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A Systematic Review of the Effect of Vitamin C Infusion and Vitamin E-Coated Membrane on Hemodialysis-Induced Oxidative Stress

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1. Introduction

It is reported that oxidative stress plays an important part in the pathogenesis of cardiovascular diseases in chronic kidney disease (CKD) patients. This contributes to the increased cardiovascular morbidity and mortality in that group of patients. Clinical studies point to links between oxidative stress, inflammation, anemia and malnutrition (Panichi et al., 2011). The presence of inflammation and the length of duration of dialysis are the most important determinants of oxidative stress, which make them additional risk factors of cardiovascular disease. There are several deficiencies of antioxidant defense mechanisms which have been found in CKD patients. These include reduced levels of vitamin C, increased levels of oxidized vitamin C, reduced intracellular levels of vitamin E, reduced selenium concentrations, and deficiency in the glutathione scavenging system (Locatelli et al., 2003).

The main interest of this chapter is particularly focused on the effect of vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress and, also setting this issue in the broader context of oxidative stress mitigation and the search for appropriate markers of oxidative stress.

The level of oxidative stress can be determined by several markers, because oxidants themselves have very short half-lives. Only lipids, proteins, carbohydrates, and nucleic acids modified by oxy-radicals are suitable as markers because of their long lifetime. According to the NKF KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients these markers include lipid peroxidation products (such as malonyldialdehyde (MDA), exhaled alkanes, oxidized low-density lipoproteins, advanced lipid oxidation products), oxidatively modified arachidonic acid derivatives (such as F2-isoprostanes and isolevuglandins); oxidatively modified carbohydrates (such as reactive aldehydes and reducing sugars); oxidatively modified aminoacids (such as cysteine/cystine, homocysteine/homocystine, 3-chlorotyrosine, 3-nitrotyrosine); oxidatively modified proteins (such as thiol oxidation, carbonyl formation, advanced oxidation protein products, 3-nitrotyrosine, advanced glycation end-products and oxidatively modified DNA (such as 8 hydroxy 2'deoxyguanine) (K/DOQI Workgroup, 2005). In the literature other oxidative stress markers are also mentioned, such as the lipid peroxidation products acrolein, 4-hydroxynonenal or thiobarbituric acid-reactive substances (TBARS); evaluation of

enzymatic anti-oxidant systems (erythrocyte content of SOD (superoxide dismutase) and GSH (glutathione), plasma levels of GSHPx (glutathione peroxidase)), non-enzymatic anti-oxidants (plasma levels of vitamin C, erythrocyte content of GSH and vitamin E) and inflammatory proteins (C-reactive protein (CRP), albumin) (Locatelli et al., 2003). With such a broad range of suitable markers of oxidative stress available, prioritizing them becomes difficult.

Several steps have been taken to minimize oxidative stress in CKD patients. They include:

1. supplementation of vitamin E

A daily supplement of 400–800 IU of vitamin E is recommended for secondary prevention of cardiovascular events and for prevention of recurrent muscle cramps (Fouque et al., 2007). In a double blind randomized trial, 60 hemodialysis patients divided into four groups received either vitamin E (400 mg), vitamin C (250 mg), both vitamins or a placebo daily for 8 weeks (Khajehdehi et al., 2001). Muscle cramps significantly declined in patients receiving both vitamins E and C (97%), vitamin E alone (54%), or vitamin C (61%) as compared with only 7% of placebo-treated patients (Khajehdehi et al., 2001). The SPACE trial tested the effect of vitamin E (800 IU/day) on a combined cardiovascular endpoint in 196 hemodialized patients with pre-existing cardiovascular disease, and showed a significant benefit from vitamin E supplementation (Boaz et al., 2003). However, the HOPE study showed no survival benefit of vitamin E in patients with mild to moderate CKD (Mann et al., 2004).

2. supplementation of vitamin C

Current recommendations for maintenance of hemodialysis patients advise supplementation with ascorbic acid 75-90 mg daily (Fouque et al., 2007) during dialysis. In addition to the potential benefits of vitamin C for anemia management, the importance of adequate vitamin C with regard to improving cardiovascular outcomes in hemodialysis patients is also the subject of research. A study by Deicher and colleagues of 138 incident hemodialysis patients examined baseline levels of plasma vitamin C and followed the cohort for occurrence of cardiovascular events (Deicher et al., 2005). Results showed that low total vitamin C plasma concentrations (less than 32 µmol/L) were associated with an almost fourfold increased risk for fatal and major nonfatal cardiovascular events compared with hemodialysis patients who had higher plasma vitamin C levels (greater than 60 µmol/L). On the other hand Nankivell and Murali reported oxalosis resulting in graft failure in a kidney transplant recipient who had been taking self-prescribed doses of vitamin C 2,000 mg daily as a dialysis patient for the three years prior to the transplant (Nankivell & Murali, 2008). Similarly, a case report by McHugh and colleagues (McHugh et al., 2008) describes mortality from vitamin C-induced acute renal failure. Vitamin C supplements appear to improve functional iron deficiency and hence the response to erythropoietin (EPO) (Keven at el., 2003). Vitamin C supplementation may help to relieve muscle cramps. In a double blind randomized trial the supplementation of vitamin C improved muscle cramps in 61% of patients as compared with only 7% of placebo-treated patients (Khajehdehi et al., 2001). In the study performed by Tarng DC. et al. vitamin C supplementation in chronic hemodialized patients resulted in the reduction of lymphocyte 8-OHdG levels and the production of intracellular reactive oxygen species (Tarng et al., 2004).

