World Journal of Clinical Urology

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DOI: 10.5410/wjcu.v3.i3.344

World J Clin Urol 2014 November 24; 3(3): 344-350
ISSN 2219-2816 (online)

MINIREVIEWS

Vitamin C supplementation in patients on maintenance dialysis

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Received: April 27, 2014 Revised: May 28, 2014
Accepted: September 6, 2014
Published online: November 24, 2014

Abstract

As one of the most important water-soluble non-enzymatic antioxidants, vitamin C consists of ascorbic acid and its oxidized form, dehydroascorbic acid. Maintenance hemodialysis (MHD) patients have a generally lower plasma vitamin C level compared with general population. Moreover, dialysis patients also exhibit a low plasma vitamin C level, which is largely related with increased inflammation, refractory anemia and oxidative stress. In this review, we described, in great detail, the vitamin C deficiency in MHD patients and its effects on anti-oxidation, anti-inflammation, pro-oxidation and secondary hyperparathyroidism. In addition, we described the possible potential value of vitamin C in anemia, and the side effects of over-doses of vitamin C supplementation in this particular population. In summary, MHD patients may benefit from vitamin C administration. However, further research should be carried out to confirm its potential beneficial effects, optimal dosage and side effects from vitamin C supplementation.

Key words: Vitamin C; Supplementation; Maintenance dialysis; Anti-oxidation; Anti-inflammation; Anemia; Oxalosis

Core tip: In this review, we described the vitamin C deficiency in maintenance hemodialysis patients and its effects on anti-oxidation, anti-inflammation, pro-oxidation and secondary hyperparathyroidism. In addition, we described the possible potential value of vitamin C in anemia, and the side effects of over-doses of vitamin C supplementation in this particular population.

Zhang KY, Zuo L. Vitamin C supplementation in patients on maintenance dialysis. *World J Clin Urol* 2014; 3(3): 344-350 Available from: URL: http://www.wjgnet.com/2219-2816/full/v3/i3/344.htm DOI: http://dx.doi.org/10.5410/wjcu.v3.i3.344

INTRODUCTION

As one of the most important water-soluble non-enzymatic antioxidants, vitamin C consists of ascorbic acid and its oxidized form, dehydroascorbic acid. The former is easily to be oxidized into the unstable dehydroascorbic acid while exposed under chronic or acute oxidant conditions, such as in smokers and in diabetes. Humans can not synthesize ascorbate due to the lack of the gene encoding the enzyme gulonolactone oxidase, which is involved in the last step in biosynthesis of L-ascorbic acid[1]. Therefore, vitamin C can be obtained only from fresh fruits and vegetables, such as strawberry, kiwi, orange juice and broccoli.

In normal population, the plasma vitamin C level ranges from 30 to 60 μmol/L[2]. Plasma level of vitamin C in maintenance hemodialysis (MHD) patients is generally lower[3,4] compared with general population. Moreover, dialysis patients exhibit a low plasma vitamin C level, which is largely related with increased inflammation, refractory anemia, oxidative stress, and secondary hyperparathyroidism (SHPT)[5-8].

Previous investigations demonstrated that vitamin C

supplementation possesses promising effects in MHD patients, such as better improvement of oxidative stress[9,10], inflammation[11] and anemia[12,13]. Therefore, vitamin C adjuvant therapy has been highly recommended for this particular group of patients.

In this review, we described the possible contents of physiological functions of vitamin C, deficiency of vitamin C in MHD patients as well as effects of vitamin C on anti-oxidation, anti-inflammation, pro-oxidation, anemia and SHPT in MHD patients. Moreover, dosages of vitamin C supplementation and side effects of vitamin C due to its metabolite, oxalosis accumulation, were also discussed.

PHYSIOLOGICAL FUNCTIONS OF VITAMIN C

Vitamin C can act as both antioxidant and as prooxidant[9,10,14-16]. It is generally regarded as a protective antioxidant due to its direct oxyradical scavenging properties[17,18]. Recent research revealed that vitamin C plays many prominent roles, and it functions in the biosynthesis collagen, norepinephrine and carnitine as a cofactor for several enzymes[19-21]. Moreover, vitamin C also plays a key role in peptide amidation and tyrosine metabolism. In addition, vitamin C has a potential to enhance the non-heme iron absorption[22] and alter the metabolism of the iron (Fe) from inert tissue stores[12,23,24]. At the gastrointestinal tract with an alkaline pH, vitamin C provides auxiliary aids in maintaining iron in a more soluble state, which is more readily absorbed across the intestinal mucos[22,25].

Scurvy is a disease resulting from deficiency of vitamin C in diet[26]. It is preceded by certain symptoms, including increased bone resorption[27], gingival problems[28], weakness, fatigue, irritability, vague myalgias, joint pains, connective tissue disorders, mood changes and poor wound healing.

