Research Article

Effect of Oral L-carnitine Supplementation on the Mortality Markers in Hemodialysis Patients

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ABSTRACT

Hemodialysis (HD) is a process of purifying the blood of a person whose kidneys are not working normally. HD patients have high mortality rate compared with general population. Serum albumin, alkaline phosphatase, white blood cell count and monocyte count were recognized as mortality markers in HD patients. L-carnitine is small endogenous molecule that its level tends to be low in HD patients. Reduced L-carnitine input in HD patients, due to low intake, impaired absorption, and reduced L-carnitine biosynthesis by kidney, combined by absence the homeostatic control of the kidney is probably behind low L-carnitine level in HD patients. This study aimed to evaluate the effect of oral L-carnitine supplementation on the mortality markers in HD patients. In this controlled clinical trial, 40 HD patients, maintained at least 6 months on HD, were randomly allocated into 2 groups: L-carnitine group in which the HD patients supplemented daily with 1000mg oral L-carnitine and control group in which the HD patients just observed (without L-carnitine supplementation), 8 weeks for both group. Blood was taken from all patients at start of study and after 8 weeks to measure the level of serum albumin, ALP, and both WBC and monocyte counts. This study showed a non-significant effect on all studied mortality markers by L-carnitine supplementation, so it can be concluded that oral L-carnitine supplementation has limited benefit to improve mortality markers in hemodialysis patients.

Keywords: Hemodialysis, L-carnitine, mortality markers.

INTRODUCTION

Chronic kidney disease (CKD) defined as progressive loss of kidney functions occurring over several months to years. Based on structural kidney damage and/or change in the glomerular filtration rate (GFR), National Kidney Foundation (NKF) staged the CKD into five stages: stage 1 to stage 5 [1]. In stage 5 CKD; there is a complete or almost a complete failure of kidneys so that patients cannot stay a live without the intervention with one of the three modalities of renal replacement therapy (RRT): hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation [2]. Hemodialysis is process that facilitates removal of excess water and toxins from the body by removing the blood from the patient to a special machine (artificial kidney) and then returning it to the patient's bloodstream [3].

In spite the large improvement over the past decades, it still mortality rate in HD patients is at least six to seven times than general population, even after adjustment of the age, gender, race, and primary cause of death, and only 50 % of dialysis patients are still alive three years after start of dialysis therapy[4]. Cardiovascular diseases, collectively, are the major cause of death and contribute to about half of deaths in this population[5]. The risk of death due to CVD in HD patients is about 10 to 30 times than general population[6]. Infection is the second highest cause of death in HD patients[7].

Over past years, many molecules or laboratory findings were recognized to be as mortality markers in HD patients, for example; C-reactive protein[8], alkaline phosphatase[9, 10], low albumin[11], white blood cell (WBC) count[12], and monocyte count[13]. Actually, all the above mentioned mortality markers are also inflammatory markers which reflect the vital role of the inflammation in contributing to the mortality in this population. L-carnitine is endogenous, low molecular weight (161.2KDa), polar, and highly soluble compound that found in all animal species, in many microorganisms, and in many plants[14]. L-carnitine plays a vital role in fatty acid oxidation, by facilitating transport of long chain fatty acids across the inner mitochondrial membrane to matrix of mitochondria, where fatty acid oxidation occurs[14]. L-carnitine also involved in modulation of the acyl CoA / CoA ratio in cellular compartments, in shuttling of short and medium chain acyl groups from peroxisomes to mitochondria, and in removal of excess and unwanted acyl groups from the body[15-17]. The Long term hemodialysis treatment is associated with significant reduction in plasma L-carnitine[15]. Because of low molecular weight, high hydrophilicity, and lack of protein binding, L-carnitine is extensively removed by the HD process, and about 74% of plasma L-carnitine lost in each dialysis session[18]. However, combination of reduced L-carnitine input in HD patients by one or more of impaired absorption, reduced intake of L-carnitine, and reduced L-carnitine biosynthesis by kidney with the absence the

homeostatic control of the kidneys is probably behind the reduced L-carnitine level in this population[19].

