Antioxidant Properties of Curcumin and Its Impact on Arteriovenous Fistula Maturation in End-Stage Kidney Disease Patient with Diabetes Mellitus Type 2

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ABSTRACT

The risk of maturation failure in arteriovenous fistula (AVF) remains high. Curcumin poses antioxidant effects may enhance AVF maturation. This study evaluates the antioxidant effect of Curcumin on AVF maturation among type 2 diabetic patients (T2DM) with end-stage renal disease (ESRD). This was a single-blinded, randomized controlled trial conducted in three tertiary hospitals in Jakarta, Indonesia. Patients underwent the first hemodialysis. A total of 67 patients divided into groups of Curcumin, acetylsalicylic acid, and placebo. After 4 weeks, TAC level among the curcumin group was significantly higher compared to acetylsalicylic acid, and placebo groups 794.2(457.4±1473.7) μM vs. 519.2(247.7±1027.7) μM and 794.2(457.4±1473.7) μM vs. 542.5(281.9±1054.6) μM, respectively (p<0.05). Also, TAC after 8 weeks was significantly higher among curcumin group compared to acetylsalicylic acid, and placebo groups (820.5(380.7±1643.7) μM vs. 509.7(341.0±981.91) μM and 820.5(380.7±1643.7) μM vs. 497.7(324.7±979.2) μM, respectively (p<0.001). The TAC level patients with mature AVF were also higher. A 2000 mg/day of curcumin increases antioxidant capacity after 4 and 8 weeks following AVF surgery among ESRD with T2DM.

INTRODUCTION

End-stage renal disease (ESRD) has become a global health challenge that impacts the higher cost and economic burden. It also has broad consequences of mortality and morbidity rates. The chronic effects of ESRD cause death due to chronic kidney disease. One of the most common causes of ESRD in type 2 Diabetes mellitus (T2DM) is also one of the most common non-transmitted diseases, especially in developing countries. Renal transplantation is the best choice of treatment for ESRD patients. However, as number of donors are not always met,
hemodialysis becomes the most common treatment of choice for ESRD patients worldwide. Arteriovenous fistula (AVF) is a gold standard for hemodialysis vascular access. To be able to be used as a hemodialysis access, The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines on vascular access recommends the criteria of “rule of 6’s” consisting of a minimum volume flow of the vein of 600 mL/min, vein depth less than 6 mm from the skin, and vein diameter at least 6 mm (Lok et al., 2020). However, the incidence of AVF maturation failure remains high (Lok et al., 2020). There is 20-60% risk of AVF failed to be mature (Robbin et al., 2018; Sidawy et al., 2008; Bylsma et al., 2017). The cause of this maturation failure is multifaceted, leading to a feeding artery and draining vein flow insufficiencies. The insufficiency is mainly caused by local stenosis of neoimal hyperplasia, hemodynamic alteration of turbulent flow. The vascular flow alteration in T2DM also plays a role in the maturation failure of AVF as it induces inflammation, reactive oxygen species production, and atherogenesis. On the one hand, early thrombosis after surgical procedures involved in the AVF maturation failure. Therefore, several studies showed the benefits of giving aspirin as an adjuvant therapy to prevent AVF maturation failure due to thrombosis. However, a study to investigate the effect of aspirin treatment and AVF maturation among ESRD patients with T2DM remains limited. A phytochemical component from Curcuma sp. plant (Curcumin), has proven antiproliferative and antitumorigenic effects. These effects are expected to prevent the migration and proliferation of vascular smooth muscle, neoimal hyperplasia, and vascular stenosis as the main cause of AVF maturation failure. A study by Santos-Parker et al. shows curcumin reduced oxidative stress and improved vascular endothelial function among healthy middle-aged and older adults. Nevertheless, the research to evaluate curcumin administration towards AVF maturation among ESRD patients with T2DM remains limited. This study aimed to identify the level of serum antioxidant capacity and AVF maturation among ESRD patients with Diabetes mellitus type 2 using curcumin and acetylsalicylic acid administrations.

**METHODS**

**Study Design**

This is a single-blinded, randomized controlled trial compared three groups of patients referred to a tertiary hospital for surgical AVF procedure, who were recruited from 3 hospitals in Jakarta and West Java, Indonesia. The operations were done by board-certified vascular surgeons who are experienced in the procedure. The patient who met inclusion criteria was given written consent before the involvement of the study. Ethical approval obtained from The Ethics Committee of Faculty of Medicine, Universitas Indonesia (KET-353/UN2.F1/ETIK/PPM.00.02/2019)

**Study Subjects**

Patients referred to Cipto Mangunkusumo General Hospital (Jakarta Capital city, Indonesia), Hermina Bekasi Hospital (Bekasi City, West Java Province, Indonesia), and Hermina Depok Hospital (Depok City, West Java Province, Indonesia) were between 18 to 75 years old. They underwent brachio-cephalic arteriovenous fistula procedure. They were with glomerular filtration rate (GFR) below 25 mL/min/1.73m², clinically and laboratory diagnosed with T2DM, and preoperative cephalic vein and brachial artery more than 2 mm. Exclusion criteria included patients with human immunodeficiency virus infection (HIV), previous AVF procedure on cubital fossa or more proximal than cubital fossa on the same extremity, or patients on anti-aggregation therapy as another cardiac comorbidity indication.