DEFICIENCY OF VITAMIN C IN MHD PATIENTS

It is well known that MHD patients have a generally lower plasma vitamin C level compared with normal population[3,4]. MHD patients exhibit remarkably low vitamin C levels in plasma, frequently < 10 μmol/L or even < 2 μmol/L[3,29]. In our previous study, a plasma vitamin C level of < 4 μg/mL (22.8 μmol/L) is presented in 64.4% dialysis patients[5]. The observed low level of plasma vitamin C might be attributed to the dietary restrictions on fruit and vegetable intake, and impaired metabolism in uremia during dialysis procedure[4,30-32], as well as increased inflammation[5], oxidative stress[6] and SHPT[8]. Previous investigations demonstrated that dialysis treatment induces a decrease in plasma vitamin C level, which is approximately reduced by 33%-50% from the baseline values[3,33] and equal to a removal of 100-300 mg vitamin C during a dialysis session[4,34]. Therefore, vitamin C deficiency might be more frequently detected in these individuals. Conventional hemodialysis (HD), on-line hemodiafiltration and high-flux hemodialysis eliminate plasma vitamin C in a similar way[5,33]. These findings could be associated with its small molecule (176.1 Da), low protein-bound and high soluble characteristic in water.

EFFECTS OF VITAMIN C ON ANTI-OXIDATION AND ANTI-INFLAMMATION IN MHD PATIENTS

Widely observed in long-term dialysis patients, oxidative stress is associated with chronic inflammation and increased mortality risk. Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species (ROS) and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage in uremic patients[35,36]. The relationship between oxidative stress and inflammation is certainly bidirectional since oxidative stress affects inflammatory status and inflammation exerts influence on the state of oxidative stress. Inflammation in uremic patients can be triggered by oxidative products during dialysis procedure, such as superoxide anion (O^{2-}) and hydrogen peroxide (H_2O_2)[37]. On the other hand, inflammation may further aggravate oxidative stress through potentiating respiratory burst activation in monocytes and neutrophils[38].

As an important anti-oxidant, vitamin C possesses beneficial effects on reducing ROS and improving inflammatory status. Acute administration of vitamin C reduces oxidant stress levels and improves NO-mediated resistance vessel dilatation in renal failure[39]. Moreover, Tarng *et al*[10] reported that in MHD patients vitamin C supplementation for 8 wk reduces the 8-OHdG level of cellular DNA, an index of oxidative DNA damage in ROS-mediated diseases[40]. Abdollahzad *et al*[9] found that malondialdehyde levels are decreased and lipid profiles are improved in MHD patients orally supplemented with 250 mg vitamin C every other day for 12 wk. In our recent crossover study, we found that the level of hypersensitive C-reactive protein (hs-CRP) in MHD patients is lowered by oral vitamin C supplementation of 200 mg/d for 3 mo, and the hs-CRP level is increased again after the vitamin C supplementation is withdrawn[11]. Considered as a co-antioxidant, vitamin C can regenerates a-tocopherol (vitamin E) from the a-tocopheroxyl radical, produced *via* scavenging of lipid-soluble radicals[41]. High doses of vitamin C administration in a low infusion rate during HD session can prevent an increase in lipid peroxidation, which might be probably associated with the enhanced rate of endogenous vitamin E regeneration[42].

However, some other studies did not show this beneficial effect in MHD patients[43-45]. For example, in Fumeron's study[45], 250 mg vitamin C is orally given to 33 MHD patients thrice weekly after each dialysis session for 2 mo, and no improved situation of oxidative/anti-oxidative stress and inflammation has been observed. Chan *et al*[44] also reported that there is no effect on markers of

oxidative stress in MHD patients after 250 mg vitamin C supplementation thrice weekly for 8 wk, either intravenously or orally. Kamgar *et al*[43] recently reported that the CRP level exhibits a decrease trend in MHD patients after an oral vitamin C supplementation of 250 mg/d for 2 mo. Similar findings have been observed by Ramos *et al*[46].

These conflicting data may be partially explained by the following reasons: (1) the inflammatory status of patients in some previous studies is altered due to daily oral vitamin C supplementation; (2) certain factors are different in the study populations, such as age, dialysis vintage, smoking status and proportion of diabetes; (3) difference in doses, duration and route of vitamin C administration; and (4) different markers of oxidative stress have been used in the above-mentioned studies.

EFFECTS OF VITAMIN C ON PRO-OXIDATION IN MHD PATIENTS

Vitamin C also acts as a pro-oxidant due to promoting Fenton chemistry, which converts the Fe^{3+} into Fe^{2+} and catalyzes the formation of ROS[47-49].

Eiselt *et al*[50] documented a pro-oxidative effect of vitamin C during intravenous iron sucrose and vitamin C administration in MHD patients. In this study, they found that intravenous administration of Fe together with vitamin C supplementation results in a greater increase in plasma thiobarbituric acid reacting substances compared with single intravenous administration of Fe. Ferretti *et al*[15] indicated that intravenous administration of vitamin C increases lipid hydroperoxides and advanced glycation end product levels and decreases paraoxonase activity in hemodialysis patients. In addition, De Vriese *et al*[16] also found similar results by oral vitamin C supplementation in MHD patients.

