leads to dyslipidemia in these patients.

Table 1. Comparison of the studied variables in the two study groups before and after intervention

Variables	Group	Time	Atorvastatin group (n = 25)	Atorvastatin + carnitine group (n = 25)	P
TG (mg/dl)		Before intervention	319.96 ± 131.66	309.24 ± 138.10	0.780
		After intervention	273.28 ± 156.32	163.12 ± 57.74	0.002
Total cholesterol (mg/dl)		Before intervention	115.40 ± 20.19	109.96 ± 22.36	0.371
		After intervention	142.32 ± 46.24	118.36 ± 22.11	0.024
LDL (mg/dl)		Before intervention	161.60 ± 42.87	145.68 ± 40.37	0.183
		After intervention	176.64 ± 59.88	126.16 ± 34.06	0.001
HDL (mg/dl)		Before intervention	41.96 ± 10.49	45.32 ± 11.96	0.296
		After intervention	37.32 ± 8.62	47.12 ± 8.89	0.001
Haemoglobin (g/dl)		Before intervention	9.81 ± 1.32	9.75 ± 1.40	0.765
		After intervention	9.93 ± 1.45	10.98 ± 8.89	0.032

TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Reduced activity of lipoprotein lipase or hepatic TG lipase has also been reported in CKD patients increasing plasma TG level.^{15,16} Moreover, carnitine deficiency, which is commonly found in hemodialysis patients, is an important contributing factor to uremic hyperlipidemia.¹⁷ Carnitine is a natural substance with the main physiological role to transfer long-chain fatty acids from the cytoplasm in order to the mitochondria for their beta-oxidation. Therefore, the presence of sufficient amounts of carnitine in the cells is essential for the normal metabolism of fatty acids in the human body.¹⁸

In this study, it was shown that administration of atorvastatin plus carnitine for six months significantly lowered the TG, cholesterol, and LDL levels compared to atorvastatin alone. In addition, treatment with this combination increases the level of HDL and haemoglobin among patients with CKD which is remarkably higher than that of atorvastatin alone.

Similarly, in a study by Fukami et al.¹⁹ it was revealed that intravenous administration of carnitine for 1 to 4 weeks decreased serum free fatty acids and increased HDL. The results of this study were consistent with the those of the current study.

In another study, Wanner et al. examined the effect of atorvastatin (20 mg/day) on 1255 hemodialysis patients with type 2 diabetes mellitus (DM) and compared it with placebo. The results of this study showed that after four weeks of treatment, LDL levels decreased by 42% in patients receiving atorvastatin, compared to a 1.3% decrease in the placebo group.²⁰ However, in the present study, the effects of simultaneous administration of atorvastatin and carnitine were compared with those of atorvastatin alone. Accordingly, after six months of receiving the relevant treatments, the lipid profile and haemoglobin profile of the patients in the carnitine-recipient group were significantly better than the other group.

In a study, Chen et al. reviewed the effect of carnitine on the lipid profile in patients with renal failure. In this study, 49 clinical

trials with 1734 patients were studied. The results of this study showed that carnitine significantly decreased the level of LDL, with no change in the level of TG, HDL, haemoglobin, and hematocrit (HCT) among patients with CKD. Moreover, no side effects were reported with L-carnitine use.²¹

On the other hand, Makhlogh et al. conducted a study to investigate the effect of carnitine on the lipid profile of hemodialysis patients suffering from heart disease. However, the results of this study showed that administration of carnitine for three months did not affect serum lipid levels in hemodialysis patients.²²

Furthermore, in another study by Ahmadi et al., it was showed that supplementation with carnitine (1 g/day) for three months did not change the mean TG as well as total cholesterol levels and serum total antioxidant capacity compared to the control group. However, it significantly reduced LDL cholesterol compared to the other group.²³

Conclusion

In conclusion, based on the results of this study and most studies in this field, the use of carnitine is an effective and safe method for treatment of dyslipidemia and also improvement of anaemia in hemodialysis patients. Moreover, its use in combination with atorvastatin is an appropriate strategy for management of dyslipidemia among patients with CKD. Some of the discrepancies observed in this regard are due to differences in sample selection and study method, duration of treatment, as well as the variables studied. Due to the lack of definitive findings in medical reference books, further studies in this field is necessary for better decision making.

Acknowledgments

The authors would like to appreciate all the patients for their contribution to the study and patience throughout the work.

Authors' Contribution

Study concept and design: Hamid Noshad, Majid Montazer

Acquisition of data: Davoud Mohammadi Nejhad, Parastou Hoseini, Majid Montazer, Behnaz Ghamari, Farid Karkon Shayan

Analysis and interpretation of data: Farid Karkon Shayan

Drafting of the manuscript: Davoud Mohammadi Nejhad, Parastou Hoseini, Majid Montazer, Behnaz Ghamari, Farid Karkon Shayan

Critical revision of the manuscript for important intellectual content: Hamid Noshad, Majid Montazer

Statistical analysis: Farid Karkon-Shayan

Administrative, technical, and material support: Hamid Noshad, Majid Montazer

Study supervision: Hamid Noshad, Majid Montazer.