3. combination of vitamin C and E supplementation

In a double blind randomized trial the combination of vitamin C and E supplementation improved muscle cramps significantly in 97% of patients as compared with only 7% of

placebo-treated patients (Khajehdehi et al., 2001). In the Kuopio Atherosclerosis Prevention Study (KAPS) the supplementation of these two vitamins slowed the progression of carotid artery lesions (Salonen et al., 1995).

4. supplementation of acetylcysteine

In the randomized, controlled trial (Tepel et al., 2003) the antioxidant supplementation was associated with a reduced number of cardiovascular events in patients undergoing hemodialysis.

5. proper management of anemia

The literature is ambiguous with regard to anemia management. Red blood cells contain a high level of antioxidants. In their research, Siems W. et al. indicated that a rise in the red blood cell count may increase total antioxidative capacity (Siems et al., 2002). However, Drueke T. et al. in their study concluded that the intravenous injection of iron may induce an increase in protein oxidation and carotid atherosclerosis (Drueke et al., 2002).

6. modified type of dialysis membrane
7. high-flux hemodialysis

Ward RA. et al. showed the association between the use of high-flux hemodialysis and an improvement in some measures of protein oxidation (Ward et al., 2003). There is also evidence of reduced levels of cytokines such as IL-6 and C-reactive protein and a positive effect on oxidative stress of high-flux hemodialysis in comparison with conventional hemodialysis (Panichi, 2006).

2. Dialysis membranes

2.1 Modified type of dialysis membrane – the vitamin E-coated dialyser

The very first human hemodialysis therapy made use of a cellulose-based material with collodion tube membranes (Haas, 1888). Cellophane and Cuprophan membranes replaced collodion tube membranes later, due to their better performance In the 1960s regenerated cellulose was established as the principal membrane material. Dialysis with unmodified cellulose membranes is associated with such bioincompatibility phenomena as leukopenia, increased expression of adhesion molecules on leukocytes, and release of reactive oxygen species. Modifications in the structure of the hydroxyl groups in cellulose membranes led to the development of another type of membrane material, modified cellulose, with improved bioincompatibility. These modifications include replacement of the hydroxyl groups with other chemical structures, such as acetyl derivatives, or their bonding with different compounds, such as vitamin E or heparin.

Vitamin E, which is well-known for being a lipophilic antioxidant of cell membranes and lipoproteins (Traber & Atkinson, 2007), was introduced to the field of hemodialysis for the first time in the late 1990s to produce a cellulose-based vitamin E-modified dialyser (on the market as Excebrane dialyser, Asahi Kasei Medical Co., Ltd, Tokyo, Japan). It was used as a modifier (or coating agent) for the blood surface of cellulosic hollow-fiber dialyser membranes. In the last few years, studies have reported the positive effect of vitamin E-coated membranes on surrogate markers of oxidative stress and inflammation in hemodialysis patients (Cruz et al., 2008). Satoh M. et al. proved that vitamin E-modified cellulose dialysis membranes have a beneficial effect on reduction of oxidative stress (Satoh et al., 2001). Miyazaki H. et al. also found good results for endothelial dysfunction (Miyazaki et al., 2000).

Study	Study design	Sample size	Study duration [months]	Age (mean, range)	Males (%)	Mean duration of dialysis (mean) [years]	
Buoncristiani 1997	Single arm	10	1,0	67	40	4,9	•
Sommerburg 1999	Single arm	10	1,5	51	70	NR	•
Mune 1999	RCT	25	24,0	57	44	7,0	•
Bonnefont-Rousselot 2000	Single arm (cross over with conventional hemodialysis)	12	3,0	50	67	1,5	• •
Galli 2001	RCT	15	One single HD session or after 3 months	64	50	2,6	• •
Eiselt 2001	RCT (cross over with conventional hemodialysis)	10	1 month or 3 month	63	NR	3,6	• •
Mydlik 2001	Single arm	8	0,8	54	38	NR	•
Shimazu 2001	RCT	6	9,0	59	50	11,2	•
Satoh 2001	Single arm	18	6,0	68	55	>3,0	•
Tsuruoka 2002	Randomized crossover	10	10,0	55	NR	9,5	•
Usberti 2002	Single arm	10	7,0	22–75[a]	55	1,5–17,0[a]	•
Triolo 2003	Single arm	10	12,0	65	60	7,2	•
Hara 2004	Single arm	13	12,0	62	31	13,1	•
Mydlik 2004	Single arm	14	3,0	43	50	NR	•

AN69, acrylonitrile 69; PMMA, polymethylmethacrylate; PA, polyamide; CU, cuprophane; CTA, cellulose triacetate; CL, Clirans series; NR, not reported; a, range

Table 1. All study characteristics, outcome measures and dialyser characteristics of all studies included in the Sosa 2006 (Bonnefont-Rousselot 2000, Eiselt 2001, Galli 2001 provided data about TBARS level).