This study aimed to evaluate the effect of oral L-carnitine supplementation on the mortality markers in HD patients.

METHODS

This study was designed as multicenter randomized controlled clinical trial with 8 weeks follow up period at dialysis units in Al-Yarmouk teaching hospital, Al-Kindi general teaching hospital, and Al-karama teaching hospital. The HD patients were randomly allocated into 2 groups: control group in which the HD patients just observed for 8 weeks (without L-carnitine supplementation), and L-carnitine group in which the HD patients receive L-carnitine tablet 1000 mg daily. Every 4 weeks, at maximum, patients in L-carnitine group were observed and asked for presence of any unusual side effects for L-carnitine.

Fourty patients of both sexes, which were on hemodialysis for at least 6 months, were included in this study. Patients younger than 40 years old, smokers, those with acute or chronic liver disease, signs of infection, cancer, and those using steroids or statins were excluded from participation in this study.

Serum ALP and albumin were measured using chemistry analyzer, cobas c311, made by Roche Diagnostic. Hematological investigation of WBC count, and monocyte count were measured by automated hematology analyzer, CELL-DYN Ruby, manufactured by Abbott Diagnostics.

Results

This study clearly showed that there was no significant difference in demographic data between the control group and L-carnitine treated group as shown in (Table 1).

In addition to that there was no significant difference within the studied parameters at the baseline levels of albumin; Alkaline Phosphatase; WBC count; and monocytes count as comparing between the control group and L-carnitine treated group (Table 2)

Regarding the effects of supplementation of 1000 mg/day L-carnitine for 8 weeks showed no significant difference on all mortality markers (albumin; Alkaline Phosphatase; WBC count; and monocytes count) as compared with pre-treatment values within the same group (Table 3).

The same results were obtained in control group after 8 weeks of observation, except there was a significant increment in Alkaline Phosphatase levels as compared with baseline levels (Table 4).

While the results of supplementation of 1000 mg/day L-carnitine for 8 weeks showed no significant difference on all mortality markers, as compared with control group for the same duration of treatment (Table 5).

Table 1: Demographic data & baseline characteristic of patients

Parameter	L-carnitine group	Control group	P value
Age(year)	52.36 ± 6.9	56.26 ± 9.4	0.086
F/M Ratio	0.42	0.81	0.327
Diabetes(N) %	(4) 20%	(6) 30%	0.465
Hypertension(N) %	(16) 80%	(15) 75%	0.705
Months on dialysis	30.22± 22.06	27.06± 18.92	0.378
Patients with symptomatic atherosclerosis disease (N) %	(1) 5%	(1) 5%	1

Table 2: Baseline difference between control and L-carnitine group

Parameter	L-carnitine group	Control group	P value
Albumin (gm/dL)	3.37 ± 0.40	3.35 ± 0.34	0.858
ALP (U/L)	145.5±120.8	106.2 ± 79.1	0.417
WBC (103 cell/µL)	6.07 ± 3.03	6.65 ± 2.47	0.417
Monocyte (103 cell/µL)	0.478 ± 0.165	0.588 ± 0.349	0.358

Values are presented as mean ± SD

Table 3: Effect of 8 week of supplementation with L-carnitine on the mortality markers in L-carnitine group

Parameter	Pre-treatment	Post-treatment	P value
Albumin (gm/dL)	3.37 ± 0.40	3.38 ± 0.43	0.502
ALP (U/L)	145.5±120.8	153.9 ±117	0.490
WBC (103 cell/µL)	6.07 ± 3.03	5.86 ± 2.159	0.627
Monocyte (103 cell/µL)	0.478 ± 0.165	0.467± 0.188	0.627

Values are presented as mean ± SD

Table 4: Effect of 8 of no supplementation with L-carnitine on the mortality markers in control group