References

1. Lynch KE, Feldman HI, Berlin JA, Flory J, Rowan CG, Brunelli SM. Effects of L-carnitine on dialysis-related hypotension and muscle cramps: a meta-analysis. *Am J Kidney Dis* 2008; 52(5): 962-71. DOI: 10.1053/j.ajkd.2008.05.031
2. Siami G, Clinton ME, Mrak R, Griffis J, Stone W. Evaluation of the effect of intravenous L-carnitine therapy on function, structure and fatty acid metabolism of skeletal muscle in patients receiving chronic hemodialysis. *Nephron* 1991; 57(3): 306-13. DOI: 10.1159/000186280
3. Schreiber BD. Debate forum: Levocarnitine therapy is rational and justified in selected dialysis patients. *Blood Purif* 2006; 24(1): 128-39. DOI: 10.1159/000089449
4. Fouque D, Holt S, Guebre-Egziabher F, Nakamura K, Vianey-Saban C, Hadj-Aissa A, et al. Relationship between serum carnitine, acylcarnitines, and renal function in patients with chronic renal disease. *J Ren Nutr* 2006; 16(2): 125-31. DOI: 10.1053/j.jrn.2006.01.004
5. Duranay M, Akay H, Yilmaz FM, Senes M, Tekeli N, Yucel D. Effects of L-carnitine infusions on inflammatory and nutritional markers in haemodialysis patients. *Nephrol Dial Transplant* 2006; 21(11): 3211-4. DOI: 10.1093/ndt/gfl356
6. Caruso U, Cravotto E, Tisone G, Elli M, Stortoni F, D'Iddio S, et al. Long term treatment with L-carnitine in uremic patients undergoing chronic hemodialysis: Effects on the lipid pattern. *Curr Ther Res Clin Exp* 1983; 33(6): 1098-104.
7. Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R, Jr., et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: A report from the Managing Dyslipidemias in Chronic Kidney Disease Work

Funding

This paper is based on the specialty dissertation conducted by Davoud Mohammadi Nejhad (94/3-12/41) submitted to the Chronic Kidney Disease Research Center, Tabriz University of Medical Sciences.

Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This RCT was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences under ethics code of TBZMED.REC.1394.767.

- Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant* 2004; 4(Suppl 7): 13-53. DOI: 10.1111/j.1600-6135.2004.0355.x
8. Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia associated with chronic kidney disease. *Open Cardiovasc Med J* 2011; 5: 41-8. DOI: 10.2174/1874192401105010041
9. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culeton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003; 42(5): 1050-65. DOI: 10.1161/01.HYP.0000102971.85504.7c
10. Afshar R, Sanavi S, Salimi J. Epidemiology of chronic renal failure in Iran: A four year single-center experience. *Saudi J Kidney Dis Transpl* 2007; 18(2): 191-4.
11. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 2013; 19(5): 576-85. DOI: 10.1038/nm.3145
12. Borum PR. Changing perspective of carnitine function and the need for exogenous carnitine of patients treated with hemodialysis. *Am J Clin Nutr* 1996; 64(6): 976-7. DOI: 10.1093/ajcn/64.6.976
13. Suchitra MM, Ashalatha VL, Sailaja E, Rao AM, Reddy VS, Bitla AR, et al. The effect of L-carnitine supplementation on lipid parameters, inflammatory and nutritional markers in maintenance hemodialysis patients. *Saudi J Kidney Dis Transpl* 2011; 22(6): 1155-9.

14. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 381(9882): 1987-2015. DOI: 10.1016/S0140-6736(13)61097-1
15. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical activity and mortality in chronic kidney disease (NHANES III). *Clin J Am Soc Nephrol* 2009; 4(12): 1901-6. DOI: 10.2215/CJN.01970309
16. Kaysen GA. Lipid and lipoprotein metabolism in chronic kidney disease. *J Ren Nutr* 2009; 19(1): 73-7. DOI: 10.1053/j.jrn.2008.10.011
17. Hurot JM, Cucherat M, Haugh M, Fouque D. Effects of L-carnitine supplementation in maintenance hemodialysis patients: a systematic review. *J Am Soc Nephrol* 2002; 13(3): 708-14.
18. Malaguarnera M, Vacante M, Avitabile T, Malaguarnera M, Cammalleri L, Motta M. L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes. *Am J Clin Nutr* 2009; 89(1): 71-6. DOI: 10.3945/ajcn.2008.26251
19. Fukami K, Yamagishi S, Sakai K, Nasu M, Okuda S. Effects of switching from oral administration to intravenous injection of l-carnitine on lipid metabolism in hemodialysis patients. *Clin Kidney J* 2014; 7(5): 470-4. DOI: 10.1093/ckj/sfu082
20. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; 353(3): 238-48. DOI: 10.1056/NEJMoa043545
21. Chen Y, Abbate M, Tang L, Cai G, Gong Z, Wei R, et al. L-Carnitine supplementation for adults with end-stage kidney disease requiring maintenance hemodialysis: A systematic review and meta-analysis. *Am J Clin Nutr* 2014; 99(2): 408-22. DOI: 10.3945/ajcn.113.062802
22. Makhlogh A, Jamshidi M, Mokheri V. The effect of carnitine on serum lipids in hemodialysis patients with heart failure. *J Sabzevar Univ Med Sci* 2006; 12(1): 14-8. [In Persian].
23. Ahmadi S, Mozaffari-Khosravi H, Dehghan-bonadaki S, Noori-majelan N, Lotfi M. The effect of oral L-carnitine supplementation on lipid profiles and antioxidant status in hemodialysis patients: A randomized clinical trial. *J Shahid Sadoughi Univ Med Sci* 2016; 24(1): 93-101. [In Persian].