Only one systematic review conducted by Sosa MA. et al. provided comprehensive data that the transfer of dialysis patients to a vitamin E-coated dialyser is associated with an improvement in circulating biomarkers of lipid peroxidation, which is of potential clinical benefit (Sosa et al., 2006). Fourteen articles were included: 11 single arm, one randomized crossover and two randomized controlled trials, with a total of 37 to 158 evaluable patients. Metanalyses were conducted for malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), combination of MDA and TBARS, low-density lipoprotein (LDL) and oxidized-LDL. There were three studies from Europe with analysis of data for TBARS[1] – Eiselt 2001, Galli 2001 and Bonnefont-Rousselot 2000. All three studies had an arm where E-coated membranes were used (single arm cross over design - Galli 2001 and Bonnefont-Rousselot 2000, randomized controlled trial – Eiselt 2001) with a total of 37 patients. Mean patient ages ranged from 44 to 65 years with mean durations of dialysis ranging from 3 months to 2,6 years. The studies lasted from 1 to 3 months.
In this systematic review, all results were metanalysed, which seems not to be methodologically correct. The summary estimate of all of the three studies revealed a non-significant decrease in pre-dialysis TBARS level of -0,4 mmol/L (CI95% -1,2; 0,4). In a sensitivity analysis excluding the study by Galli 2001, the overall mean decrease in pre-dialysis TBARS level was similar (-0.6 mmol/L, CI95% -1,4; 0,2), and expressed extremely low baseline values. Bonnefont-Rousselot 2000 had a younger group of patients, a shorter duration of dialysis, and in addition, high flux dialysis was used. Additionally, the results of all three trials were presented for 3 different periods – after one session – Eiselt 2001, after 1 month – Galli 2001 and after 3 months - Bonnefont-Rousselot 2000.

Study	Unit and parameter	Excebrane	Control	P value	Assessment
Bonnefont-Rousselot 2000	µmol/L Median (range)	1,72 (1,02-3,0)	1,65 (0,75 - 2,25)	ns	Pre-dialysis level and after 3 months of HD
Eiselt 2001	µmol/L Mean ± SEM	3,9 ± 0,15	4,09 ± 0,14	ns	Pre-dialysis level and after single session of HD
Galli 2001	nmol/l - measured by HPLC and espressed as malonaldehyde equivalents Mean ± SD	4,8 ± 2,4	12,9 ± 5,2	<0,001	Excebrane hemodialysis in comparison with CLS hemodialysis after 1 month

HD, hemodilaysis; HPLC, high performance liquid chromatography; SD, standard deviation; ns, not statistically significant.

Table 2. Thiobarbituric acid reacting substances (TBARS) – mode of measure, units and p value results in Sosa 2006.

The overall conclusion from the systematic review (Sosa 2006) based on the MDA and TBARS results was presented as the standardized effect size. The mean decrease in these biomarkers of lipid peroxidation (from 13 studies) was statistically significant at -1.7 units (CI95%, -2.7, -0.7).

[1] This is only one possibile biomarker to compare Excebrane with the results of data from trials regarding the efficacy of vitamin C infusion and vitamin E-coated membrane hemodialysis.