Parameter	baseline	After 8 weeks	P value
Albumin (gm/dL)	3.35 ± 0.34	3.40± 0.38	0.602
ALP (U/L)	106.2 ± 79.1	125.5 ± 72.4 *	0.035
WBC (103 cell/µL)	6.65 ± 2.47	7.03 ± 2.051	0.402
Monocyte (103 cell/µL)	0.588 ± 0.349	0.586 ± 0.211	0.490

Values are presented as mean ± SD

Table 5: Difference in the effect on mortality markers between treated and control group

Parameter	L-carnitine group	Control group	P value
Change in albumin	0.0015 ± (0.347)	0.047± (0.396)	0.705
Change in ALP	8.3 ± (37.54)	19.4 ± (46.13)	0.091
Change in WBC	0.208 ± (1.776)	0.384 ± (1.999)	0.329
Change in Monocyte	0.011 ± (0.132)	0.0012 ± (0.302)	0.194

Values are presented as mean ± SD

DISCUSSION

Many studies confirmed that the low serum albumin is prevalent and associated with higher mortality in HD patients[11, 20-23]. Malnutrition and inflammation are the main incriminated causes behind low serum albumin in HD patients[24-26]. Theoretically, L-carnitine could improve inflammation & malnutrition due to its anti-inflammatory, anabolic, and protein balance improving effects[27, 28]. However, in reality, the results of studying L-carnitine supplementation on the serum albumin in HD patients are inconsistent. While Savica et al[28], Duranay et al[29] , and Vesela et al[30] found that the intravascular L-carnitine administration had improved serum albumin in HD patients, Suchitra et al[31] and Ahmad et al[32] reported that there is no effect of intravenous L-carnitine on serum albumin. The most reasonable explanation of this inconsistency is that the inflammation & malnutrition are not well adjusted or even not adjusted at all, at least in some of these studies. I n this presented study, the oral route was used for L-carnitine administration; therefore, whatever the results of this study were, they should not be compared with results from studies in which intravascular L-carnitine is used because the large metabolic and pharmacokinetic differences between the two route[19]. Before this study, two studies had evaluated serum albumin after oral L-carnitine administration in HD patients which are Orasan et al and Mortazavi et al, and their results regarding serum albumin are compatible with the result of this study[33, 34].

Regardless of the cause, the elevated ALP in HD patients had found to be associated with many bad outcomes including secondary hyperparathyroidism[35], reduced left ventricular ejaculation fraction[36], left ventricular hypertrophy[37], and the more importantly, increased mortality & hospitalization rate[9, 38-40]. Based on the claiming that L-carnitine has ability to reduce ALP levels in many animal studies[41-44], this study has tried to evaluate the effect of oral L-carnitine on the ALP levels in HD patients. After 8 weeks, the result of this study showed a significant increase (p=0.035) in ALP levels in the control group and only miner insignificant (p=0.490) increase at L-carnitine group, compared with their baseline. Although this study had showed that there is no significant (p=0.091) difference in ALP levels between L-carnitine group & control group after 8 weeks, It is not impossible to assume L-carnitine supplementation had prevented the significant increase in ALP level that occur in the control group. No identical studies are available to compare the result of this study on serum ALP with them. However there is a one, although not identical but it is relatively similar study in which the effect of L-carnitine on secondary hyperparathyroidism and bone metabolism in HD Patients has been evaluated[45]. Over six months in this close study, the L-carnitine had been given intravenously for 44 HD patients while placebo for another 39 HD patients. One of the assessed parameters between the two groups was bone alkaline phosphatase (b-ALP), which represents a significant portion of the total ALP[46] that measured in the presented study. As with presented study, there is insignificant difference in b-ALP between L-carnitine group & control group after six months, but in contrast to presented study, there was significantly decrease in b-ALP in both L-carnitine group & control group[45]. The limitation of the presented study on ALP result is that although all the patients at the start of enrollment in this study had reported, by data sheet, that they are taking vitamin D analogous (alfacalcidol) which reduce plasma ALP by reduction of plasma b-ALP[47, 48] but the dose and compliance with alfacalcidol are not checked throughout or at the end of the this study.

