

## THE EFFECTS OF CURCUMIN AND ACETYLSALICYLIC ACID TO ARTERIOVENOUS FISTULA MATURATION IN END-STAGE RENAL DISEASE PATIENTS WITH DIABETES MELLITUS

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### ABSTRACT

**Background:** *The study of diabetic arteriovenous fistula (AVF) in end-stage renal disease is essential in order to know on how to maintain the AVF in good function. We studied to support the AVF using Curcumin, Acetylsalicylic acid, and Placebo.*

**Methods:** *This is a randomized, parallel, placebo-controlled, double-blinded, clinical trial involving 65 patients with diabetes mellitus type-2 who underwent brachiocephalic shunt in the left or right cubital fossa. The patients were divided into three groups, namely curcumin group (n = 23), acetylsalicylic acid group (n = 21), and placebo group (n = 21). The statistical analysis was performed using SPSS version 25. All statistical tests were two-tailed, and a p-value < 0.05 was considered significant.*

**Results:** *After 4 weeks of treatment: the AVF maturation of Curcumin versus Placebo (26.1 % vs. 23.8 %), Acetylsalicylic acid versus Placebo (42.9 % vs. 23.8 %), Curcumin vs. Acetylsalicylic acid (26.1 % vs. 42.9 %). Statistically, no significant difference was found in maturation and draining vein diameter. Draining vein Intimal-Media Thickness (IMT) in Curcumin group is significantly better than other groups (p=0.003) after 8 weeks.*

*After eight weeks of treatment, the AVF maturation treated by the Curcumin has a higher percentage of maturation (82.6 %) versus Placebo (57.1 %), p=0.099, but the Curcuma (82.6.1 %) noted had a significant difference with Acetylsalicylic acid (71.4 %) (p = 0.481). A significant difference in draining vein diameter was noted between the Curcumin vs. Placebo (p<0.05), but Curcumin vs. Acetylsalicylic acid was not significant (p = 0.481).*

**Conclusions:** *Daily high dose curcumin was able to increase draining vein diameter, and a higher maturation rate. However, there is no significant difference in all of the maturation parameters between the Curcumin and Acetylsalicylic.*

**KEYWORDS:** *Curcumin, Acetylsalicylic Acid, Arteriovenous Fistula Maturation, End-Stage Kidney Disease, Diabetes Mellitus*

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### Article History

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## INTRODUCTIONS

### Background

End-stage kidney disease is a global health problem that contributes to catastrophic health expenditure, and have as significant effect in high morbidity and high mortality rate related to chronic illness.<sup>1</sup>The study by the global burden of

disease in 2015 predicted that 1.2 million people died due to end-stage kidney disease, increased by 32 % from 2005.<sup>2</sup> Globally, the most common cause of the end-stage renal disease is diabetes mellitus.<sup>2,3</sup> Kidney transplantation is the first-line treatment of end-stage kidney disease. However, for most people, hemodialysis is still the treatment of choice for end-stage kidney disease.<sup>3,4</sup> In 2010, there were 2.62 million people in the world that were undergoing routine hemodialysis. This number was predicted two-fold to increase by the year 2030.<sup>4</sup>

The golden standard of hemodialysis access is using autologous vessels.<sup>5,6</sup> According to The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), the functional AVF fulfills the “rule of 6s”. However, AVF in the diabetic patient has a high risk of maturation failure; only 26 % can mature in 6 months.<sup>3,7</sup> The cause for AVF maturation includes insufficient flow from feeding artery and draining vein.<sup>6,8</sup> Both inadequate flow from the feeding artery and the draining vein were caused by neointima hyperplasia, thrombus, and local stenosis, which was influenced by AVF hemodynamic.<sup>8</sup> Early thrombus formation after surgery is one of the leading causes of maturation failure of AVF. Thus, some systematic reviews and clinical trials suggest the administration of antithrombocyte aggregation, such as acetylsalicylic acid.<sup>9</sup> However, most of the studies showed no significant difference compared to the placebo.<sup>10</sup>

Curcumin is a phytochemical substance from *Curcuma* sp. It has anti-proliferative, anti-inflammatory, reduces oxidative stress, and anti-tumorigenic potency.<sup>11, 12</sup> Thus, curcumin might prevent migration and proliferation of vascular smooth muscle, neointima hyperplasia, and vascular stenosis.<sup>11, 12</sup> However, there is a limitation in the usage of curcumin for AVF maturation in the end-stage kidney of diabetic patients. The study compares the AVF maturation in diabetic end-stage kidney patients taking curcumin to acetylsalicylic acid, and placebo.

