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Effect of the tunneled-cuffed central venous catheters on oxidative stress indices and inflammation in chronic hemodialysis patients

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ABSTRACT

Objectives: The use of central venous catheters as hemodialysis (HD) vascular access is associated with worse morbidity and mortality in HD patients. This occasion is often attributed to comorbidities of the patients with central venous catheters. Studies reveal that a biofilm layer occurs on most of the tunneled-cuffed central venous catheters (TC-CVCs). This study aimed to determine the oxidative stress (OS) and systemic inflammation (SI) status in patients with TC-CVCs as HD vascular access without clinical signs and symptoms of infection.

Methods: The study is composed of eighty-five patients with a minimum HD vintage of one year. Patients with a history of infection or a cardiovascular event within six months, malignancy, systemic inflammatory diseases, or malnutrition were excluded. OS indices and SI markers were studied and compared in patients with arteriovenous fistula (AVF) and TC-CVCs.

Results: Mean native thiol/total thiol (NT/TT) ratio was significantly higher and mean disulphide/total thiol (DT/TT) ratio was significantly lower in AVF group comparing TC-CVC group (0.46 ± 0.17 and 0.36 ± 0.17, $p = 0.03$ for NT/TT; 0.27 ± 0.08 and 0.31 ± 0.08, $p = 0.04$ for DS/TT; respectively). Mean OS index was significantly lower in the AVF group comparing TC-CVC group (0.15 ± 0.14 and 0.24 ± 0.23, $p = 0.04$; respectively]. Median hs-CRP levels and median IL-6 levels were significantly lower in AVF group comparing TC-CVC group (5.8 [min: 3.0-max: 82.5] mg/L and 9.7 [min: 3.0-max: 45.4] mg/L, $p = 0.004$ for hs-CRP; 6.2 [min: 2.0-max:159.0] pg/mL and 12.2 [min: 2.6-max: 41.3) pg/mL, $p = 0.01$ for IL-6; respectively).

Conclusions: TC-CVCs inversely affect OS and systemic inflammatory status in HD patients, presumably due to foreign body reactions and biofilm layers.

Keywords: Arteriovenous fistula, central venous catheters, hemodialysis vascular access, oxidative stress, systemic inflammation

Hemodialysis (HD) is the most frequent renal replacement therapy (RRT) modality. HD requires a proper functioning vascular access (VA) such as arteriovenous fistula (AVF), arteriovenous graft (AVG), or central venous catheter (CVC). The use of CVCs is associated with worse morbidity and mortality in HD patients, which is usually attributed to patients' comorbidities, and these results are thought to be related to

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selection bias [1-4].

CVCs are widely produced from polyurethane, which is shown to induce mild foreign body reactions, although it is one of the most biocompatible substances [5]. CVCs interact with proteins and cells in the circulatory system and form an adherent biological material. When microorganisms settle on this material, it is called a biofilm layer [6]. Studies using quite sensitive techniques, including electron microscopy have reported the incidence of the biofilm layers at rates ranging from 36% to 100% in removed catheters of HD patients [7-9]. Thus, there is an increasing number of attempts to make polyurethane catheters more compatible and lead to less bacterial colonization [10].

Cardiovascular diseases (CVDs) are the most frequent cause of mortality in patients under RRT [11]. The two of the most critical factors for CVDs are oxidative stress (OS), and systemic inflammation (SI). The HD procedure and kidney disease itself are triggers of OS and SI [12, 13]. On the other hand, in HD patients, smoking, serum uric acid levels, fluid overload, dialyzer type, dialysate purity, anemia, intravenous iron, and diabetes have also been associated with OS and SI [14]. However, this foreign substance in the vessel may be contributing to morbidity and mortality via triggering OS and SI as a potential biofilm carrier without any signs of infection.

This study aimed to determine the OS and SI status in patients with tunneled-cuffed CVCs (TC-CVCs) as HD VA without clinical signs and symptoms of infection comparing patients with AVF.