POTENTIAL VALUE OF VITAMIN C IN ANEMIA IN MHD PATIENTS

Although anemia management has been improved in patients with chronic kidney disease (CKD), anemia is still prevalent in these patients[51]. Approximately 35% of patients with end stage renal disease have refractory anemia[52]. This persistent anemia might be explained by relative resistance to erythropoietin (EPO) due to functional iron deficiency, which is a situation characterized by low transferrin saturation[52].

Latest study showed that the level of plasma vitamin C has a positive correlation with the hemoglobin level[53] as well as a negative correlation with the EPO resistance index[54-56], and ascorbic acid has also been used to improve response to erythropoiesis-stimulating agents. Vitamin C plays an important role in the utilization of iron from storage sites. As an electron donor, vitamin C can reduce ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) in order to mobilize storage iron, including the portion of tissue iron as hemosiderin[57], resulting in an activated iron bioavailability and enhanced production of red blood cells.

Previous work showed that ascorbic acid administration ameliorates the hemoglobin level in MHD patients with iron-overloading[12,13]. These findings have been subsequently confirmed in anemic MHD patients receiving iron administration accompanied by vitamin C[7,54,58]. However, in patients with normal iron status, the situation of EPO needs and transferrin saturation is not improved with vitamin C supplementation[12]. A recent meta-analysis[52] of the available studies indicated that vitamin C supplementation is closely related to a decreased rHuEPO dose and an increased transferring saturation, but no apparent effect on ferritin levels has been observed.

Patients on dialysis have a shortened red blood cell half-life compared with the normal level of 120 d[59,60]. A series of factors have been demonstrated to contribute to this reduced lifespan of red blood cells, including increased oxidative stress and decreased antioxidant products[60,61], the breakdown of phospholipid asymmetry in red blood cell membranes[61,62], increased level of parathyroid hormone[63,64] as well as deficiencies of carnitine[65] and zinc[66]. In addition, although the exact mechanism remains unclear, the half-life of circulating red cells might be extended by vitamin C supplementation[67].

VITAMIN C DEFICIENCY AND SHPT

SHPT is common in chronic hemodialysis patients[68], and it develops because of the increased parathyroid hormone (PTH) synthesis, secretion and the impaired renal clearance[69]. About 50% MHD patients have increased PTH levels[68]. High level of plasma PTH has been linked to uraemic toxin[70], leading to an increased cardiovascular mortality in MHD patients[71].

The effect of vitamin C on SHPT remains unknown in MHD patients. Richter *et al*[8] showed that higher level of plasma vitamin C is correlated with lower level of bio-intact PTH in MHD patients. Vitamin C has an effect on post-receptor events in the calcium-sensing receptors on parathyroid cells, which might partially explain the inverse interaction between the vitamin C level and PTH[72]. Moreover, the cyclic adenosine monophosphate response to PTH can be also enhanced by vitamin C supplementation[73]. Sanadgol *et al*[74] reported that the mean level of serum PTH is decreased in the first 2 mo compared with baseline after a 3-mo intravenous administration of vitamin C (200 mg, thrice weekly). However, this effect is gradually diminished at month 3, which might be explained by the reduced sensitivity of calcium-sensing receptors on parathyroid gland cells with the passage of time. Interestingly, Biniaz *et al*[75] did not find the beneficial effect of vitamin C on SHPT in a double blinded, placebo-controlled study in MHD patients.

DOSAGES OF VITAMIN C SUPPLEMENTATION

In healthy subjects, a daily administration of 90 mg or

75 mg vitamin C is enough for men or women, respectively[76]. For MHD patients, the recommended dosages are more controversial. Generally speaking, vitamin C supplementation is recommended for MHD patients due to the restrictions on their dietary intake as well as losses during dialysis procedure. Many clinicians only recommend vitamin C to a conservative range of 60-100 mg/d with the consideration of oxalate accumulation in the tissues of renal failure patients. These recommendation may not be optimal, because the loss of vitamin C during a single dialysis treatment may reach several hundred milligrams of vitamin C[4,34], resulting in vitamin C deficiency common in MHD patients.

Many literatures documented that the oral doses of vitamin C in the range of 100-200 mg/d[11,77-80] are considered as the sufficient and safe dosages[79], or intravenous administration of 300 to 500 mg vitamin C thrice weekly at the end of dialysis is regarded as "guidelines for intravenous ascorbic acid adjuvant therapy"[56,81,82]. However, some other studies hold a contrary opinion[83]. This conservative recommendation is mainly due to the side effects of oxalosis following the vitamin C administration.

OXALOSIS

In the past several decades, researchers have also investigated side effects of vitamin C supplementation. Since oxalate is one of the products of vitamin C metabolism, vitamin C supplementation in MHD patients may enhance oxalate plasma levels in patients with uremia. Significant plasma oxalate levels induced by vitamin C supplementation (500-1000 mg/d for 3 or more than 3 wk) have been observed[7,84-86]. Canavese *et al*[83] reported that plasma oxalate levels are progressively increased even the dosage of vitamin C is set at 500 mg/wk. The peak level is observed after 1 year of treatment, and then it is leveled off thereafter. Therefore, the safety of this protocol in terms of oxalate metabolism should be carefully considered.