## **METHODS**

### **Study Design and Participants**

The experiment is a randomized, parallel, placebo-controlled, double-blinded clinical trial in 65 patients of diabetes mellitus type-2 complicated end-stage kidney failure. It evaluates the effect of curcumin, acetylsalicylic acid, and placebo treatment on AVM maturation.

Inclusion criteria: 1) Patients man / woman aged 2160 years old with an estimated glomerular filtration rate (below 25ml to 5ml / minute / 1.73m<sup>2</sup>) and diabetes mellitus type-2. 2) The diameter of the cephalic vein of more than 2 mm. 3) brachial-cephalic (end to side anastomosis) arteriovenous fistula surgery from September 2019 until April 2020. 4) The patient understood the study and ready to participate and put their signature of the agreement.

Exclusion criteria: Patients with severe organ diseases, human immune deficiency infection, or those who consumed thrombocyte anti-aggregation drugs. Steal syndrome, postoperative hematoma.

Baseline characteristics of each patient were taken prior to AVF surgery and directly after surgery.

### **Treatment Allocation**

Patients were randomized to receive 2000 mg / day of curcumin, acetylsalicylic acid 80mg / day, or placebo. The curcumin given to the patient is 2000 mg / day (CURCUMIN® optimized curcumin 500 mg, Sabinsa Corporation, New Jersey USA), which is the dose that shows significant endothelial function protection in the previous study.<sup>11</sup>

The acetylsalicylic acid dose given to the patient is 80mg / day (Aspilets® tablet, Medifarma Lab., Depok, Indonesia), the treatment-dose used in cardiovascular disease prevention in the high-risk patient.<sup>13</sup>

Placebo, in the form of a tablet, made like the aspilets tablet, containing Saccharum lactis (produced by Indofarma, Jakarta, Indonesia), was given to the patients one tablet once a day.

The portable ultrasonography of GE U.S.A LOGIQ™ e Pro Edition Ultrasound System was used as a calibrated ultrasonography which explicitly measures blood vessel.

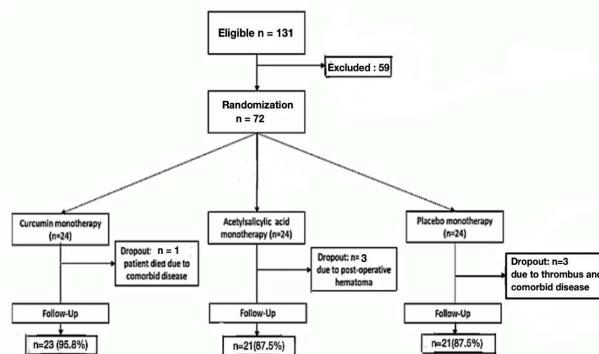
**BLINDINGS AND DATA COLLECTIONS**

Ultrasonography was performed in three participating hospitals during the 4<sup>th</sup> and 8<sup>th</sup> weeks following the surgery in an outpatient clinic. The treatment of each patient concealed from the examiner. The data collection included vein diameter, vein volume flow, vein Intima-Media Thickness (IMT), and vein peak systolic velocity in juxta-anastomosis. The dropout criteria for this trial are infection, thrombosis, post-surgical bleeding, hematoma, pseudoaneurysm, steal syndrome, comorbidity, antiplatelet treatment, unrelated to AVF surgery, or loss to follow up.

**Statistical Analysis**

We performed a descriptive analysis of baseline patient characteristics. Continuous data summarized as median (minimum-maximum) or mean (standard deviation), as appropriate, and discrete data was presented as a percentage. The outcome with continuous variables were analyzed with a one-way ANOVA test with post hoc of Bonferroni or Tamhane test or Kruskal-Wallis test with post hoc of Mann Whitney test with alpha or type-1 error adjustment for multiple testing by dividing alpha with several of pairwise comparisons. The outcome with the discrete variable was analyzed using the Fisher exact test, and the risk ratio with its 95 % confidence intervals also calculated. All statistical tests were two-tailed, and a p-value <0.05 was considered significant statistical analyses using SPSS for Windows V.25.0 (SPSS, Chicago, Illinois, USA).

