Effect Of Omega-3 Fatty Acids On Vascular Access Patency In Chronic Hemodialysis Patients

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ABSTRACT: Background: Thrombosis of hemodialysis vascular access represents a major medical and economic burden. Omega-3 fatty acids play an important modulatory role in the immune and inflammatory responses and the progression of arteriosclerosis. Fish oils have been demonstrated to have anti-platelet effects, and reduce intimal hyperplasia in autogenous grafts. Such effects may improve arteriovenous fistula (AVF) and arteriovenous graft (AVG) patency. **Objective**: To determine the effect of fish oil on native AVF and synthetic graft patency in chronic hemodialysis patients. **Patients and Methods**: Prospective Case control study conducted on 80 chronic hemodialysis patients selected from El-Maadi Liver & Kidney Transplantation Hospital in Egypt. The study was conducted through a period of time spanning 6 months. Patients were divided randomly into two groups, group (1) composed of 40 hemodialysis patients receiving four Omega-3 fatty acids capsules/day (1-g per capsule) for the 6-months duration of the study and group (2) composed of 40 hemodialysis patients not receiving omega-3 fatty acids. Full clinical examination of AVF and grafts was done to all patients in every hemodialysis session during the six months period of the study. Angiography was done whenever indicated. **Results**: 82.5% out of our patients were having AVF as their vascular access while the remaining 17.5% were having AVG. There was highly significant statistical decrease in serum triglyceride, total cholesterol and LDL levels in group (1) compared to group (2) over the 6 months period (p<0.001). Highly significant statistical increase in HDL level and URR in group (1) compared to group (2) over the 6 months period (p <0.001). Angiography was done to 8 indicated patients (10%), 3 patients in group (1) (7.5%) and 5 patients in group (2) (12.5%).**Conclusion**: Fish oil leads to significant decrease in serum triglyceride level, total cholesterol level and LDL together with increase in HDL level in chronic hemodialysis patients. Vascular access blood flow also changed but not in a significant manner.

[Howayda El-Shinnawy, Walid Bichari, Yahya Makkeyah, Maha Behairy, Ahmed Shabaan. **Effect Of Omega-3 Fatty Acids On Vascular Access Patency In Chronic Hemodialysis Patients.** *Life Sci J* 2015;12(1):82-88]. (ISSN:1097-8135). http://www.lifesciencesite.com. 12

Key words: Omega 3 fatty acids, vascular access, AVF, Blood flow.

1. Introduction

Chronic dialysis patients experience a host of conditions that limit quality and length of life.[1] Maintaining functioning vascular access is vital for hemodialysis (HD) patients and its management accounts for a significant proportion of the cost of dialysis that included around 20% of their hospital admissions.[2] Strategies to reduce complication rates (for example thrombosis, infection, stenosis, aneurysm formation and distal limb ischemia) are needed.[3-6]

Thrombosis occurs in more than 50% of all arteriovenous grafts within 1 year after placement, necessitating a salvage procedure in more than 75%.[7, 8] Multiple studies have attempted to use different pharmacological approaches to minimize vascular access failure induced by thrombosis most of them were equivocal and needed further time to reassess. [9-11]

In patients with end-stage renal disease (ESRD) changes in lipid metabolism occur, creating a complex form of dyslipidemia.[12] Elevated levels of serum triglycerides (TG), increased levels of lipoprotein(a) and low high-density lipoprotein (HDL) cholesterol are part of the uremic dyslipidemia.[13, 14] While levels of low-density lipoprotein (LDL) cholesterol tend to be normal or near normal, other modifications of LDL cholesterol develop in relation to ESRD,[15] such as a prolonged half-life of LDL cholesterol,[16] increased oxidation of LDL cholesterol[17] and a high frequency of atherogenic small dense LDL particles.[18] In addition to the uremic dyslipidemia, patients with ESRD have a very high incidence of cardiovascular disease (CVD), [19] which may partly be explained by these lipid abnormalities.[20]

Omega-3 (ω-3) fatty acids play an important modulatory role in the immune and inflammatory responses, the progression of arteriosclerosis, vascular reactivity and blood pressure control, cell membrane function, and gene expression.[1] By mediating cell membrane function and structure and the synthesis of lipid mediators such as eicosanoids, ω-3fatty acids may offer HD patients a host of therapeutic benefits. ω-3 fatty acids are derived primarily from dietary sources, and cold-water fish is the main source of eicosapentanoic and

docosahexanoic acids, the two major bioactive ω-3 fatty acids.[1]

Fish oils have been demonstrated to have anti-platelet effects, and reduce intimal hyperplasia in autogenous grafts. [21] In addition, reductions in neointimal hyperplasia formation and enhanced endothelial function have been reported.[22] Such effects may improve arteriovenous fistula (AVF) and arteriovenous graft (AVG) patency by addressing the problem of both thrombosis and stenosis and enhanced endothelial function may also contribute to improved AVF maturation.[4]

We aimed to observe the effect of omega3 fatty acids supplements on dyslipidemia and vascular access patency in chronic hemodialysis patients.

2. Patients and Methods

Eighty chronic hemodialysis patients were selected from El-Maadi Liver & kidney transplantation hospital in Cairo, Egypt. They were undergoing hemodialysis three sessions per week for more than 6 months. Patients were selected and divided into two groups; Group (1) composed of 40 hemodialysis patients receiving ω-3 fatty acids (1 gm ω-3 capsule every 6 hours daily for 6 months) and Group (2) composed of 40 hemodialysis patients not receiving ω-3 fatty acids. Omega-3 composed of 18% eicosapentaenoic acid (EPA) and 12% docosahexaenoic acid (DHA). Each patient provided written informed consent before enrollment. The study was conducted with strict adherence to El-Maadi Liver & kidney transplantation hospital ethical committee.