**Inclusion criteria**

1. Males or females undergoing maintenance hemodialysis.
2. Age 18 year-75 year.
3. Brachial artery diameter of > 2 mm, with minimal of plaque, and triphasic spectrum waveform on duplex ultrasonography.
4. Cephalic vein diameter of > 2mm, left hand cubital fossa, compressible, continuum to proximal central vein, and no obstructed flow due to stenosis of thrombosis.

**Exclusion criteria**

1. Had previous AVF surgical procedure on cubital fossa brachial artery and cephalic vein, or other location more proximal in the same extremity.
2. Previously known or confirmed with stenosis of draining vein.
3. Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS).
4. Critically ill and need an intensive care.
5. On thrombolytic therapy for other cardiovascular indications.

6. On other medication or antioxidant supplementation.

7. Hepatitis, cirrhosis, and hepatocellular carcinoma.

8. Early haemorrhage and hematoma post-operation.

9. AVF infection.

10. Anastomosis complication.

11. Early access thrombosis (>30 days).

12. Access malfunction.

**Randomization**

It confirmed the patient’s eligibility, baseline data collected, and patient’s informed consent. The research used simple randomization for the curcumin group, acetylsalicylic acid group, and a placebo group.

**Experimental protocol**

Following the study’s recruitment, patients underwent surgical brachiophalic AVF construction procedure measured their baseline characteristics. Subsequently, patients were randomly assigned to give different treatment: curcumin 2000 mg/day (Curcumin 500 mg, Sabinsa Corporation, New Jersey, USA), acetylsalicylic acid 80mg/day (Aspilets tablet, Medifarma Lab, Depok, Indonesia), or placebo (Saccharum lactis, Indoefarma, Jakarta, Indonesia). The evaluation period was done 4 weeks apart: post-surgery, 4 weeks after surgery, and 8 weeks after surgery. Patients were also followed-up weekly for their drug compliance. In addition, patients were also advised to do hand exercise supplemented with a guidebook given to the patients.

Total antioxidant capacity was analyzed in this study. A heparin tube was used to collect venous blood samples that were taken 10 cm downstream from AVF anastomosis. Blood samples were centrifuged for 15 min at 3,000 rpm. Quantification of total antioxidant capacity (TAC) levels was done using oxidation-reduction colorimetric methods.

An AVF was considered as mature if the patients fulfilled the following characteristics according to The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) “rule of 6s”: fistula blood flow of 600 mL/min, vein diameter of 6 mm, and vein depth of 6 mm (Lok et al., 2020).

**Statistical analysis**

The numerical variable was presented as mean with standard deviation or median with minimum and maximum values, as appropriate. Analysis of numerical variable was done using analysis of variance (ANOVA) with a post-hoc test of Bonferroni or Kruskal-Wallis with a post-hoc test of Mann Whitney, as appropriate. All statistical analysis was performed using IBM SPSS ver.25 software for Windows with α-level of 0.05 was considered as statistically significant.

**RESULTS**

A total of 72 patients with a mean age of 57 years were enrolled in the study. Among 72 patients, an equal allocation of 1:1:1 was implemented: 24 patients received Curcumin, 24 patients received acetylsalicylic acid, and 24 patients received a placebo.

Within the study period, a total of 7 patients were excluded from further analysis due to thrombosis on AVF, postoperative hematoma, and died 8 weeks post-operation. There was no significant difference in baseline characteristics among different groups (Table 1).

The serum TAC of patients in each group was measured (Table 2). The postoperative TAC among groups was not different. Subsequently, on the 4th week after AVF surgery, a total serum antioxidant capacity among patients in the curcumin group was significantly higher compared to the acetylsalicylic acid group 794.2(457.4; 1473.7) μM vs. 519.2(247.7;1027.7) μM, and placebo group 794.2(457.4; 1473.7) μM vs. 542.5(281.9;1054.6) μM, respectively (p<0.05).