However, some studies showed that this potential hazard may be prevented by taking certain measures, such as avoiding vitamin B_6 deficiency[87] and improving dialysis technology[88,89]. Tomson *et al*[88] showed that tissue oxalate accumulation is completely absent in well-dialyzed CKD patients.

CONCLUSION

Taken together, vitamin C deficiency is common in MHD patients. Therefore, vitamin C supplementation is crucial for MHD patients. Patients can potentially benefit from vitamin C supplementation by its effects on anti-oxidative stress, anti-inflammation, SHPT and improved anemia. However, vitamin C overdose should be avoided due to its secondary oxalosis.

To date, recommendations of vitamin C therapy in MHD patients can not reach consensus because of the wide use of variety of dosages, route of administration, durations and the severe side effects of oxalosis. Oral doses of vitamin C in the range of 100-200 mg/d, or intravenous administration of 300 to 500 mg vitamin C thrice weekly at the end of dialysis are commonly regarded as adequate to prevent ascorbate deficiency in MHD patients.

In summary, MHD patients may benefit from vitamin C administration. However, further large-scale randomized-controlled clinical trials should be carried out to confirm its beneficial effects, optimal dosage and side effects from vitamin C supplementation.

REFERENCES

1 **Nishikimi M**, Yagi K. Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. *Am J Clin Nutr* 1991; **54**: 1203S-1208S [PMID: 1962571]

2 **Levine M**, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. *JAMA* 1999; **281**: 1415-1423 [PMID: 10217058]

3 **Wang S**, Eide TC, Sogn EM, Berg KJ, Sund RB. Plasma ascorbic acid in patients undergoing chronic haemodialysis. *Eur J Clin Pharmacol* 1999; **55**: 527-532 [PMID: 10501823]

4 **Morena M**, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, Delcourt C, Papoz L, Descomps B, Canaud B. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. *Nephrol Dial Transplant* 2002; **17**: 422-427 [PMID: 11865087]

5 **Zhang K**, Liu L, Cheng X, Dong J, Geng Q, Zuo L. Low levels of vitamin C in dialysis patients is associated with decreased prealbumin and increased C-reactive protein. *BMC Nephrol* 2011; **12**: 18 [PMID: 21548917 DOI: 10.1186/1471-2369-12-18]

6 **Washio K**, Inagaki M, Tsuji M, Morio Y, Akiyama S, Gotoh H, Gotoh T, Gotoh Y, Oguchi K. Oral vitamin C supplementation in hemodialysis patients and its effect on the plasma level of oxidized ascorbic acid and Cu/Zn superoxide dismutase, an oxidative stress marker. *Nephron Clin Pract* 2008; **109**: c49-c54 [PMID: 18544955 DOI: 10.1159/000137628]

7 **Sirover WD**, Siddiqui AA, Benz RL. Beneficial hematologic effects of daily oral ascorbic acid therapy in ESRD patients with anemia and abnormal iron homeostasis: a preliminary study. *Ren Fail* 2008; **30**: 884-889 [PMID: 18925528 DOI: 10.1080/08860220802353884]

8 **Richter A**, Kuhlmann MK, Seibert E, Kotanko P, Levin NW, Handelman GJ. Vitamin C deficiency and secondary hyperparathyroidism in chronic haemodialysis patients. *Nephrol Dial Transplant* 2008; **23**: 2058-2063 [PMID: 18353890 DOI: 10.1093/ndt/gfn084]

9 **Abdollahzad H**, Eghtesadi S, Nourmohammadi I, Khadem-Ansari M, Nejad-Gashti H, Esmaillzadeh A. Effect of vitamin C supplementation on oxidative stress and lipid profiles in hemodialysis patients. *Int J Vitam Nutr Res* 2009; **79**: 281-287 [PMID: 20533214 DOI: 10.1024/0300-9831.79.56.281]

10 **Tarng DC**, Liu TY, Huang TP. Protective effect of vitamin C on 8-hydroxy-2′-deoxyguanosine level in peripheral blood lymphocytes of chronic hemodialysis patients. *Kidney Int* 2004; **66**: 820-831 [PMID: 15253739]

11 **Zhang K**, Li Y, Cheng X, Liu L, Bai W, Guo W, Wu L, Zuo L. Cross-over study of influence of oral vitamin C supplementation on inflammatory status in maintenance hemodialysis patients. *BMC Nephrol* 2013; **14**: 252 [PMID: 24228847 DOI: 10.1186/1471-2369-14-252]