Figure 1 shows Out of 65 patients, 23 patients received curcumin intervention, 21 patients received the acetylsalicylic acid intervention, and 21 patients received placebo intervention. One patient of the Curcumin group, three patients of the acetylsalicylic group, and three patients of the placebo group dropped out (Figure 1)



**Figure 1: Recruitment and Selection Flow Chart**

**RESULTS**

**Baseline Characteristics**

We observed a non-statistical difference in baseline characteristics between curcumin, acetylsalicylic acid, and placebo group. The curcumin group has the highest number of smoking patients (n=9; 37.5 %), followed by the acetylsalicylic acid group (n=8; 33.3 %), and placebo (n=6; 25 %). The baseline characteristics of these three groups were comparable (Table 1).

**Table 1: Baseline Characteristic of Patients Between Curcumin, Acetylsalicylic Acid, and Placebo Groups**

	Curcumin (n=23)	Acetylsalicylic Acid (n=21)	Placebo (n=21)
BMI (kg / m <sup>2</sup> )	23.22(0.71)	23.45 (0.99)	24.45 (0.91)
Systolic blood pressure (mmHg)	141.22(4.30)	147.10(4.88)	147.90(3.81)
Diastolic blood pressure (mmHg)	83.17(1.88)	83.05(1.88)	84.62(2.02)
Age (years)	55.7(1.52)	57.48 (1.92)	58.05 (2.13)
Hemoglobin (g / dl)	9.09(0.35)	9.66(0.33)	9.35(0.18)
Hematocrit (%)	25.56(1.43)	28.5(1.07)	26.70(1.48)
Leucocyte (/ $\mu$ L)	8044.78(515.90)	8607.14(503.05)	8671.43(428.97)
Thrombocyte (10 <sup>3</sup> / $\mu$ L)	255.83(13.16)	283.76 (14.23)	265.23(12.78)
Random glucose (mg / dL)	161.48(15.91)	186.1(14.19)	177.19(21.92)
Total Cholesterol (mg / dL)	189.35(6.34)	195.76(9.61)	177.29(10.14)
Triglyceride (mg / dL)	157.35(15.06)	166.38(13.6)	182.19(16.75)
HDL (mg / dL)	45.39(3.59)	43.00(2.47)	47.05(6.30)
LDL (mg / dL)	110.71(7.27)	118.73(8.56)	113.15(7.77)
Smoking, n	9	8	6
Brachial artery diameter (mm)	4.30(0.13)	4.23(0.13)	3.93(0.21)
Brachial artery volume flow	61.29(52.3, 77.7)	49.13(38.9, 59.3)	47.32(31.9, 62.7)
Brachial Artery IMT (mm)	0.42(0.02)	0.36(0.03)	0.42(0.04)
Cephalic vein diameter (pre-op) (mm)	3.53(0.72)	3.22(0.23)	2.87(0.22)
Cephalic vein diameter (post-op) (mm)	4.04(0.18)	4.09(0.16)	3.98(0.18)
Draining vein volume flow (post-op) (mL / min)	482.40(57.44)	437.37(58.77)	528.83(70.37)
Cephalic vein IMT (mm)	0.33(0.02)	0.30(0.03)	0.47(0.12)
Depth of draining vein from the skin (mm)	3.19(0.20)	3.68(0.30)	3.74(0.46)

Data were presented as mean (standard deviation) or median (minimum, maximum) as appropriate

BMI = Body Mass Index; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; IMT = Intima Media Thickness; Post-op = Post-Operative; Pre-op: Pre-Operative

### Maturation after Four Weeks of Intervention

There was no significant difference statistically in draining vein diameter, draining vein depth, volume flow, and draining vein IMT between curcumin, acetylsalicylic acid, and placebo group. Although not statistically significant ( $p = 0.143$ ), patients treated with acetylsalicylic acid showed higher volume flow than the other two groups (Table 2). The acetylsalicylic acid maturation rate (42.9 %) was higher than with placebo (RR: 1.80, 95 % CI (0.72, 4.47),  $p=0.326$ ). Curcumin group also showed fewer maturation numbers compared to acetylsalicylic acid ( $p=0.342$ ). Curcumin vs. Placebo, RR: 1.10 (0.39, 3.06),  $p=1.000$ .