METHODS

Participants and Study Design

The study is composed of eighty-five patients with a minimum HD vintage of one-year. Informed consent was obtained from all patients. Patients with a history of infection or a cardiovascular event within six months were excluded. Patients with a history of malignancy, systemic inflammatory diseases, and malnutrition also excluded. Patients with AVGs, tunneled femoral or temporary catheters, patients treated with high-flux dialyzers or anticoagulated with citrate or low molecular weight heparin, and patients with catheters locked with antibiotics were also excluded for standardization (Fig. 1). Patients undergoing hemodialysis with TC-CVC were those with unfunctional AVF/AVG (68.2 %) and those who choose catheter use because of renal transplantation plan from a living donor in the near future (31.8 %).

All of the patients were under a standard HD procedure via AVF or polyurethane TC-CVC, thriceweekly (12 hours/week), using bicarbonate-containing dialysate and low-flux polysulfone membrane. All patients were anticoagulated with heparin. The blood flow rate ranged from 300 to 350 mL/min, and the dialysate flow rate was 500 mL/min. All tunneled-cuffed CVCs locked with heparinized saline after HD.

The average of ultrafiltration rate within the last month, cumulative intravenous iron and erythropoiesis-stimulating agent (ESA) doses applied within the last six months were calculated. Doses of darbepoetin were converted to equivalent doses of epoetin for standardization [15]. Patients with >100 ml/day urine output were considered to have a residual renal function (RRF) [16].

Blood Specimen Collection

Blood specimens were collected at the initiation of a mid-week session. Specimens were allowed to clot at room temperature for 30 minutes. Clot removed by centrifuging samples at 3500 rpm for 10 minutes. The serum immediately transferred into a polypropylene tube and stored at -80oC.

Materials and Measurements

The thiol measurements, OS indices, and inflammatory parameters were measured from freshly collected serum. Laboratory parameters (within three months for intact parathormone and two weeks for others) and demographic features were recorded from patients' files.

Single pool Kt/V calculated by Daugirdas' second-generation formula. Urea reduction ratio (URR) calculated by taking the difference between pre- and post-dialysis urea levels and divided by predialysis urea levels.

Biochemical study

Thiol/disulfide homeostasis measured using a novel automatic spectrophotometric method (Rel Assay Diagnostics, Turkey) [17]. Total oxidant status (TOS) and total antioxidant status (TAS) levels were measured using commercially available kits (Rel