2.2 Vitamin C infusion and E-coated membrane hemodialysis

In order to assess the influence of vitamin C infusion and E-coated membrane hemodialysis a systematic review was conducted. The primary sources used to identify clinical studies included a literature search in PubMed (last search on 11th March in 2011) limited to clinical trials on humans using the searched terms 'dialysis', 'hemodialysis', 'renal replacement therapy', 'membrane', 'vitamin E', 'vitamin C' and 'infusion', and a literature search in the Cochrane Central Register of Controlled Trials, using the same searched terms without period limitations. Additionally, study references from relevant articles were reviewed and the relevant articles themselves. Non-English language studies were excluded. All primary studies meeting the following criteria concerning study population, interventions and reference interventions and study types were included: study population - patients with chronic renal failure (or renal transplantation), hemodialysis. Both patients with and without history of cardiovascular disease were included. Interventions and comparators: vitamin C alone or combined with defined dosage and vitamin E-coated dialysers for hemodialysis patients. Acceptable reference technologies include either placebos or a dialyser without vitamin E coating, with biocompatibility similar to the vitamin E-coated dialyser. We searched the data published as randomized controlled clinical trials. No restrictions were placed on minimal study duration or sample size. The inclusion and exclusion criteria defined above were used to pre-select articles by screening titles and abstracts primarily thematically, and a full text version of articles that might meet the inclusion criteria was ordered. Two independent reviewers (T.M. and M.W.)[2] evaluated the abstracts for relevance to the study topic. The data were extracted if they examined the impact on changes in circulating pre-dialysis biomarkers of lipid peroxidation, including malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS) and other parameters. The laboratory methods used to determine the levels of these biomarkers were also evaluated. The initial literature search returned 118 citations from PubMed, 368 citations from the Cochrane database. A total of 44 citations met the initial screening criteria and were retrieved and evaluated. Out of those, 40 studies were excluded for the following reasons: 5 studies examined the effect of oral vitamin E and vitamin C supplementation, 13 studies examined only the effect of vitamin C supplementation with or without additional substances (oral or infusions in comparison with placebo), 14 studies focused on the biocompatibility of the Excebrane dialyser or other E-coated membrane dialyser, 3 citations were review articles, editorials or case reports, 1 study documented changes exclusively in pre-dialysis hemoglobin level and/or recombinant human erythropoietin (rHuEpo) dosing requirement, 1 study measured biomarkers of oxidative stress in vitro, 3 studies compared a different type of membrane without vitamin C infusion. Finally, 3 studies (2 fully published trials (Yang 2006, Eiselt 2001) and 1 conference abstract (Racek 1999) met the review criteria and examined the effect of the vitamin C infusion and E-coated membrane hemodialysis on biomarkers of oxidative stress. In these two trials patients were randomized to groups with or without vitamin E-coated membrane dialyser and with or without vitamin C infusion. The overall duration of individual studies ranged from one dialysis session to 12 weeks. Duration of dialysis ranged from 3 to 153 months (no data for Yang 2006). Male gender distribution ranged from 50 to 70%. Mean age is about 65 (no data for Yang 2006). Causes of end-stage renal disease were documented in 2 trials.

[2] M.W. – Magdalena Wladysiuk, T.M. – Teresa Malecka-Massalska

Author and year	Country	Study design	Study duration	Sample size	Age (mean, range)	Males (%)	Mean duration of dialysis (mean, range) [months]	
Eiselt 2001A	Czech Republic	Randomized controlled trial	Single dialysis session (before/ after)	24 (4 groups with 6 persons)	66 (41-85)	58	41 (8-153)	• • • • •
Eiselt 2001B	Czech Republic	Randomized controlled trial	12 weeks	20 (2 groups – 10 patients)	64 (37-79)	50	32 (3-84)	
Yang 2006	Taiwan	Randomized controlled trial	8 weeks	80 (4 groups for 20 patients)	NR	69	NR	• • • • • • • • • •
Racek 1999	Czech Republic	NR	NR	24	NR	LD	NR	• • • • •

NR, not reported; AOS, antioxidant capacity; GSH, glutathione; GSHOx, glutathione peroxidase; SOD, superoxide dismutase; MDA, malondialdehyde; VC, vitamin C; RH2O2, reference H2O2; ROS, reactive oxygen species; TAS, total antioxidant status; TBARS, thiobarbituric acid reacting substances; metHb, methemoglobin; PCOOH, phosphatidylcholine hydroperoxide.

Table 3. The characteristics of the individual studies and outcome measures in the present systematic review.

Author and year	Type of intervention in group - membrane type (dialyser name)	Vitamin C infusion dosage
Eiselt 2001A	Protocol O – CL C15NL cellulose dialyser (Terumo Corp., Tokyo, Japan) Protocol OC - CL C15NL and vitamin C infusion Protocol E - CL E15NL dialyser (vitamin E-modified cellulose membrane Excebrane, Terumo Corp.) Protocol EC - CL E15NL dialyser (Excebrane) with vitamin C infusion	Vitamin C (acidum ascorbicum, Biotika, Czech Republic) in 20 ml of saline before the blood entered the dialyser. The infusion rate was 2.1 mg/min - 504 mg per dialysis.
Eiselt 2001B	1 group - HD with vitamin C during dialysis 2 group – HD without any treatment The CL C15NL membrane was used for the first 4 weeks, to be followed by the E membrane (4 weeks), and again CL C15NL for the last 4 weeks of the study.	
Yang 2006	1 group - HD with vitamin C infusion 2 group - HD with VE-coated dialyser 3 group - HD with VE-coated dialyser and vitamin C infusion 4 group - HD with neither 1 and 4 group - PSN (Polysynthane membrane, Baxter Healthcare Co., Deerfield, IL, USA) 2 and 3 group – VE-coated - EE18 Excebrane (Terumo Co., Shibuyaku, Japan)	1 g of ascorbic acid in 250 ml of saline infused over 4 h of HD
Racek 1999	No data about the division patients to groups - CL C15NL cellulose dialyser (Terumo) conventional or E-modified membrane – with or without vitamin C infusion	500 mg of ascorbic acid infused over 4 h of HD

HD, hemodialysis; PA, polyamide; CU, cuprophane; CTA, cellulose triacetate; CL, Clirans series; NR, not reported.

Table 4. Type of interventions in group, membrane type (dialyser name) and vitamin C dosage in the present systematic review.