**Table 2: After Four Weeks of Intervention: Draining Vein of AVF Maturation in Curcumin, Acetylsalicylic Acid, and Placebo Groups**

	Curcumin (n=23)	Acetylsalicylic Acid (n=21)	Placebo (n=21)	p value
Draining vein diameter (mm)	5.67 (0.73)	5.76 (1.20)	5.51 (1.01)	0.746
Draining vein depth from the skin (mm)	3.30 (3.11, 3.83)	3.30 (3.06, 4.24)	3.00 (2.71, 3.93)	0.492
Draining vein volume flow (mL / min)	1006.04 (444.14)	1173.84 (462.83)	909.74 (386.84)	0.143
Draining vein IMT (mm)	0.50 (0.12)	0.49 (0.17)	0.48 (0.11)	0.826

Data were presented as mean (standard deviation) or median (minimum, maximum) as appropriate

IMT = Intima Media Thickness

**Table 3: After Four Weeks of Intervention: AVF Maturation in Curcumin, Acetylsalicylic Acid, and Placebo Groups**

	Maturation No / Total (%)			Risk Difference	Risk Ratio	P Value
	Curcumin	Acetylsalicylic Acid	Placebo			
Curcumin vs Placebo	6 / 23(26.1 %)	-	5 / 21 (23.8 %)	0.023	1.10 (0.39, 3.06)	1.000*
Acetylsalicylic acid vs Placebo	-	9 / 21(42.9 %)	5 / 21 (23.8 %)	0.190	1.80 (0.72, 4.47)	0.326*
Curcumin vs Acetylsalicylic acid	6 / 23(26.1 %)	9 / 21(42.9 %)	-	-0.168	0.61 (0.26, 1.42)	0.342*

Fisher exact-test

**Maturation after 8 Weeks of Intervention**

We observed a significant difference in draining vein diameter between curcumin, acetylsalicylic acid, and placebo group (p = 0.003). Post-hoc analysis between each group shows a considerable difference in diameter between curcumin and the placebo group (p < 0.001).

Other maturation parameter shows no significant difference between the three groups event post eight weeks of intervention. There is an increase in volume flow after eight weeks of intervention compared to four weeks of intervention in curcumin and placebo group. But, we could not find increment in the acetylsalicylic acid group (Table 3 and Table 5).

The curcumin group has a higher percentage of maturation (82.6 %) compared with the acetylsalicylic group (71.4 %) and placebo group (57.1 %) (Table 5). Curcumin compared to Acetylsalicylic acid shows 1.16 (95 % CI 0.83, 1.61) relative risk (p= 0.481) (Table 5). The number of patients with a mature AVF between each treatment in week four and week eight are presented in Figure 2. It shows that the Curcuma group has better maturation compared with the others.

**Table 5: After Eight Weeks of Intervention: Parameter of AVF Maturation in Curcumin, Acetylsalicylic Acid, and Placebo Groups**

	Curcumin (N=23)	Acetylsalicylic Acid (N=21)	Placebo (N=21)	P Value
Draining vein diameter (mm)	6.60 (0.13)	6.35 (0.23)	5.83 (0.14)	0.003*
Draining vein depth (mm)	2.60 (2.38, 3.89)	3.00 (2.65, 3.66)	2.90 (2.29, 4.41)	0.687
Draining vein volume flow (mL / min)	1254.51 (69.79)	1186.31 (122.23)	1271.23 (648.66)	0.857
Draining vein IMT (mm)	0.47 (0.45, 0.51)	0.43 (0.35, 0.53)	0.42 (0.43, 0.52)	0.472

Data were presented as mean (standard deviation) or median (minimum, maximum) as appropriate

IMT = Intima Media Thickness

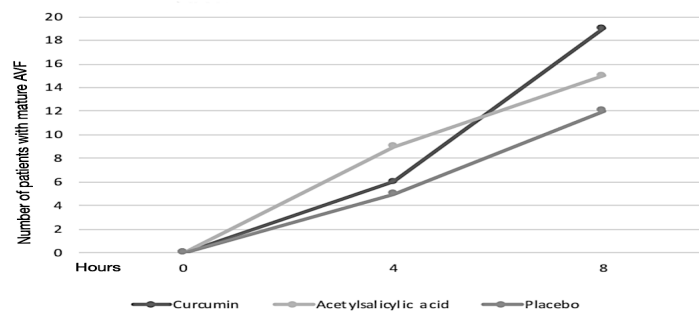
\*Post hoc Mann Whitney test between each treatment group: Curcumin vs Acetylsalicylic acid p=0.390;

Curcumin vs Placebo p< 0.001; Acetylsalicylic Acid vs Placebo p=0.063.