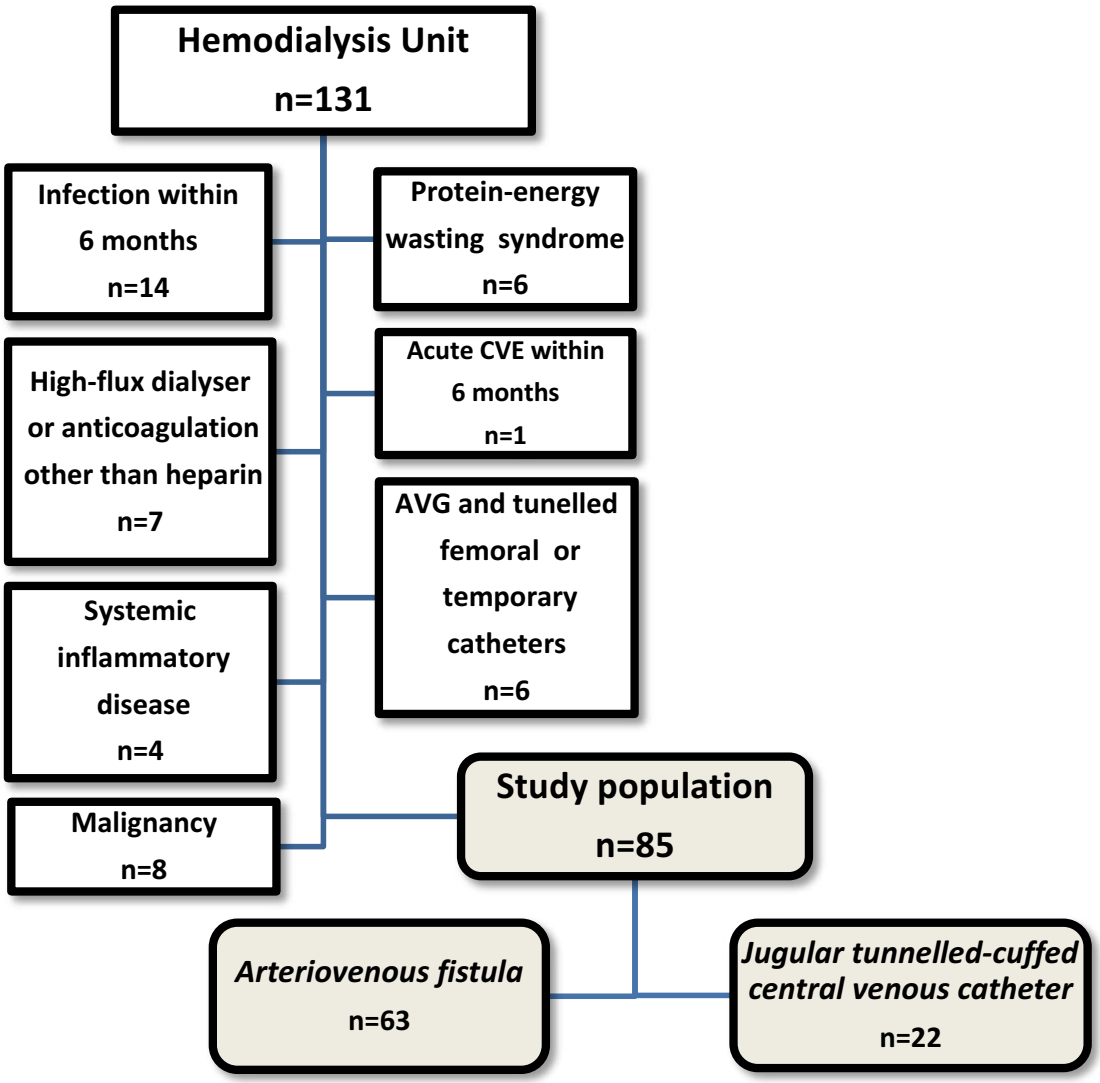

Fig. 1. Study design, study population, and groups. CVE = Cardiovascular event, AVG = Arteriovenous graft.

Assay Diagnostics, Turkey) [18]. The ratio of TOS to TAS accepted as the OS index (OSI). For calculation, the unit of TAS converted to μmol/L, and the OSI calculated according to the following formula: OSI (arbitrary unit) = TOS (μmol H2O2 equivalent/L) / TAS (μmol Trolox equivalent/L). For regression analysis, cases with a TOS > 5 μmol H2O2 equivalent/L were grouped as elevated score according to the manufacturer's recommendation.

Serum hs-CRP levels determined by a nephelometric technique using BNII/BN Pro-Spec (Siemens, Marburg, Germany); serum IL-6 levels determined by chemiluminescence immunoassay technique using Immulite 2000 (Siemens Diagnostics, Gwynedd, UK).

Ethical statements

The institute's committee (Kırıkkale University Clinical Research Ethics Committee) has approved the study protocol on human research (Decision No: 14/03, dated 27.6.2019).

Statistical Analysis

Data were expressed as mean ± standard deviation or medians with ranges. For data normally distributed; Student's t-test is used for comparison between two groups. Inflammatory markers were non-normal distributed, and the Kruskal-Wallis test performed. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for personal computers, version 21.0.

RESULTS

Baseline characteristics

Demographic features, frequencies of comorbid diseases, frequency of smokers, laboratory parameters, HD adequacy indices, mean ultrafiltration rates, and cumulative doses of iron and ESAs were similar between groups. The frequency of patients with the RRF was higher in the TC-CVC group (Table 1).

Oxidative stress measurements

Mean TT and DS levels were significantly lower in the AVF group comparing the TC-CVC group (Fig. 2). The mean NT/TT ratio was significantly higher, and the mean DS/TT ratio was significantly lower in the AVF group comparing the TC-CVC group (Table 2, Fig. 3).

Mean TOS levels were significantly lower in the AVF group comparing the TC-CVC group. Mean TAS levels were similar between groups. Mean OSI was significantly lower in the AVF group comparing TC-CVC group (Table 2, Figs. 3 and 4).