Eiselt 2001 presented the data for TBARS level in the short- and long-term observational period. After single session no change in the plasma levels of TBARS was observed after the dialysis with vitamin E-coated membrane with or without vitamin C infusion. In single session dialysis a rise from the baseline was only significant at the end of dialysis in the group with a nonmodified membrane (Protocol O - without vitamin C infusion).

TBARS level in plasma	before HD		after HD		
μmmol/L	Mean	SEM	Mean	SEM	P value
O	3,95	0,11	4,26	0,11	p<0,002
OC	4,28	0,15	4,18	0,15	Ns
E	3,90	0,15	4,09	0,14	Ns
EC	4,05	0,16	4,06	0,15	Ns

HD, hemodialysis; O, cellulose membrane; OC, cellulose membrane and vitamin C infusion; E, vitamin E-modified membrane; EC, vitamin E-modified membrane and vitamin C infusion, ns – non statistical significance

Table 5. Thiobarbituric acid reacting substances (TBARS) in plasma before and after hemodialysis (HD) in the short-term period in Eiselt 2001.

For long-term data on predialysis TBARS levels were comparable in two groups with and without vitamin C infusion. A significant decrease in TBARS, regardless of whether or not vitamin C was infused, was demonstrated in the results with the vitamin E-coated membrane after 4 weeks of nonmodified dialysis. Additionally, there was a significant difference in the group with vitamin E-coated membrane and vitamin C infusion also with baseline (p<0,02). TBARS returned to baseline in both groups after switching patients to a nonmodified membrane. In Eiselt 2001 no changes over time or differences between the study groups were noted with the intracellular antioxidants glutathione, superoxide dismutase, and glutathione peroxidase.

Parameter and units		Eiselt 2001			
		E-coated membrane		E-coated membrane and vitamin C infusion	
Mean and range		Before	After	Before	After
GSH (mmol/L erythrocyte)	Single session	1,40 (1,11–1,9)	1,42 (1,01–1,96)	1,39 (1,07–2,13)	1,46 (1,01–1,77)
	1 month	1,82 (1,13–2,05)	1,66 (1,31–1,90)	1,71 (1,41–2,02)	1,62 (1,36–2,41)
SOD (IU/g Hb)	Single session	908 (603–1 217)	920 (595–1 394)	958 (677–1 235)	930 (623–1 239)
	1 month	1 014 (893–1 284)	946 (873–1,469)	1 040 (854–1 269)	972 (771–1 383)
GSHPx (IU/g Hb)	Single session	40,2 (29,0–54,9)	38,8 (29,5–63,1)	36,9 (26,2–61,3)	37,0 (28,2–61,1)
	1 month	33,1 (21,8–73,7)	33,65 (21,7–72,1)	40,6 (19,8–51,9)	44,6 (25,2–51,3)

Table 6. Glutathione (GSH) and superoxide dismutase (SOD) in erythrocytes and glutathione peroxidase (GSHPx) in blood in the short-term and long-term study in Eiselt 2001.

In Racek 1999 conventional dialysis without vitamin C infusion was only significantly connected with increasing MDA level (from 3,8 0,5 to 4,2 0,6 μmol/l). Switching to vitamin

E-coated membrane did not increase the level of MDA neither with or without vitamine C infusion. The intracellular antioxidants glutathione, superoxide dismutase, and glutathione peroxidase during the study did not change in any of the group.

2.3 Vitamin E-coated polysulfone membrane

Lately, in its search for biocompatible biomaterials, hemodialysis technology has introduced a vitamin E-coated dialyser using polysulfonemembranes to the market (VitabranE ViE, Asahi Kasei Kuraray Medical Co., Tokyo, Japan). A significant reduction in plasma C-reactive protein in hemodialysis has been observed with the vitamin E-coated dialyser using polysulfonemembranes (Cruz et al., 2008). A reduced need for erythropoietin-stimulating agents (ESAs) has also been reported with a vitamin E-coated dialyser using polysulfonemembranes. This may be due to the longer red blood cell survival resulting from reduced oxidative stress and inflammation (Cruz et al., 2008). This new vitamin E-coated polysulfone membrane has been demonstrated to have a redox capacity and to actively react with redox-active substances in the blood (Floridi et al., 2009). It has also been reported that the vitamin E-coated polysulfone membrane combines the antioxidant and antithrombotic activities of α-tocopherol with the biocompatibility of polysulfone membranes, which have excellent clearance and permeability properties (Sasaki, 2006). Evidence show that vitamin E-coated polysulfone membrane plays a great role in the management of uremic anemia. However, there is a limited number of preliminary studies on that area. For example, one preliminary study published as a pilot study states a positive effect of vitamin E-bonded membranes on anemia in hypo-responder dialysis patients (Andrulli et al., 2010). Another study shows new positive effects of vitamin E-coated membranes on blood pressure level in dialysed patients (Matsamura et al., 2010). Recently, there are findings that these membranes may play an effective role in the management of uremic anemia and lead to a reduction in the chronic low-grade inflammatory response of patients with uremic syndrome (Panichi et al., 2011).