**Table 5: After Eight Weeks of Intervention, the AVF Maturation in Curcumin, Acetylsalicylic Acid, and Placebo Groups**

	Maturation No / Total (%)			Risk Difference	Risk Ratio	P Value
	Curcumin	Acetylsalicylic Acid	Placebo			
Curcumin vs Placebo	19 / 23(82.6 %)	-	12 / 21 (57.1 %)	0.397	1.45 (0.95, 2.19)	0.099*
Acetylsalicylic acid vs Placebo	-	15 / 21(71.4 %)	12 / 21 (57.1 %)	0.143	1.25 (0.79, 1.98)	0.520*
Curcumin vs Acetylsalicylic acid	19 / 23(26.1 %)	15 / 21(71.4 %)	-	0.112	1.16 (0.83-1.61)	0.481*

Fisher exact-test.



**Figure 2: The AVF Maturation Shows between Curcumin, Acetylsalicylic Acid, and Placebo Group in Four Weeks and Eight Weeks. it Shows that the Curcumin Group has Better Maturation Compared with the Others.**

**DISCUSSIONS**

The previous study revealed that the factors of age, vein diameter, lipid profile, smoking, obesity, and diabetes might become a risk factor for AVF failure or delayed maturation.<sup>14</sup>

A higher rate of maturation and draining vein volume flow was observed in the Acetylsalicylic group after four weeks of treatment compared to the Curcumin and Placebo group. This result was consistent with the previous study and might relate to the mechanism of action of acetylsalicylic acid.<sup>9, 15</sup> Acetylsalicylic acid has anti-thrombotic effects by inhibiting platelet-dependent thromboxane-A2 formation.<sup>9</sup> Acetylsalicylic acid can reduce the platelet activation through interfering with different mechanisms such as nitric oxide (NO) / cGMP-dependent process and increases the NO production in endothelial cells.<sup>16</sup> Interestingly, even a higher rate of maturation of Acetylsalicylic acid was noted after four weeks of intervention, it was lower compared to Curcumin in 8 weeks (Figure 2). The previous study stated that the administration of clopidogrel could reduce the number of AV fistula maturation failure due to thrombosis in the early state, but no significant increase in maturation rate.<sup>15</sup>

After four weeks of treatment, patients treated with Curcumin did not show any significant difference in all the AVF maturation parameters. However, after eight weeks of treatment, the Curcumin group showed a significant draining vein diameter than the Placebo group. Vein diameter is one of three key components to determine AVF maturation alongside depth of draining vein and volume flow in the juxta anastomosis region. Although not statistically significant, patients treated with Curcumin showed a high maturation rate compared to Placebo and Acetylsalicylic acid after eight weeks of intervention. In the linear graph, we observed that patients treated with Curcumin showed the highest maturation rate in four weeks and eight weeks. Curcumin exhibits a variety of pharmacological effects, including inhibiting platelet

aggregation, anti-tumor, antioxidant, anti-inflammatory, and anti-infectious.<sup>17,18</sup> Curcumin also lowered the level of secretion and protein expression of MMP-9, which have a role in intima hyperplasia, which might lead to atherosclerosis.<sup>11,12</sup> Atherosclerosis becomes more prevalent in diabetic patients, which will cause further inflammation in blood vessels and maturation delay of AVF.<sup>10</sup> The larger draining vein diameter in a patient treated with Curcumin might be related to anti-inflammatory, anti-thrombogenic activity, and anti-tumorigenic that prevent the inflammation, hyperplasia of neointima, and stenosis that might delay the AVF maturation.<sup>17,18</sup>

## LIMITATIONS

This study has several limitations, including small sample sizes. However, this study can use as a reference for future studies that used a larger sample size.

## CONCLUSIONS

Daily high dose curcumin was able to increase draining vein diameter, and a higher maturation rate. However, there is no significant difference in all of the maturation parameters between the Curcumin and Acetylsalicylic.

## CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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