Similarly, after 8 weeks following AVF surgery, the level of TAC among the curcumin group was higher than both the acetylsalicylic acid group and placebo group 820.5(380.7; 1643.7) μM vs. 509.7(341.0; 981.91) μM and 820.5(380.7; 1643.7) μM vs. 497.7(324.7; 979.2) μM, respectively, p<0.001.

We compared the level of TAC between mature AVF and non-mature AVF groups (Table 3). Our finding showed that although not statistically significant, the level of TAC after 4 weeks following surgery was higher among patients with mature AVF 665.75±205.17 vs. 607.77±291.04) μM (p=0.166). In the 8th week of follow-up after AVF surgery, the level of TAC in the mature AVF group was higher, although not statistically significant 689.29±250.98 vs. 562.92±190.88 μM (p=0.052).
### Table 1: Baseline characteristics

|                      | Curcumin (n=24) | Salicylic acid (n=21) | Placebo (n=22) | p-value   |
|----------------------|-----------------|-----------------------|---------------|-----------|
| **Sex (male)**       | 17              | 10                    | 7             | <0.001    |
| **BMI (kg/m²)**      | 23.22 ± 3.42    | 23.45 ± 4.55          | 24.45 ± 4.15  | 0.572     |
| **Systolic blood pressure (mmHg)** | 134 (115; 189)   | 140 (120; 190)        | 150 (120; 180) | 0.316     |
| **Diastolic blood pressure (mmHg)** | 82 (65; 100)    | 80 (70; 100)          | 85 (65; 108)  | 0.797     |
| **Age (years)**      | 55.7 ± 7.27     | 57.48 ± 8.80          | 58.05 ± 9.77  | 0.640     |
| **Hematocrit (%)**   | 25.2 (18; 36)   | 28 (17; 40.7)         | 27 (16; 36)   | 0.114     |
| **Leukocyte (1000/µL)** | 8.045 ± 2.474   | 8.607 ± 2.305         | 8.671 ± 1.965 | 0.600     |
| **Platelet count (103/µL)** | 255.83 ± 63.12  | 283.76 ± 65.19        | 265.23 ± 58.57 | 0.330     |
| **Random blood glucose (mg/dL)** | 151 (74; 414)   | 163 (101; 321)        | 142 (54; 512) | 0.318     |
| **Total cholesterol (mg/dL)** | 184 (116; 246)  | 181 (144; 289)        | 168 (117; 316) | 0.194     |
| **Triglyceride (mg/dL)** | 139 (44; 320)   | 165 (65; 264)         | 171 (74; 432) | 0.515     |
| **HDL (mg/dL)**      | 43 (24; 98)     | 40 (27; 75)           | 43 (23; 160)  | 0.913     |
| **LDL (mg/dL)**      | 110.71 ± 34.88  | 118.73 ± 39.21        | 113.15 ± 35.62 | 0.391     |
| **Smoking, (yes)**   | 9               | 8                     | 6             | 0.821     |
| **Brachial artery diameter (mm)** | 4.30 ± 0.61    | 4.23 ± 0.59           | 3.93 ± 0.85   | 0.144     |
| **Cephalic vein diameter (mm)** | 3.1 (2.0; 4.8)  | 3.1 (2.0; 5.2)        | 2.5 (2.0; 5.4) | 0.336     |

Variables are listed as mean ± SD with green shade as they were normally distributed and median (minimum; maximum) with clear shade as they were not normally distributed. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

### Table 2: TAC on Curcumin, acetylsalicylic acid, and Placebo groups following AVF procedure

|                      | Placebo (n=22) | Salicylic acid (n=21) | Curcumin (n=24) | p-value   |
|----------------------|----------------|-----------------------|-----------------|-----------|
| Post-operative (µM)  | 532.94(265.7; | 480.7(333.73; | 522.67(295.55; | 0.508     |
|                      | 1293.73)      | 1076.7)               | 761.00)         |           |
| 4 weeks post-        | 542.5(281.91; | 519.2(247.7; | 794.2(457.4; | 0.001*    |
| operative (µM)       | 1054.64)      | 1027.7)               | 1473.7)         |           |
| 8 weeks post-        | 497.7(324.7; | 509.7(341.0; | 820.5(380.7| <0.001**  |
| operative (µM)       | 979.2)        | 981.91)               | 1643.7)         |           |

Variables are listed as mean ± SD with green shade as they were normally distributed

* Post hoc Mann-Whitney Curcumin vs. acetylsalicylic acid p<0.05; Curcumin vs. Placebo p<0.05; acetylsalicylic acid vs. Placebo p=0.981.

** Post hoc Mann-Whitney Curcumin vs Salicylic acid p<0.001; Curcumin vs Placebo p<0.001; Salicylic acid vs Placebo p=0.671.