Table 1. Baseline characteristics and health parameters

	AVF (n = 63)	TC-CVC (n = 22)	*p* value
Female/male	22/41	12/10	0.07
Age (years)	55.2 ± 17.0	63.9 ± 18.7	0.28
BMI (kg/m^2)	24.9 ± 5.5	24.9 ± 4.8	0.97
DM, n (%)	13 (20.6)	3 (13.6)	0.50
CAD, n (%)	17 (26.9)	7 (31.8)	0.61
PAD/CVD, n (%)	8 (12.6)	3 (13.6)	0.87
Smoking, n (%)	10 (15.8)	4 (18.1)	0.56
Urea nitrogen (mg/dL)	62.8 ± 14.8	61.6 ± 15.8	0.59
Creatinine (mg/dL)	8.4 ± 1.9	7.1 ± 2.5	0.15
Sodium (mEq/L)	139.5 ± 2.3	138.8 ± 2.0	0.42
Potassium (mEq/L)	4.9 ± 0.7	4.7 ± 0.6	0.39
Uric acid (mg/dL)	5.3 ± 0.9	5.2 ± 1.0	0.80
Hemoglobin (g/dL)	11.2 ± 1.5	10.5 ± 1.6	0.09
Albumin (g/dL)	3.8 ± 0.3	3.6 ± 0.4	0.13
Calcium (mg/dL)	8.8 ± 0.8	8.7 ± 0.7	0.85
Phosphorus (mg/dL)	4.9 ± 1.2	4.7 ± 1.3	0.49
iPTH (pg/mL)	452.7 ± 422.9	349.3 ± 336.8	0.31
Kt/V	1.6 ± 0.2	1.6 ± 0.3	0.85
URR (%)	73.7 ± 6.8	74.2 ± 8.0	0.80
HD vintage (months)	76.0 ± 67.1	71.1 ± 47.8	0.61
Mean UF (mL)	2400 (500-3500)	2300 (1700-3000)	0.08
RRF n (%)	17 (26.9)	9 (40.9)	0.05
Cum. IV Iron (mg)	749.2 ± 434.7	713.6 ± 425.7	0.71
Cum. ESA (IU)	60000 (0-180800)	64000 (0-176000)	0.82

Data are shown as mean±standard deviation or n (%) or median (minimum-maximum). AVF = Arteriovenous fistula, TC-CVC = Tunneled cuffed central venous catheter, BMI = Body mass index, DM = Diabetes mellitus, CAD = Coronary artery disease, PAD/CVD = Peripheral artery disease/cerebrovascular disease, iPTH = intact Parathormone, URR = Urea reduction ratio, HD = Hemodialysis, UF = Ultrafiltration, RRF = Residual renal function, Cum. IV Iron = Cumulative intravenous iron, Cum. ESA = Cumulative erythropoiesis-stimulating agents

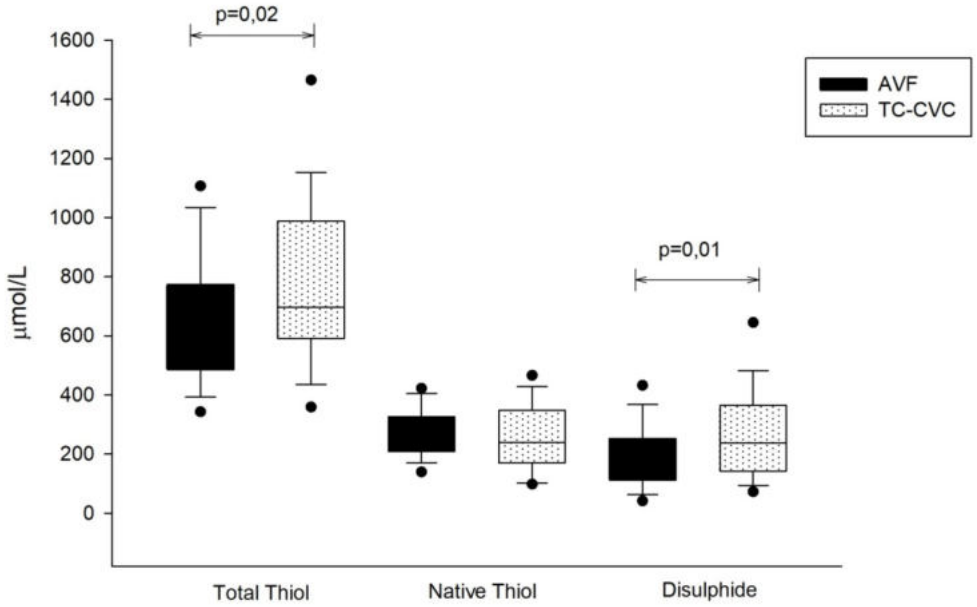

Fig. 2. Thiol measurements of the groups. AVF = Arteriovenous fistula, TC-CVC = Tunneled cuffed central venous catheter.