12 **Gastaldello K**, Vereerstraeten A, Nzame-Nze T, Vanherweghem JL, Tielemans C. Resistance to erythropoietin in iron-overloaded haemodialysis patients can be overcome by

ascorbic acid administration. *Nephrol Dial Transplant* 1995; **10** Suppl 6: 44-47 [PMID: 8524494]
13 **Tarng DC**, Huang TP. A parallel, comparative study of intravenous iron versus intravenous ascorbic acid for erythropoietin-hyporesponsive anaemia in haemodialysis patients with iron overload. *Nephrol Dial Transplant* 1998; **13**: 2867-2872 [PMID: 9829492]
14 **Chen WT**, Lin YF, Yu FC, Kao WY, Huang WH, Yan HC. Effect of ascorbic acid administration in hemodialysis patients on in vitro oxidative stress parameters: influence of serum ferritin levels. *Am J Kidney Dis* 2003; **42**: 158-166 [PMID: 12830468]
15 **Ferretti G**, Bacchetti T, Masciangelo S, Pallotta G. Lipid peroxidation in hemodialysis patients: effect of vitamin C supplementation. *Clin Biochem* 2008; **41**: 381-386 [PMID: 18194672 DOI: 10.1016/j.clinbiochem.2007.12.011]
16 **De Vriese AS**, Borrey D, Mahieu E, Claeys I, Stevens L, Vanhaeverbeke A, Roelens M, Langlois MR. Oral vitamin C administration increases lipid peroxidation in hemodialysis patients. *Nephron Clin Pract* 2008; **108**: c28-c34 [PMID: 18087169]
17 **Hong SY**, Hwang KY, Lee EY, Eun SW, Cho SR, Han CS, Park YH, Chang SK. Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication. *Toxicol Lett* 2002; **126**: 51-59 [PMID: 11738270]
18 **Heller R**, Werner-Felmayer G, Werner ER. Alpha-Tocopherol and endothelial nitric oxide synthesis. *Ann N Y Acad Sci* 2004; **1031**: 74-85 [PMID: 15753135]
19 Third Conference on Vitamin C. *Ann N Y Acad Sci* 1987; **498**: 1-538 [PMID: 3475992]
20 **Sauberlich HE**. Pharmacology of vitamin C. *Annu Rev Nutr* 1994; **14**: 371-391 [PMID: 7946525]
21 **Friedman S**, Kaufman S. 3,4-dihydroxyphenylethylamine beta-hydroxylase. Physical properties, copper content, and role of copper in the catalytic acttivity. *J Biol Chem* 1965; **240**: 4763-4773 [PMID: 5846992]
22 **Fidler MC**, Davidsson L, Zeder C, Walczyk T, Hurrell RF. Iron absorption from ferrous fumarate in adult women is influenced by ascorbic acid but not by Na2EDTA. *Br J Nutr* 2003; **90**: 1081-1085 [PMID: 14641967]
23 **MAZUR A**, BAEZ S, SHORR E. The mechanism of iron release from ferritin as related to its biological properties. *J Biol Chem* 1955; **213**: 147-160 [PMID: 14353914]
24 **Lipschitz DA**, Bothwell TH, Seftel HC, Wapnick AA, Charlton RW. The role of ascorbic acid in the metabolism of storage iron. *Br J Haematol* 1971; **20**: 155-163 [PMID: 5548483]
25 **Derman D**, Sayers M, Lynch SR, Charlton RW, Bothwell TH, Mayet F. Iron absorption from a cereal-based meal containing cane sugar fortified with ascorbic acid. *Br J Nutr* 1977; **38**: 261-269 [PMID: 911745]
26 **Levine M**. New concepts in the biology and biochemistry of ascorbic acid. *N Engl J Med* 1986; **314**: 892-902 [PMID: 3513016]
27 **Fain O**. Musculoskeletal manifestations of scurvy. *Joint Bone Spine* 2005; **72**: 124-128 [PMID: 15797491]
28 **Iwasaki M**, Manz MC, Taylor GW, Yoshihara A, Miyazaki H. Relations of serum ascorbic acid and α-tocopherol to periodontal disease. *J Dent Res* 2012; **91**: 167-172 [PMID: 22166583 DOI: 10.1177/0022034511431702]
29 **Jackson P**, Loughrey CM, Lightbody JH, McNamee PT, Young IS. Effect of hemodialysis on total antioxidant capacity and serum antioxidants in patients with chronic renal failure. *Clin Chem* 1995; **41**: 1135-1138 [PMID: 7628087]
30 **Alkhunaizi AM**, Chan L. Secondary oxalosis: a cause of delayed recovery of renal function in the setting of acute renal failure. *J Am Soc Nephrol* 1996; **7**: 2320-2326 [PMID: 8959621]
31 **Durose CL**, Holdsworth M, Watson V, Przygrodzka F. Knowledge of dietary restrictions and the medical consequences of noncompliance by patients on hemodialysis are not predictive of dietary compliance. *J Am Diet Assoc* 2004; **104**: 35-41 [PMID: 14702581]