### Table 3: TAC levels among mature and non-mature AVF

|                      | Mature (n=47) | Non-mature (n=20) | p-value |
|----------------------|--------------|------------------|--------|
| 4 weeks post-operative (µM) | 665.75 ± 205.17 | 607.77 ± 291.04 | 0.166  |
| 8 weeks post-operative (µM) | 689.29 ± 250.98 | 562.92 ± 190.88 | 0.052  |

Variables displayed as mean ± SD with green shade as they were normally distributed.
DISCUSSION

The level of oxidative stress level tends to be higher in patients with renal failure by uremia, Diabetes mellitus, and hypertension. Furthermore, hemodialysis contributes to this markedly higher level of oxidative stress resulted in the local injury of endothelium and dramatic alteration of blood flow through an AVF. The high level of oxidative stress will stimulate the production of reactive oxygen species (ROS) that will activate several signaling pathways for smooth muscle migration and proliferation to modulate AVF remodeling. The persistence of AVF remodeling as the result of an excessive level of oxidative stress will eventually lead to AVF stenosis and maturation failure. Hence, the antioxidant (curcumin) is needed to counterbalance the high oxidative stress level and prevent its consequences.

In this present study, we found the TAC level on the curcumin group was significantly higher compared to the acetylsalicylic acid group and placebo group after 4 and 8 weeks following AVF surgery in ESRD patient. This finding was in line with a previous study that shows curcumin supplementation reduces oxidative stress after 12 weeks compared to placebo among healthy middle-aged and older adults (Santos-Parker et al., 2017). In a previous double-blind, randomized controlled trial study involving patients who underwent hemodialysis, a 500mg Curcumin supplementation for 2 months was accompanied by increased in antioxidant products and reduced ROS (Pakfetrat et al., 2015). There are a lot of mechanisms explaining the antioxidant effect of Curcumin. Studies on Curcumin supplementation’s antioxidant effects on rats found the Curcumin inhibits ROS and inflammation by upregulating antioxidant enzymes by macrophages (Soetikno et al., 2013, 2011). Curcumin suppresses the expression of IL-6, TNF-α, and p47phox as a key subunit of NADPH enzyme in angiotensin II-induced inflammation (Li et al., 2017). The expression of heme-oxygenase-1 (HO-1) increased by Curcumin through antioxidant response element (ARE) activation (Pae et al., 2007; Fleenor et al., 2013).

The high oxidative stress and low antioxidant capacity can induce AVF maturation failure in patients with ESRD. The level of TAC on the mature AVF group was also compared with non-mature AVF in this study. Although not statistically significant, our result shows the level of TAC among the mature AVF group was higher compared to the non-mature AVF group. In addition, if we look at the mere p values, the difference of TAC level was even larger after 8 weeks following AVF surgery compared to 4 weeks after AVF surgery. To date, there is no study contrasting the level of TAC between two different AVF maturation-outcome groups. However, several previous studies support this present study’s findings. An increase of CD68 (a macrophage marker, an inflammation marker) and decreased antioxidant enzyme superoxide dismutase 1 (SOD1) in the veins were significantly associated with maturation success (Tong et al., 2017). This previous study results suggest a decrease of oxidant state of the vein was associated with maturation success (Tong et al., 2017). Another study found that monoamine oxidases (MAOs) as a source of vascular oxidative stress contribute to AVF maturation failure (Utu et al., 2017). A similar study concluded using an MAO inhibitor to counter the oxidative state might improve AVF maturation and long-term patency of the vascular access in patients who underwent hemodialysis (Utu et al., 2017). Significantly, the increased TAC level over time adds another benefit as a patient with T2DM needs a longer time for AVF to be mature than a patient without T2DM (4.2 ± 2.91 vs. 2.9 ± 1.62 months, p<0.05) (Fitzgerald, 2004).

This present study has several limitations. This study was only conducted in 3 centers in Java, Indonesia. This study’s follow-up period was only 8 weeks, as patients with T2DM require a long period to attain mature AVF compared to patients without T2DM.

CONCLUSION

This is the first study to report the effect of curcumin and salicylic acid on TAC serum levels in ESRD patients with T2DM who underwent AVF surgery. A high-dose of curcumin increases antioxidant capacity after 4 and 8 weeks following AVF surgery among ESRD with T2DM patients. A 2000 mg/day of curcumin increases antioxidant capacity after 4 and 8 weeks following AVF surgery among ESRD with Diabetes mellitus type patients. The total serum antioxidant capacity curcumin group was higher than both the acetylsalicylic acid group and placebo group. Furthermore, on a massive scale, the multi-centered study is required to understand better curcumin supplementation and its effect on AVF maturation among ESRD patients with T2DM.

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Conflict of interest
The authors declare that they have no conflict of interest for this study.

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