Table 2. Oxidative stress indices and inflammatory markers of the groups

	AVF (n = 63)	TC-CVC (n = 22)	*p* value
TT (µmol/L)	647 ± 233.5	788.2 ± 285.1	**0.02**
NT (µmol/L)	272.2 ± 86.6	256.2 ± 110.3	0.49
DS (µmol/L)	187.5 ± 112.9	265.9 ± 152.9	**0.01**
NT/TT	0.46 ± 0.17	0.36 ± 0.17	**0.03**
DS/TT	0.27 ± 0.08	0.31 ± 0.08	**0.02**
TOS (µmol/L)	3.4 ± 3.2	5.5 ± 5.7	**0.04**
TAS (mmol/L)	2.3 ± 0.2	2.2 ± 0.2	0.29
OSI)	0.15 ± 0.14	0.24 ± 0.23	**0.04**
hs-CRP (mg/L)	5.8 (3.0-82.5)	9.7 (3.0-45.4)	**0.004**
IL-6 (pg/mL)	6.2 (2.0-159.0)	12.2 (2.6-41.3)	**0.01**

Data are shown as mean±standard deviation or median (minimum-maximum). AVF = Arteriovenous fistula, TC-CVC = Tunneled cuffed central venous catheter, TT = Total thiol, NT = Native thiol, DS = Disulphide, TOS = Total oxidant status, TAS = Total antioxidant status, OSI = Oxidative stress index, hs-CRP = high sensitive C-reactive protein, IL-6 = Interleukin-6.

Inflammatory markers

Median hs-CRP levels and median IL-6 levels were significantly lower in the AVF group comparing the TC-CVC group (Table 2, Fig. 4).

Logistic regression analysis of risk factors for elevated total oxidative status

When corrected for all possible risk factors, TC-CVC significantly increases the risk of elevated TOS scores [OR: 6.90 (min: 1.09 – max: 43.6), $p = 0.04$] (Table 3).

DISCUSSION

CVCs are recommended to be the last choice for

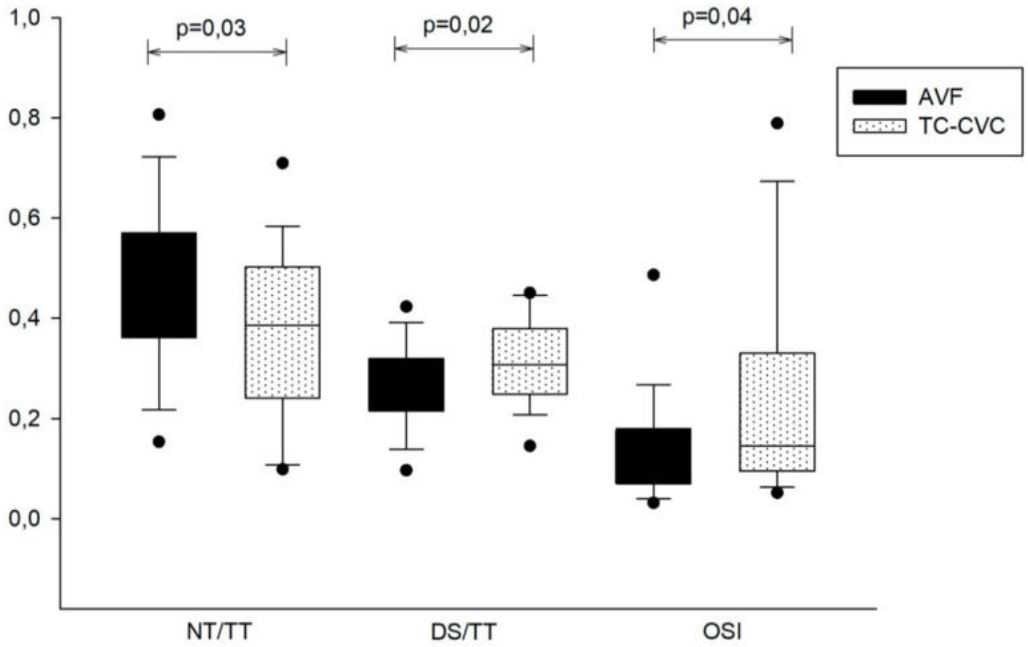

Fig. 3. Thiol balances of the groups. AVF = Arteriovenous fistula; TC-CVC = Tunneled cuffed central venous catheter.