32 **Sundl I**, Roob JM, Meinitzer A, Tiran B, Khoschsorur G, Haditsch B, Holzer H, Winklhofer-Roob BM. Antioxidant status of patients on peritoneal dialysis: associations with inflammation and glycoxidative stress. *Perit Dial Int* 2009; **29**: 89-101 [PMID: 19164258]
33 **Fehrman-Ekholm I**, Lotsander A, Logan K, Dunge D, Odar-Cederlöf I, Kallner A. Concentrations of vitamin C, vitamin B12 and folic acid in patients treated with hemodialysis and on-line hemodiafiltration or hemofiltration. *Scand J Urol Nephrol* 2008; **42**: 74-80 [PMID: 18210337 DOI: 10.1080/00365590701514266]
34 **Böhm V**, Tiroke K, Schneider S, Sperschneider H, Stein G, Bitsch R. Vitamin C status of patients with chronic renal failure, dialysis patients and patients after renal transplantation. *Int J Vitam Nutr Res* 1997; **67**: 262-266 [PMID: 9285256]
35 **Sies H**. Oxidative stress: oxidants and antioxidants. *Exp Physiol* 1997; **82**: 291-295 [PMID: 9129943]
36 **Galle J**. Oxidative stress in chronic renal failure. *Nephrol Dial Transplant* 2001; **16**: 2135-2137 [PMID: 11682656]
37 **Yoon JW**, Pahl MV, Vaziri ND. Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. *Kidney Int* 2007; **71**: 167-172 [PMID: 17136029]
38 **Zeller JM**, Sullivan BL. C-reactive protein selectively enhances the intracellular generation of reactive oxygen products by IgG-stimulated monocytes and neutrophils. *J Leukoc Biol* 1992; **52**: 449-455 [PMID: 1328445]
39 **Cross JM**, Donald AE, Nuttall SL, Deanfield JE, Woolfson RG, Macallister RJ. Vitamin C improves resistance but not conduit artery endothelial function in patients with chronic renal failure. *Kidney Int* 2003; **63**: 1433-1442 [PMID: 12631359]
40 **Kasai H**. Analysis of a form of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. *Mutat Res* 1997; **387**: 147-163 [PMID: 9439711]
41 **Bowry VW**, Mohr D, Cleary J, Stocker R. Prevention of tocopherol-mediated peroxidation in ubiquinol-10-free human low density lipoprotein. *J Biol Chem* 1995; **270**: 5756-5763 [PMID: 7890704]
42 **Eiselt J**, Racek J, Trefil L, Opatrný K. Effects of a vitamin E-modified dialysis membrane and vitamin C infusion on oxidative stress in hemodialysis patients. *Artif Organs* 2001; **25**: 430-436 [PMID: 11453871]
43 **Kamgar M**, Zaldivar F, Vaziri ND, Pahl MV. Antioxidant therapy does not ameliorate oxidative stress and inflammation in patients with end-stage renal disease. *J Natl Med Assoc* 2009; **101**: 336-344 [PMID: 19397224]
44 **Chan D**, Irish A, Croft KD, Dogra G. Effect of ascorbic acid supplementation on plasma isoprostanes in haemodialysis patients. *Nephrol Dial Transplant* 2006; **21**: 234-235 [PMID: 16204285]
45 **Fumeron C**, Nguyen-Khoa T, Saltiel C, Kebede M, Buisson C, Drüeke TB, Lacour B, Massy ZA. Effects of oral vitamin C supplementation on oxidative stress and inflammation status in haemodialysis patients. *Nephrol Dial Transplant* 2005; **20**: 1874-1879 [PMID: 15972322]
46 **Ramos R**, Martínez-Castelao A. Lipoperoxidation and hemodialysis. *Metabolism* 2008; **57**: 1369-1374 [PMID: 18803940]
47 **Galley HF**, Davies MJ, Webster NR. Ascorbyl radical formation in patients with sepsis: effect of ascorbate loading. *Free Radic Biol Med* 1996; **20**: 139-143 [PMID: 8903690]
48 **Herbert V**. Prooxidant effects of antioxidant vitamins. Introduction. *J Nutr* 1996; **126**: 1197S-1200S [PMID: 8642456]
49 **Minetti M**, Forte T, Soriani M, Quaresima V, Menditto A, Ferrari M. Iron-induced ascorbate oxidation in plasma as monitored by ascorbate free radical formation. No spin-trapping evidence for the hydroxyl radical in iron-overloaded plasma. *Biochem J* 1992; **282** (Pt 2): 459-465 [PMID: 1312330]
50 **Eiselt J**, Racek J, Opatrný K, Trefil L, Stehlík P. The effect of intravenous iron on oxidative stress in hemodialysis patients