3. Discussion

In patients with CKD, markers of oxidative modification of lipids (Handelman et al., 2001; Oberg et al. 2004) and proteins (Nguyen-Khoa et al., 2001) are present at high levels. Moreover, various markers of oxidative stress seem to be associated with higher mortality and cardiovascular disease in dialysis patients (Bayes et al., 2005; Descamps-Latscha et al., 2005). When talking about the oxidative stress among hemodialyzed patients, there is a question that should be taken into great consideration; that is, what are the most appropriate biomarkers in relation to the disease state. The relevant biomarkers can be divided into three groups: enzymatic (superoxide dismutase, catalase, glutathione peroxidase), non-enzymatic (gluthatione, vitamin E, vitamin C, ferritin, transferrin, albumin) and the third group of lipids, proteins, carbohydrates and nucleic acids modified by oxy-radicals. None of these groups seem to be perfect for assessment of oxidative stress levels. The markers from the enzymatic group have a half-life of seconds, which makes their determination in vivo infeasible (Locatelli et al., 2003). The level of markers from the second group may vary a lot due to malnutrition, anemia and inflammation among hemodialyzed patients, common problems in that group of patients. The markers from the third group

have lifetimes from hours to weeks. From the diagnostic point of view this makes them ideal, but their large number makes it difficult to prioritize any one as the most ideal for the hemodialyzed patient group. Giustarini et al. describes the characteristic of the "ideal marker" (see Table 7; Giustarini, et al., 2009). Upon reviewing these characteristics, it becomes clear that finding "the ideal and the most reliable one" for that group of patients would be almost impossible.

No	Characteristic of biomarker
1	Chemically stable molecule
2	Directly implicated in the onset and/or progression of disease
3	Specific for the reactive oxygen/nitrogen species in question
4	Non-invasive assessment
5	Low intra- and inter-variability in humans
6	accurate, precise, specific, sensitive, interference-free, and validated assays for quantitative analysis
7	Consensus and establishment of reference intervals and values
8	Consensus and establishment of animal models

Table 7. Characteristics of and requirements for suitable biomarkers of oxidative stress (Giustarini, et al., 2009).

A review of the literature offers examples of how different markers were used to examine the oxidative stress among patients with end-stage renal disease. This makes it difficult to compare research on the same subject, because studies that measure the same process with different, nonstandardized markers. Here are examples: 8-hydroxy 2'-deoxyguanosine (8-OHdG) is known as a product of DNA damage (Tarng et al., 2000) and a novel marker for the assessment of oxidative DNA damage in reactive oxygen species-mediated diseases (Kasai, 1997). Zocalli et al. found asymmetric dimethyloarginine (ADMA) to be a strong and independent predictor of overall mortality and cardiovascular outcome in hemodialysis patients (Zocalli et al., 2001). In the study of Kamgar et al., the panel of following markers of oxidative stress were used: plasma protein carbonyl, F-2 isoprostane, C-reactive protein and plasma IL-6 (Kamgar et. al., 2009). Interestingly, the authors of this paper came to the conclusion that the addition of a potent antioxidant cocktail to conventional vitamin supplements had no effect on the severity of end-stage renal disease-induced oxidative stress, inflammation, hypertension, anemia or nutritional disorders in hemodialysis patients (Kamgar et al., 2009). There are some studies where TBARS were used as markers of oxidative stress (Ramos et al., 2008; Galli et al., 2001) whereas others made use of advanced glycation end products (AGEs), free pentosidine (FP), protein-bound pentosidine (BP), autoantibodies against oxidized LDL (ox-LDL-autoantibodies (Baragetti et al., 2006), and MDA (Giardini et al., 1984). The table below summarizes different biomarkers of oxidative stress used among hemodialyzed patients (Giustarini, et al., 2009). The table was created on the basis of studies of human subjects published on PubMed between January and June 2006 (Giustarini, et al., 2009). This indicates how many biomarkers have been used to assess oxidative stress; these studies used different methods and took samples from different tissues.