Table 3. Logistic regression analysis of risk factors for elevated total oxidative status

	OR (95% CI)	*p*-value
Age	1.10 (0.95-1.08)	0.17
BMI (kg/m^2)	1.78 (0.59-1.20)	0.93
DM	3.24 (0.24-42.6)	0.37
Vascular disease*	5.68 (0.40-80.7)	0.19
Smoking	6.16 (0.44-85.8)	0.17
Cum. IV iron (mg)	0.99 (0.99-1.00)	0.07
Mean UF (mL)	0.65 (0.99-1.00)	0.65
hs-CRP (mg/L)	0.34 (0.96-1.11)	0.34
TC-CVC	**6.90 (1.09-43.6)**	**0.04**

BMI = Body mass index, DM = Diabetes mellitus, Cum. IV Iron = Cumulative intravenous iron, UF = Ultrafiltration, hs-CRP = high sensitive C-reactive protein, TC-CVC = Tunneled cuffed central venous catheter

*Coronary artery disease, peripheral artery disease and/or cerebrovascular disease

HD VA by current guidelines. This approach is due to the observed higher mortality in patients with CVCs [1-3, 19, 20]. Most of these studies have not reported the causes of death. A recent well-designed study revealed a discordance in mortality rates and reported acute catheter complications [21].

Following the placement of the CVC, a layer of macromolecules, cells, and fibrinogen are rapidly deposited on the surface [6]. Microbial contamination of the layer can be as short as 24 hours. Intraluminal colonization, in particular, is reported to be detected in 49-75% of patients with chronic HD catheters [9]. Bacteriae adhered to the biofilm produces an extracellular matrix that facilitates the adhesion of other pathogens and forms resistance to antibiotics and the host immune system [22]. The planktonic bacteriae can spread in circulation and cause bloodstream infections. However, there are emerging suspicions that this biofilm layer can also lead to OS and a silent SI [23].

OS is a risk factor for cardiovascular mortality

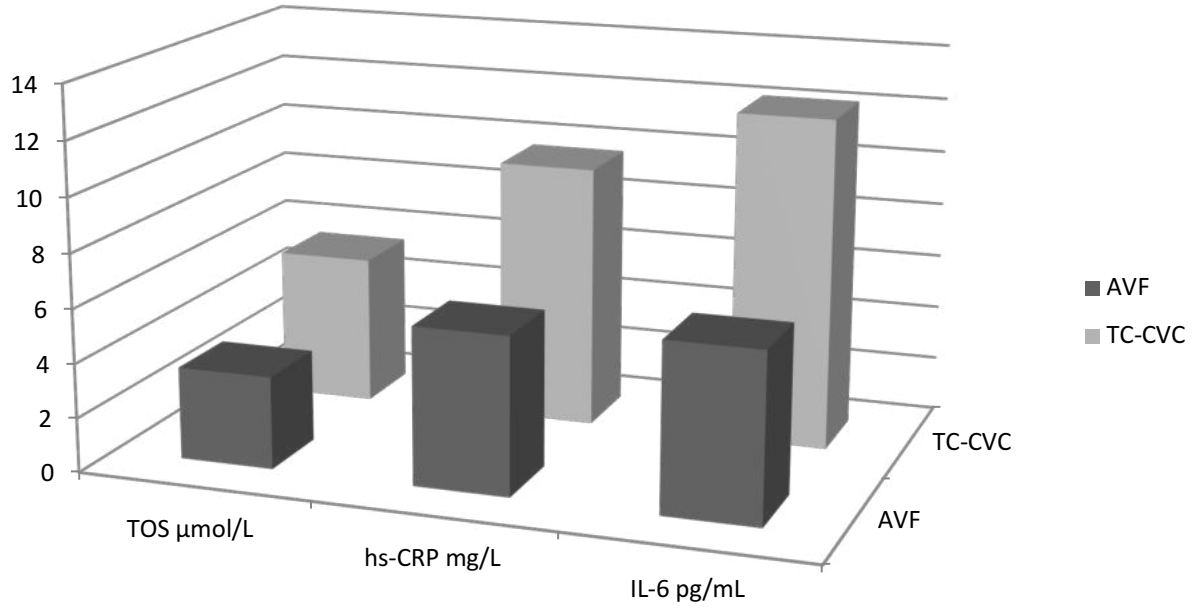

Fig. 4. Thiol balances of the groups. AVF = Arteriovenous fistula; TC-CVC = Tunneled cuffed central venous catheter.