at various levels of vitamin C. *Blood Purif* 2006; **24**: 531-537 [PMID: 17077626]
51 **Jacobs C**, Frei D, Perkins AC. Results of the European Survey on Anaemia Management 2003 (ESAM 2003): current status of anaemia management in dialysis patients, factors affecting epoetin dosage and changes in anaemia management over the last 5 years. *Nephrol Dial Transplant* 2005; **20** Suppl 3: iii3-ii24 [PMID: 15824128]
52 **Deved V**, Poyah P, James MT, Tonelli M, Manns BJ, Walsh M, Hemmelgarn BR. Ascorbic acid for anemia management in hemodialysis patients: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **54**: 1089-1097 [PMID: 19783342 DOI: 10.1053/j.ajkd.2009.06.040]
53 **Finkelstein FO**, Juergensen P, Wang S, Santacroce S, Levine M, Kotanko P, Levin NW, Handelman GJ. Hemoglobin and plasma vitamin C levels in patients on peritoneal dialysis. *Perit Dial Int* 2011; **31**: 74-79 [PMID: 20558814]
54 **Attallah N**, Osman-Malik Y, Frinak S, Besarab A. Effect of intravenous ascorbic acid in hemodialysis patients with EPO-hyporesponsive anemia and hyperferritinemia. *Am J Kidney Dis* 2006; **47**: 644-654 [PMID: 16564942]
55 **Deicher R**, Ziai F, Habicht A, Bieglmayer C, Schillinger M, Hörl WH. Vitamin C plasma level and response to erythropoietin in patients on maintenance haemodialysis. *Nephrol Dial Transplant* 2004; **19**: 2319-2324 [PMID: 15299098]
56 **Keven K**, Kutlay S, Nergizoglu G, Ertürk S. Randomized, crossover study of the effect of vitamin C on EPO response in hemodialysis patients. *Am J Kidney Dis* 2003; **41**: 1233-1239 [PMID: 12776276]
57 **Smith CH**, Bidlack WR. Interrelationship of dietary ascorbic acid and iron on the tissue distribution of ascorbic acid, iron and copper in female guinea pigs. *J Nutr* 1980; **110**: 1398-1408 [PMID: 7381603]
58 **Lin CL**, Hsu PY, Yang HY, Huang CC. Low dose intravenous ascorbic acid for erythropoietin-hyporesponsive anemia in diabetic hemodialysis patients with iron overload. *Ren Fail* 2003; **25**: 445-453 [PMID: 12803508]
59 **Sato Y**, Mizuguchi T, Shigenaga S, Yoshikawa E, Chujo K, Minakuchi J, Kawashima S. Shortened red blood cell lifespan is related to the dose of erythropoiesis-stimulating agents requirement in patients on hemodialysis. *Ther Apher Dial* 2012; **16**: 522-528 [PMID: 23190511 DOI: 10.1111/j.1744-9987.2012.01089.x]
60 **Weinstein T**, Chagnac A, Korzets A, Boaz M, Ori Y, Herman M, Malachi T, Gafter U. Haemolysis in haemodialysis patients: evidence for impaired defence mechanisms against oxidative stress. *Nephrol Dial Transplant* 2000; **15**: 883-887 [PMID: 10831646]
61 **Kruse A**, Uehlinger DE, Gotch F, Kotanko P, Levin NW. Red blood cell lifespan, erythropoiesis and hemoglobin control. *Contrib Nephrol* 2008; **161**: 247-254 [PMID: 18451684 DOI: 10.1159/000130698.]
62 **Lang KS**, Duranton C, Poehlmann H, Myssina S, Bauer C, Lang F, Wieder T, Huber SM. Cation channels trigger apoptotic death of erythrocytes. *Cell Death Differ* 2003; **10**: 249-256 [PMID: 12700653]
63 **Ureña P**, Eckardt KU, Sarfati E, Zingraff J, Zins B, Roullet JB, Roland E, Drüeke T, Kurtz A. Serum erythropoietin and erythropoiesis in primary and secondary hyperparathyroidism: effect of parathyroidectomy. *Nephron* 1991; **59**: 384-393 [PMID: 1758526]
64 **Meytes D**, Bogin E, Ma A, Dukes PP, Massry SG. Effect of parathyroid hormone on erythropoiesis. *J Clin Invest* 1981; **67**: 1263-1269 [PMID: 7229028]
65 **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**: 708-714 [PMID: 11856775]
66 **Fukushima T**, Horike H, Fujiki S, Kitada S, Sasaki T, Kashihara N. Zinc deficiency anemia and effects of zinc therapy in maintenance hemodialysis patients. *Ther Apher Dial* 2009; **13**: 213-219 [PMID: 19527468 DOI: 10.1111/j.1744-9987.2009.00656.x]
67 **Raimann JG**, Levin NW, Craig RG, Sirover W, Kotanko P, Handelman G. Is vitamin C intake too low in dialysis patients? *Semin Dial* 2013; **26**: 1-5 [PMID: 23106569 DOI: 10.1111/sdi.12030]
68 **Salem MM**. Hyperparathyroidism in the hemodialysis population: a survey of 612 patients. *Am J Kidney Dis* 1997; **29**: 862-865 [PMID: 9186071]
69 **Brossard JH**, Lepage R, Cardinal H, Roy L, Rousseau L, Dorais C, D'Amour P. Influence of glomerular filtration rate on non-(1-84) parathyroid hormone (PTH) detected by intact PTH assays. *Clin Chem* 2000; **46**: 697-703 [PMID: 10794753]
70 **Vanholder R**, De Smet R, Glorieux G, Argilés A, Baurmeister U, Brunet P, Clark W, Cohen G, De Deyn PP, Deppisch R, Descamps-Latscha B, Henle T, Jörres A, Lemke HD, Massy ZA, Passlick-Deetjen J, Rodriguez M, Stegmayr B, Stenvinkel P, Tetta C, Wanner C, Zidek W. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int* 2003; **63**: 1934-1943 [PMID: 12675874]
71 **Ganesh SK**, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001; **12**: 2131-2138 [PMID: 11562412]
72 **McCauley LK**, Koh AJ, Beecher CA, Cui Y, Rosol TJ, Franceschi RT. PTH/PTHrP receptor is temporally regulated during osteoblast differentiation and is associated with collagen synthesis. *J Cell Biochem* 1996; **61**: 638-647 [PMID: 8806088]
73 **Friedman PA**, Coutermarsh BA, Kennedy SM, Gesek FA. Parathyroid hormone stimulation of calcium transport is mediated by dual signaling mechanisms involving protein kinase A and protein kinase C. *Endocrinology* 1996; **137**: 13-20 [PMID: 8536604]
74 **Sanadgol H**, Bayani M, Mohammadi M, Bayani B, Mashhadi MA. Effect of vitamin C on parathyroid hormone in hemodialysis patients with mild to moderate secondary hyperparathyroidism. *Iran J Kidney Dis* 2011; **5**: 410-415 [PMID: 22057074]
75 **Biniaz V**, Nemati E, Tayebi A, Sadeghi Shermeh M, Ebadi A. The effect of vitamin C on parathyroid hormone in patients on hemodialysis with secondary hyperparathyroidism: a double blind, placebo-controlled study. *Nephrourol Mon* 2013; **5**: 962-966 [PMID: 24693502 DOI: 10.5812/numonthly.12404]
76 **Institute Of Medicine U**. Panel on Dietary Antioxidants and Related Compounds. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids : a report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Washington, D.C.: National Academy Press, 2000
77 **Kalantar-Zadeh K**, Braglia A, Chow J, Kwon O, Kuwae N, Colman S, Cockram DB, Kopple JD. An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients: a pilot/feasibility study. *J Ren Nutr* 2005; **15**: 318-331 [PMID: 16007562]
78 **Khajehdehi P**. Effect of vitamins on the lipid profile of patients on regular hemodialysis. *Scand J Urol Nephrol* 2000; **34**: 62-66 [PMID: 10757273]
79 **Descombes E**, Hanck AB, Fellay G. Water soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney Int* 1993; **43**: 1319-1328 [PMID: 8315945]
80 **Sato M**, Matsumoto Y, Morita H, Takemura H, Shimoi K, Amano I. Effects of vitamin supplementation on microcirculatory disturbance in hemodialysis patients without peripheral arterial disease. *Clin Nephrol* 2003; **60**: 28-34 [PMID: 12872855]