In 2003, Hsu et al had found that WBC count could predict one year mortality in hemodialysis patients[12]. Although it is only one study, but its result is compatible with the fact that WBC count is inflammatory marker and the inflammation contribute to the all-cause and cardiovascular mortality in HD patients[49, 50]. The result of Hsu et al study also consistent with the results of studies that correlate WBC count with mortality & CVD in the

general population[51-54], and in populations close to HD patients (patients on peritoneal dialysis and patients with CKD not on dialysis)[55, 56]. Based on papers that claimed the ability of L-carnitine supplementation to decrease the inflammatory markers levels in HD patients[29, 31, 57, 58], the presented study had investigated the effect of 1000mg oral L-carnitine/day for 8 weeks on WBC count in HD patients. After 8 weeks, the presented study had revealed that WBC count decreased (3.43%) in L-carnitine group, while it increased (5.78%) in the control group, compared with their baselines. However, WBC count in L-carnitine group had no statistically significant difference (P=0.329) from the WBC count in control group (P=0.329). The result of this study on WBC count is consistent with the two studies that had evaluated the WBC count after L-carnitine administration in HD patients and their results were insignificant change in WBC count after L-carnitine administration, although in these two studies the L-carnitine given intravenously and for six month[29, 59].

Monocyte count is associated with atherosclerosis, CVD, and increased mortality in the general population[60-67]. Recently, 3 studies evaluated the correlation of mortality and CVD with monocyte count in CKD and HD patients[13, 68, and 69]. While Kato et al found that monocyte count is independent predictor of long term mortality in chronic HD patients[13], Heine et al reported that a higher number of CD14++CD16+ monocyte subset rather than total monocyte count is associated with cardiovascular events and death in HD patients[69]. However, the presented study had evaluated the effect of oral L-carnitine on total monocyte count in HD patients and its result revealed that although the percent of reduction of monocyte count was 11.3 times higher in L-carnitine group than control group, but difference in the monocyte count between the two groups was statistically insignificant (P= 0.194). Although no identical study is available to compare with its result, but this result is consistent with effect of L-carnitine on the other assessed inflammatory markers (CRP, WBC count, and low albumin) in this presented study i.e. insignificant change after 8 weeks of oral 1000mg of L-carnitine.

CONCLUSION

Daily 1000 mg oral L-carnitine supplementation has limited benefit to improve mortality markers (Albumin, ALP, WBC and monocyte count) in hemodialysis patients.