preferentially via oxidation of low-density lipoprotein in endothelium forming plaques [24]. SI is also a plaque trigger and a risk factor for CVDs [25]. The increased OS and SI have also been demonstrated in HD patients and associated with CVDs [26]. In our study, considering the proven OS factors in HD patients, we investigated the relationship between the presence of TC-CVC and the relationship between OS and SI using novel and sensitive markers.

Reactive oxygen species results in oxidation between two electrons or redox modification of radical-based amino acid residues. In this redox reaction, the –SH groups of organosulfur compounds (thiols) such as cysteine oxidized and form a disulfide [27]. Thus, the dynamic thiol/disulfide homeostasis moves towards the disulfide form, which is the first sign of radical-mediated protein oxidation. This shift is the reflection of increased OS. Together with thiol-disulfide equilibrium, TAS and TOS measurements were made, and the OSI was calculated. Hs-CRP and IL-6 levels were used to determine SI.

The TC-CVC group had higher TT levels and DS levels, and more importantly, had lower NT/TT ratios that reflect superior antioxidant capability and higher DT/TT ratios that reflect oxidant stress. TOS levels and calculated OSI were also significantly higher in the TC-CVC group comparing the AVF group. On the other hand, the TC-CVC group had significantly higher hs-CRP and IL-6 levels.

The study revealed a clear difference between AVF and TC-CVC groups in terms of SI, consonant to the literature [28]. Furthermore, this is the first study to demonstrate the relationship between TC-CVC and OS with novel sensitive markers. All possible factors that may interact with these parameters such as, diabetes prevalence, vascular diseases, smoking, iron, and ESA therapies were similar between the groups. Also, TC-CVC was found to be an independent risk factor for elevated TOS. Moreover, patients who had an infectious disease and had any vascular event within the last six months were excluded from the study.

A meta-analysis composed of 62 studies reported that the proportion of access-related fatal infections in available studies was not precise, and in one study, only 23% of all infection-related hospitalizations were caused by access infection, suggesting that infections do not entirely explain the increased mortality associated with access types. In this meta-analysis, patients with CVCs had higher risks for all-cause mortality and cardiovascular events [29]. In a study of 4854 patients, AVF use 90 days after dialysis initiation was found to be associated with lower cardiovascular mortality compared with CVC use. The authors hypothesized that the biofilm in synthetic CVCs might increase the risk of CVD in HD patients via systemic inflammation [30].

Clinicians should bear in mind that OS and SI further increased by the use of TC-CVC may be a cause of worsening cardiovascular outcomes in HD patients. AVGs should be applied when AVF is not possible due to the patient's vascular structure. However, it should be remembered that peritoneal dialysis (PD) is an equivalent method applicable in almost all patients. PD should be introduced to every dialysis patient and encouraged to be used more frequently. For a small number of patients with no AVF or AVG chance and contraindications for PD, more biocompatible, less biofilm-producing CVCs with added antimicrobial properties may be used.

CONCLUSION

In HD patients, TC-CVCs inversely affect OS and SI status, presumably due to foreign body reactions and biofilm layers. However, VA through AVF is associated with a less oxidant state, and it is practically predictable that these more favorable effects will have ameliorating effects on adverse cardiovascular outcomes in these patients.

Authors' Contribution

Study Conception: BK; Study Design: BK, HHY, EBB; Supervision: MKD; Funding: BK; Materials: BK, HHY, EBB; Data Collection and/or Processing: BK, HHY, EBB; Statistical Analysis and/or Data Interpretation: BK, HHY, MKD; Literature Review: BK, HHY, MKD; Manuscript Preparation: BK and Critical Review: MKD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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