81 **Tarng DC**, Wei YH, Huang TP, Kuo BI, Yang WC. Intravenous ascorbic acid as an adjuvant therapy for recombinant erythropoietin in hemodialysis patients with hyperferritinemia. *Kidney Int* 1999; **55**: 2477-2486 [PMID: 10354297]

82 **Giancaspro V**, Nuzziello M, Pallotta G, Sacchetti A, Petrarulo F. Intravenous ascorbic acid in hemodialysis patients with functional iron deficiency: a clinical trial. *J Nephrol* 2000; **13**: 444-449 [PMID: 11132761]

83 **Canavese C**, Petrarulo M, Massarenti P, Berutti S, Fenoglio R, Pauletto D, Lanfranco G, Bergamo D, Sandri L, Marangella M. Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. *Am J Kidney Dis* 2005; **45**: 540-549 [PMID: 15754276]

84 **Tomson CR**, Channon SM, Parkinson IS, McArdle P, Qureshi M, Ward MK, Laker MF. Correction of subclinical ascorbate deficiency in patients receiving dialysis: effects on plasma oxalate, serum cholesterol, and capillary fragility. *Clin Chim Acta* 1989; **180**: 255-264 [PMID: 2743578]

85 **Pru C**, Eaton J, Kjellstrand C. Vitamin C intoxication and hyperoxalemia in chronic hemodialysis patients. *Nephron* 1985; **39**: 112-116 [PMID: 3974772]

86 **Tomson CR**, Channon SM, Ward MK, Laker MF. Ascorbate-induced hyperoxalaemia has no significant effect on lactate generation or erythrocyte 2,3,diphosphoglycerate in dialysis patients. *Eur J Clin Invest* 1990; **20**: 411-415 [PMID: 2121500]

87 **Rolton HA**, McConnell KM, Modi KS, Macdougall AI. The effect of vitamin C intake on plasma oxalate in patients on regular haemodialysis. *Nephrol Dial Transplant* 1991; **6**: 440-443 [PMID: 1876286]

88 **Tomson CR**, Channon SM, Parkinson IS, Morley AR, Lennard TW, Parrott NR, Laker MF. Plasma oxalate concentration and secondary oxalosis in patients with chronic renal failure. *J Clin Pathol* 1988; **41**: 1107-1113 [PMID: 3192733]

89 **Franssen CF**. Oxalate clearance by haemodialysis--a comparison of seven dialysers. *Nephrol Dial Transplant* 2005; **20**: 1916-1921 [PMID: 15998647]

P- Reviewer: Friedman EA, Lai S **S- Editor**: Ji FF
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