	Precursor	Bio marker	Method	Tissue	Healthy	Disease	Reference
1	**CRF**	MDA	TBA spectrophotometry	Plasma	6,20 nmol/L	11,9	Ece et al., 2006
2	**HD**	MDA	TBA spectrophotometry	Plasma	2,29 µmol/L	4,36	Zwolinska et al., 2006
3	**CRF**	15-F2t-IsoP	ELISA commercial kit, Assay Design	Plasma	84,3 pg/mL	328	Cottone et al., 2006
4	**HD**	PCO	Fluoresceinamine spectrophotometry	Plasma	2,06 nmol/mg protein	2,51	Mera et al., 2005
5	**HD**	SOD	ELISA commercial kit, BenderMedSystm	Plasma	58,6 ng/mL	305	Pawlak et al., 2006
6	**HD**	GPx	EIA commer cial kit, Byoxy tech	Plasma	116 U/L	N.A.	Huerta et al., 2006
7	**HD**	Ab anti oxi-LDL	ELISA commer cial kit, Bio medica	Plasma	210 mU/ mL	380	Pawlak et al., 2006
8	**HD**	Oxi-LDL	ELISA anti-oxidized phosphate dylcholine	Plasma	0,2 ng/µg LDL protein	1,8	Sasaki, 2006
9	**HD**	4-HNE	HPLC UV/vis detection	Plasma	3,0 µmol/mg protein	7,6	Odetti et al., 2006
10	**HD**	AGE	fluorescence	Plasma	232 fluorescece intensity	746	Mera et al., 2005
11	**HD**	HMA	HPLC fluorescence detection	Plasma	55,7%	45,3	Mera et al., 2005
12	**HD**	HNA1	HPLC fluorescence detection	Plasma	36,5%	44,8	Mera et al., 2005
13	**HD**	HNA2	HPLC fluorescence detection	Plasma	7,8%	9,3	Mera et al., 2005
14	**HD**	Organic hydro peroxides	Ferrous oxidation xylenol orange assay spectrophotometry	Plasma	0,65 µmol/L	1,99	Zwolinska et al., 2006
15	**CRF**	GSH	Acid deprote inization/DTNB spectrophotometry	Whole blood	1684 µmol/L	938	Ece et al., 2006
16	**CRF**	SOD	NTB/riboflavin spectrophotometry	Red blood cells	3457 U/gHb	2072	Ece et al., 2006
17	**HD**	SOD	Epinephrine spectrophotometry	Red blood cells	1750 U/g Hb	1240	Zwolinska et al., 2006
18	**HD**	Gpx	NADPH/ GSH spectrophotometry	Red blood cells	83,2 U/gHb	38,4	Zwolinska et al., 2006
19	**CRF**	Catalase	H2O2 spectrophotometry	Red blood cells	1705 k/gHb	1212	Ece et al., 2006
20	**HD**	Catalase	H2O2 spectrophotometry	Red blood cells	0,49 U/gHb	0,36	Zwolinska et al., 2006
21	**CRF**	GSH	Acid deproteinization/ DTNB spectrophotometry	Red blood cells	14,2 µmol/gHb	20,5	Stepniewska et al., 2006
22	**HD**	MDA	TBA spectrophotometry	Red blood cells	5,86 µmol/L	11,34	Zwolinska et al., 2006
23	**CRF**	GR	GSSG/ NADPH spectrophotometry	Red blood cells	1,95 U/gHb	2,57	Stepniewska et al., 2006
24	**CRF**	G6PDH	NADP spectrophotometry	Red blood cells	2,54 U/gHb	4,91	Stepniewska et al., 2006

Table 8. Summary of different biomarkers of oxidative stress used among hemodialyzed patients on the basis of studies of human subjects published between January and June 2006 (Giustarini, et al., 2009).

AGEs, advanced glycation end-products; CRF, chronic renal failure; DTNB, 5,5'-dithiobis-(2-nitrobenzoic acid); EIA, enzyme immunoassay; G6PDH, glucose-6 phosphate dehydrogenase; GPx, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfide; GR, glutathione reductase; HD, hemodialysis; HMA, albumin reduced; HNA1, mixed disulfide between albumin an low molecular mass thiols; HNA2, SH groups in albumin oxidized to sulfenic, sulfinic, sulfonic acid; HPLC, high-performance liquid chromatography; 4-HNE, 4-hydroxy-2-Nonenal; MDA, malondialdehyde; N.A., not applicable; oxi-LDL- oxidized low molecular lipoproteins; NBT, nitroblue tetrazolium; PCO, protein carbonyls; SOD, superoxide dismutase; TBA, thiobarbituric acid; TBARS, thiobarbituric acid-reactive substances. (Giustarini, et al., 2009)

In the systematic review conducted in 2006 (Schnell-Inderst 2006) only two studies analyzed the clinical endpoints of cardiovascular disease, results that are meaningful to patients. Due to the absence of clinically-meaningful endpoints, the relevance of studies analyzing the effect of anti-oxidative vitamins on intermediate endpoints like oxidative stress markers is fundamentally limited. In 17 studies with intermediate endpoints, supplementation with vitamins was associated with a change of one or several of the examined endpoints in the expected direction, such as a decrease in concentrations of biomarkers for oxidative stress, an improvement of the lipid profile, a reduced progression of aortic calcification or decrease of intimate media thickness. Due to the methodological quality of studies (heterogeneity of population, lack of standardization for interventions, and others) and contradictory results, the statement that anti-oxidative vitamins can play any role in secondary prevention for cardiovascular disease among patients with end-stage renal disease is neither supported nor rejected. Additionally, there is no relevant data for primary prevention of cardiovascular disease.