REFERENCES

1. Kidney disease: Improving Global Outcomes (KDIGO) CKD Work Group, KIDGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, *Kidney International*, Supplement, 2013, 3, 1-150.
2. Schonder KS, Chronic and end-stage renal disease, in: ChisholmBurns MA, Wells BJ, Schwinghammer TL, Malone PM, Kolesar JM, Rotschafer JC, DiPiro JT, editors, Pharmacotherapy: principle & practice, China, McGrawHill Companies Inc, 2008, 467-500.
3. Munar MY, Renal dialysis, In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors, Applied therapeutics: the clinical use of drugs, 10th Edition, China, Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013, 797-826.
4. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, Kasiske B, Kutner N, Liu J, St Peter W, Guo H, Gudtafson S, Heubner B, Lamb K, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L, 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & endstage renal disease in the United States, *Am J Kidney Dis*, 2012 Jan, 59 (1 Suppl 1), A7, e1-420.
5. AlDadah A, Omran J, Nusair MB, Dellsperger KC, Cardiovascular mortality in dialysis patients, *Advances in peritoneal dialysis,* 2012, 28, 56-9.
6. [6 Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, *Klag MJ*, Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study, *J Am SocNephrol,* 2002 Jul, 13(7), 1918-27.
7. Wakasugi M, Kawamura K, Yamamoto S, Kazama JJ, Narita I, High mortality rate of infectious diseases in dialysis patients: a comparison with the general population in Japan, *TherApher Dial*, 2012 Jun, 16(3), 226-31.
8. Kawaguchi T, Tong L, Robinson BM, Sen A, Fukuhara S, Kurokawa K, *Canaud B, Lameire N, Port FK, Pisoni RL,* Creactive protein and mortality in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS), *Nephron,* 2011, 117(2), c167-78.
9. Yamashita T, Shizuku J, Ohba T, Kabaya T, Nitta K, Serum alkaline phosphatase levels and mortality of chronic hemodialysis patients, *International Journal of Clinical Medicine*. 2011, 2, 388-393.
10. Damera S, Raphael KL, Baird BC, Cheung AK, Greene T, Beddhu S, Serum alkaline phosphatase levels associate with elevated serum Creactive protein in chronic kidney disease, *Kidney Int,* 2011 Jan, 79(2), 228-33.
11. De Mutsert R, Grootendorst DC, Indemans F, Boeschoten EW, Krediet RT, Dekker FW, *et al*. Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition, *J RenNutr*, 2009 Mar, 19(2), 127-35.
12. Hsu CW, Lin JL, LinTan DT, Yen TH, Chen KH, White blood cell count predicts all cause, cardiovascular disease cause and infection cause one year mortality of maintenance hemodialysis patients, *Ther Apher Dial,* 2003 Dec, 14(6), 552-9.
13. Kato A, Takita T, Furuhashi M, Maruyama Y, Kumagai H, Hishida A, Blood monocyte count is a predictor of total and cardiovascular mortality in hemodialysis patients, *Nephron Clin Pract,* 2008, 110, c235 – c243.
14. Bremer J, Carnitine metabolism and functions, *Physiol Rev,* 1983 Oct, 63(4), 1420-80.
15. Reuter SE, Evans AM, Carnitine and acylcarnitines: pharmacokinetic, pharmacological and clinical aspects, *Clin Pharmacokinet,* 2012 Sep 1, 51(9), 553-72.
16. Reuter SE, Faull RJ, Evans AM, L-carnitine supplementation in the dialysis population: are Australian patients missing out? *Nephrology (Carlton),* 2008 Feb, 13(1), 3-16.
17. Rebouche CJ, L-Carnitine and Acetyl L-Carnitine, In: Coates PM, Blackman MR, Mark GC, Moss LJ, White JD, editors, Encyclopedia of dietary Supplements, New York, Marcel Dekker, 2005, 73-80.
18. Evans AM, Faull R, Fornasini G, Lemanowicz EF, Longo A, Pace S, Nation RL, Pharmacokinetics of L-carnitine in patients with end-stage renal disease undergoing long-term hemodialysis, *Clin Pharmacol Ther,* 2000 Sep, 68(3), 238-49.
19. Evans A, Dialysis-related carnitine disorder and levocarnitine pharmacology, *A m J Kidney Dis,* 2003 Apr, 41(4 Suppl 4), S13-26.

20. Lowrie EG, Lew NL, Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities, *Am J Kidney Dis,* 1990 May, 15(5), 458-82.

21. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM, The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis, *N Engl J Med,* 1993 Sep 30, 329(14), 1001-6.

22. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE, Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease, *J Am SocNephrol,* 1996 May, 7(5), 728-36.

23. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H, Jr, Kopple JD, Greenland S, Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction, *Nephrol Dial Transplan,* 2005 Sep, 20(9), 1880-8.

24. Kim Y, Molnar MZ, Rattanasompattikul M, Hatamizadeh P, Benner D, Kopple JD, Kovesdy CP, Kalantar-Zadeh K, Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis, *Int Urol Nephrol,* 2013 Feb, 45(1), 215-27.

25. Thijssen S, Wystrychowski G, Usvyat L, Kotanko P, Levin NW, Determinants of serum albumin concentration analyzed in a large cohort of patients on maintenance hemodialysis, *J RenNutr,* 2007 Jan, 17(1), 70-4.

26. Kaysen GA, Dubin JA, Muller HG, Rosales L, Levin NW, Mitch WE, Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients, *Kidney Int,* 2004 Apr,65(4), 1408-15.

27. Silverio R, Laviano A, Rossi Fanelli F, Seelaender M, L-carnitine and cancer cachexia: Clinical and experimental aspects, *J Cachexia Sarcopenia Muscle,* 2011 Mar, 2(1), 37-44.

28. Savica V, Santoro D, Mazzaglia G, Ciolino F, Monardo P, Calvani M, Bellinghieri G, Kopple JD, L-carnitine infusions may suppress serum C-reactive protein and improve nutritionalstatus in maintenance hemodialysis patients, *J RenNutr,* 2005 Apr, 15(2), 225-30.

29. 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 Nov, 21(11), 3211-4.

30. Vesela E, Racek J, Trefil L, Jankovy'ch V, Pojer M, Effect of L-carnitine supplementation in hemodialysis patients, *Nephron,* 2001 Jul, 88(3), 218-23.

31. Suchitra MM, Ashalatha VL, Sailaja E, Rao AM, Reddy VS, Bitla AR, Sivakumar V, Rao PV, The effect of L-carnitine supplementation on lipid parameters, inflammatory and nutritional markers in maintenance hemodialysis patients, *Saudi J Kidney Dis Transpl,* 2011 Nov, 22(6), 1155-9.

32. Ahmad S, Robertson HT, Golper TA, Wolfson M, Kurtin P, Katz LA, Hirschberg R, Nicora R, Ashbrook DW, Kopple JD, Multicenter trial of L-carnitine in maintenance hemodialysis patients, II, Clinical and biochemical effects, *Kidney int,* 1990 Nov, 38(5), 912-8.

33. Orasan R, Awon R, Racasan S, Patiu IM, Samasca G, Kacso IM, Caprioara MG, Effects of L-carnitine on endothelial dysfunction, visfatin, oxidative Sterss, inflammation and anemia in hemodialysis patients, *ActaEndocrinologica (Buc),* 2011, 7(2), 219-228.

34. Mortazavi M, SeirafianS, Eshaghian A, Ghassami M, Taheri S, Atapour A, Hassanzadeh A, Bayat A, Moinzadeh F, Associations of oral L-carnitine with hemoglobin, lipid profile, and albumin in hemodialysis patients, *Journal of Research in Medical Sciences,* 2012, 17 (Special Issue, Part 1, Clinical trial), S33-S37.

35. Petrauskiene V, Bumblyte IA, Kuzminskis V, Sepetauskiene E, Early risk factors for secondary hyperparathyroidism in hemodialysis patients, *Medicina (Kaunas)*, 2005, 41 Suppl 1, 44-9.

36. [36 Nasri H, Baradaran A, Naderi AS, Close association between parathyroid hormone and left ventricular function and structure in end-stage renal failure patients under maintenance hemodialysis, *Acta Med Austriaca,* 2004 Aug, 31 (3), 67-72.

37. Harnett JD, Parfrey PS, Griffiths SM, Gault MH, Barre P, Guttmann RD, Left ventricular hypertrophy in end-stage renal disease, *Nephron,* 1988, 48(2), 107-15.

38. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD, Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients, *Kidney Int,* 2006 Aug, 70(4), 771-80.

39. Regidor DL, Kovesdy CP, Mehrotra R, Rambod M, Jing J, McAllister CJ, Van Wyck D, Kopple JD, Kalantar-Zadeh K, Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients, *J Am SocNephrol,* 2008 Nov, 19(11), 2193-203.