In the present systematic review the main objectives was to find any evidence that vitamin C infusion added to the vitamin E-coated membrane dialyser could change the level of biomarkers. The Sosa 2006 systematic review and the results for Excebrane should be a reference's level to assess the effect of additional C infusion. Varying conclusions for the TBARS outcome drawn by individual studies in Sosa maybe due to methodological differences. The cross over design of the same group of patients with small and insufficient sample size, different baseline risk of patients (comorbidity, time of dialysis) and, especially, the lack of parallel randomized control did not allow for the control of confounders (Sosa 2006). Additionally, a lack of standardized measurement of biomarkers and the time of measurement (single session, 1 month or longer) of biomarker assays probably does not allow any metanalyses to be performed. In this case only a qualitative systematic review could be made with separate conclusions for each of the subpopulations or patient groups. Single-arm groups (from observational or randomized trials) were metanalyzed as a measure of baseline level and then change over the time proposed by the authors of included studies. Natural fluctuations of biomarkers and their changes over time due to other interventions (comorbidities, diet, stress, age) could bias the results. There are existing head–to-head trials of Excebrane directly with other dialysers which could provide more reliable data. The same problems with population, interventions and measured outcomes were raised by the present systematic review. Additionally, the number of biomarkers and the lack of an answer to the question of which of them is the most ideal indicator of oxidative stress prevents us from coming to the final conclusion regarding the effect of

vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress.

For our systemic review, TBARS was used as oxidative stress marker in order to compare the effect of vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress. TBARS and MDA are recommended by the National Kidney Foundation (NKF) guidelines to assess oxidative stress; however, they are not perfect measures of oxidative stress. MDA is a product of lipid peroxidation. During that process there are other end-products such as pentane, isoprostanes, and conjugated dienes (Esterbauer, 1993). The TBARS determination is the most-used assay to assess lipid peroxidation. In this assay, thiobarbituric acid (TBA) reacts with aldehydes to produce a relatively stable chromophore that can be quantified using either spectrophotometry or high-performance liquid chromatography (HPLC) (Pompella et al., 1997). What is worth noting is that there are several problems with the use of TBARS in human fluids. Griffiths et al. underlines that aldehydes other than MDA may react with TBA to produce derivatives that absorb light in the same wavelength range; degradation of fatty acids can occur during the analysis, leading to false information about the actual MDA content in the fluid before testing (Griffiths et al., 2002). Halliwell and Chirico add that the presence of metal ions can increase the rate of this decomposition, whereas metal-chelating molecules can decrease this rate, making reliability a problem. What is more, the routine use of different anticoagulants to prevent blood clotting, *i.e.,*EDTA or heparin, may yield different values even on the same blood sample, and most TBA-reactive materialin human body fluids, including MDA, is not a specific product of lipid peroxidation and may produce false-positive results (Halliwell & Chirico, 1993). These problems led some researchers to use an HPLC modification of the TBARS method. This approach uses HPLC to separate the MDA-TBA adduct from interfering chromophores, thereby resulting in improved specificity (Halliwell & Chirico, 1993). Lipid hydroperoxides and aldehydes can also be absorbed from the diet and excreted in urine. It follows that measurements of MDA in plasma or urine can be confounded by diet and should not be used as an index of whole-body lipid peroxidation unless diet is strictly controlled (Wilson et al., 2002). This illustrates the difficulty in assessing which method is the best for assessment of oxidative stress. Moreover, it also underlines the need for analytical methodologies which validate the stability of the biomarker and extraction yield, accuracy and precision, selectivity and specificity, robustness and limits of detection and quantitation (Shah et al., 2000).

Currently, there is no consensus regarding an ideal marker of oxidative stress. So far, a panel of markers might be a better solution than just one (Locatelli et al., 2003). In order to analyze the process of oxidative stress there is no doubt that biomarkers should firstly be adequately validated, as too many have been proposed and used. Only under these circumstances can adequate conclusions be drawn and compared.

4. Conclusion

The available evidence is not sufficient to support an additional effect of the anti-oxidative role (measured by TBARS level) of a vitamin C infusion added to E-coated membrane dialyser in comparison to the vitamin E-coated dialyser alone. Methodological differences among three studies which used TBARS as a biomarker of oxidative stress prevent any

significant conclusion regarding this supplementation from being made. These results together with the systematic review of Sosa 2006 have limited importance in light of the lack of evidence that measurement of some biomarkers can give conclusive results regarding oxidative stress in cardiovascular morbidity of dialysis patients.
Finally, finding the most appropriate single biomarker or the most appropriate panel of biomarkers of oxidative stress in dialysis patients should be the first and most crucial step taken in order to decrease methodological uncertainty in future research on the issue.

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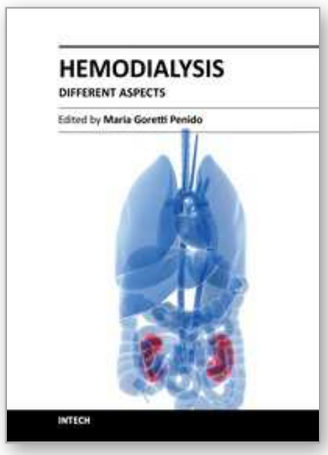

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