40. Blayney MJ, Pisoni RL, Bragg-Gresham JL, Bommer J, Piera L, Saito A, Akiba T, Keen ML, Young EW, Port FK, High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death, *Kidney Int* 2008 Sep, 74(5), 655-63.

41. Hooshmand S, Balakrishnan A, Clark RM, Owen KQ, Koo SI, Arjmandi BH, Dietary L-carnitine supplementation improves bone mineral density by suppressing bone turnover in aged ovariectomized rats, *Phytomedicine,* 2008 Aug, 15(8), 595-601.

42. Mishra S., Singh RB, Effect of mushroom on the lipid profile, lipid peroxidation and liver functions of Aging Swiss Albino rats, *The open nutraceuticals journal,* 2010, 3, 248-253.

43. Elgazzar UB, Ghanema IIA, kalaba ZM, Effect of dietary L-carnitine supplementation on the concentration of circulating serum metabolites in growing new zealand rabbits, *Australian Journal of Basic and Applied Sciences,* 2012, 6(2), 80-84.

44. Gaafar AM, Yossef HE, Ibrahim HH. Protective effects of mushroom and their ethyl extract on aging compared with L-carnitine, *I nternational Journal of Nutrition and Metabolism,* 2010, 2(4), 63-69.

45. Cibulka R, Racek J, Pikner R, Rajdl D, Trefil L, Vesela E, Studenovska M, Siroka R, Effect of L-carnitine supplementation on secondary hyperparathyroidism and bone metabolism in hemodialyzed patients, *Calcif Tissue Int,* 2007 Aug, 81(2), 99-106.

46. Tibi L, Chhabra SC, Sweeting VM, Winney RJ, Smith AF, Multiple forms of alkaline phosphatase in plasma of hemodialysis patients, *C lin Chem,* 1991 Jun, 37(6), 815-20.

47. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease, *Am J Kidney Dis,* 2003 Oct, 42(4 Suppl 3), 1-201.

48. Urena P, BernardPoenaru O, CohenSolal M, de Vernejoul MC, Plasma bonespecific alkaline phosphatase changes in hemodialysis patients treated by alfacalcidol, *Clin Nephrol,* 2002 Apr, 57(4), 261-73.

49. Qureshi AR, Alvestrand A, Divino-Filho JC, Gutierrez A, Heimbürger O, Lindholm B, Bergström J, Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients, *J Am SocNephrol,* 2002, 13, S28–S36.

50. Selim G, Stojceva-Taneva O, Ivanovski N, Zafirovska K, Sikole A, Trajcevska L, Asani A, Polenakovic M, Inflammation and anaemia as predictors of cardiovascular mortality in hemodialysis patients, *Hippokratia,* 2007, 11(11), 39-43.

51. Aggelopoulos P, Chrysohoou C, Pitsavos C, Papadimitriou L, Liontou C, Panagiotakos D, Tsiamis E, Stefanadis C, Comparative value of simple inflammatory markers in the prediction of left ventricular systolic dysfunction in postacute coronary syndrome patients, *Mediators Inflamm,* 2009, Article ID 826297.

52. Madjid M, Awan I, Willerson JT, Casscells SW, Leukocyte count and coronary heart disease: implications for risk assessment, *J Am CollCardiol,* 2004 Nov 16, 44(10), 1945-56.

53. Brown DW, Ford ES, Giles WH, Croft JB, Balluz LS, Mokdad AH, Associations between white blood cell count and risk for cerebrovascular disease mortality: NHANES II Mortality Study, 19761992, *Ann Epidemiol,* 2004 Jul, 14(6), 425-30.

54. Weijenberg MP, Feskens EJ, Kromhout D, White blood cell count and the risk of coronary heart disease and allcause mortality in elderly men, *ArteriosclerThrombVasc Biol,* 1996 Apr, 16(4), 499-503.

55. Johnson DW, Wiggins KJ, Armstrong KA, Campbell SB, Isbel NM, Hawley CM, Elevated white cell count at commencement of peritoneal dialysis predicts overall and cardiac mortality, *Kidney Int,* 2005 Feb, 67(2), 738-43.

56. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K, Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease, *Am J ClinNutr,* 2009 Aug, 90(2), 407-14.

57. Shakeri A, Tabibi H, Hedayati M, Effects of L-carnitine supplement on serum inflammatory cytokines, C-reactive protein, lipoprotein (a), and oxidative stress in hemodialysis patients with Lp (a) hyperlipoproteinemia, *H emodial Int,* 2010 Oct, 14 (4), 498-504.

58. Hakeshzadeh F, Tabibi H, Ahmadinejad M, Malakoutian T, and Hedayati M, Effects of L-Carnitine supplement on plasma coagulation and anticoagulation factors in hemodialysis patients, *Ren Fail,* 2010, 32(9), 1109-14.

59. Wanic-Kossowska M, Kazmierski M, Pawliczak E, Kobelski M, Combined therapy with L-carnitine and erythropoietin of anemia in chronic kidney failure patients undergoing hemodialysis, *Pol Arch Med Wewn,* 2007 Jan-Feb, 117(12), 14-9.

60. Kim KI, Lee J, Heo NJ, Kim S, Chin HJ, Na KY, Chae DW, Kim CH, Kim S, Differential white blood cell count and all-causemortality in the korean elderly, *ExpGerontol,* 2013 Feb, 48 (2), 103-8.

61. Pinto EM, Huppert FA, Morgan K, Mrc C, Brayne C, Neutrophil counts, monocyte counts and cardiovascular disease in the elderly, *ExpGerontol*, 2004 Apr, 39(4),615-9.

62. Olivares R, Ducimetiere P, Claude JR, Monocyte count: a risk factor for coronary heart disease?, *Am J Epidemiol,* 1993 Jan 1, 137(1), 49-53.

63. Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA, White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study, *Am J Epidemiol,* 2001 Oct 15, 154(8), 758-64.

64. Hong YJ, Jeong MH, Ahn Y, Yoon NS, Lee SR, Hong SN, Moon JY, Kim KH, Park HW, Kim JH, Cho JG, Park JC, Kang JC, Relationship between peripheral monocytosis and nonrecovery of left ventricular function in patients with left ventricular dysfunction complicated with acute myocardial infarction, *Circ J,* 2007 Aug, 71(8), 1219-24.

65. Chapman CM, Beilby JP, McQuillan BM, Thompson PL, Hung J, Monocyte count, but not C-reactive protein or interleukin-6, is an independent risk marker for subclinical carotid atherosclerosis, *Stroke,* 2004 Jul, 35 (7), 1619-24.

66. Johnsen SH, Fosse E, Joakimsen O, Mathiesen EB, StenslandBugge E, Njølstad I, Arnesen E, Monocyte count is a predictor of novel plaque formation: a 7year followup study of 2610 persons without carotid plaque at baseline the Tromsø Study, *Stroke,* 2005 Apr, 36 (4), 715-9.

67. Nasir K, Guallar E, Navas-Acien A, Criqui MH, Lima JA, Relationship of monocyte count and peripheral arterial disease: results from the National Health and Nutrition Examination Survey 19992002, *ArteriosclerThrombVasc Biol*, 2005 Sep, 25(9), 1966-71.

68. Rogacev KS, Seiler S, Zawada AM, Reichart B, Herath E, Roth D, Ulrich C, Fliser D, Heine GH, 14++CD16+ monocytes and cardiovascular outcome in patients with chronic kidney disease, *Eur Heart J*, 2011 Jan, 32(1), 84-92.

69. Heine GH, Ulrich C, Seibert E, Seiler S, Marell J, Reichart B, Krause M, Schlitt A, Köhler H, Girndt M, CD14(++)CD16+ monocytes but not total monocyte numbers predict cardiovascular events in dialysis patients, *Kidney Int,* 2008 Mar, 73 (5), 622-9.

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