Exclusion criteria included age <18 year old, patients with acute renal failure, diabetic patients, patient with history of thrombophilia or hypercoagulable state, active major bleeding in the prior month, active malignancy, pregnancy, uncontrolled hypertension, patients receiving >2 antiplatelet agents or anticoagulant treatment, patients with surgical revision of a previous access, patients with temporary or permanent hemodialysis catheters, and patients with history of allergy to fish or fish products.

All patients were subjected to history taking and clinical examination including duration on dialysis, etiology of ESRD, and history of smoking. Examination of vascular access was done in every hemodialysis session during study duration. Fasting serum samples were obtained in the early morning before the mid-week HD session and before heparin administration. Laboratory tests included hemoglobin (Hb), serum calcium (S.Ca), serum phosphorous (S.PO4), intact parathyroid hormone (iPTH) and lipid profile (total cholesterol, TG, LDL and HDL) were recorded as a baseline and then every month. Colored Doppler was used to measure vascular access blood flow monthly for 6 months. Duplex mapping documented the size and patency of the cephalic and basilic veins, the principal outflow sites for forearm bridge and autogenously AVF.

The entire vascular access was examined, including the inflow artery, the proximal anastomosis, the graft/fistula itself, the distal anastomosis, and the outflow vein. The peak systolic frequencies or velocities were then recorded and ratios determined by comparing the frequency at the site of the stenosis with the baseline frequency in the inflow artery proximal to the anastomosis. For calculation of stenosis, the minimal intraluminal cross-sectional area was compared with the diameter of a nearby normal segment using the formula:

(Original lumen – residual lumen) / Original lumen × 100= percent stenosis.

In case of changing in access blood flow for more than 20% of its original value, angiography was performed. To obtain initial venous access, the access was cannulated using an 18 gauge (for AVG) or a 21 gauge (for AVF) thin-walled needle. A guide wire was then passed into the access, and the needle was exchanged for a vascular sheath, which was used to inject radiocontrast for imaging of the access. If the cannulation was in the downstream direction, a retrograde occlusive arteriogram was performed to evaluate the artery and the juxta anastomotic region. If more than 50% of the lumen was found stenosed by angiography, this was considered an end point.

The degree of change (Δ) and percentage of change (%Δ) reflect the actual difference changed through the follow-up study; it was calculated for each patient, from which, the mean Δ and mean %Δ were compared with other group. It is defined as follow: Δ = value at 6^{th} month –baseline value; while %Δ = (value at 6^{th} month– baseline value)*100/baseline value. Negative Δ indicates a decrease in the level of the studied parameter while positive Δ indicated an increase in the level of the studied parameter.

IBM SPSS statistics (Version 21.0, IBM Corp., USA, 2012) was used for data analysis. Data was expressed as Mean ±SD for quantitative parametric measures in addition to both number and percentage for categorized data. Independent Student t test was used for comparison of quantitative variables among two independent groups. Chi-square test was used to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered significant.

3. Result

Both groups were matched regarding the sex distribution, etiology of ESRD, type of vascular access, AVF site, and history of smoking. There was no statistically significant difference when comparing the mean age, mean duration of dialysis, mean BMI among the studied groups. Only 8 patients (20%) underwent angiographic study for the vascular access, all of them had stenosis <50% of lumen and no interventions were performed. Despite these results no statistically significant difference was found between the two groups regarding the need of angiography (X^2=0.556, *P*=0.456).

There was no statistically significant difference when comparing the mean baseline TG, mean baseline HDL, mean baseline URR, mean baseline hemoglobin (Hb), mean baseline S.Ca, mean baseline $S.PO_4$, and mean baseline iPTH among the studied groups. While there was a statistically significant difference when comparing both group as regard mean baseline cholesterol (higher among group 2), mean baseline LDL (higher in group 1), and vascular access blood flow (higher in group 1).

When comparing both groups regarding the mean change (Δ) and mean percentage of change (%Δ) of different studied parameters only vascular access blood flow rate (decreased in both groups) didn't show any statistically significant difference, while TG (decreased in group 1 & increased in group 2), cholesterol (decreased in group 1 & increased in group 2), LDL (decreased in group 1 & increased in group 2), HDL (increased in group 1 & decreased in group 2), and URR (increased in group 1 & decreased in group 2) showed a statistically significant difference between the studied groups.

When correlating Δ access blood flow with change in the serum lipid parameters among each group alone, only significant positive correlation was found between Δ access blood flow with Δ TG and Δ LDL among group 1, while the only significant negative correlation was found between Δ access blood flow and Δ HDL among group 2.

When correlating %Δ access blood flow with percentage of change in the serum lipid parameters among each group alone, the only significant negative correlation was found between %Δ access blood flow and %Δ HDL among group 2.

Table 1: Comparison between Baseline patient characteristics among studied groups

Characteristics		Group 1 (n=40)	Group 2 (n=40)	*P* value
Sex	Male	20 (50.0%)	20 (50.0%)	1.000
	Female	20 (50.0%)	20 (50.0%)	
Age		51.05±10.36	53.83±6.26	0.151
Etiology of ESRD	Hypertension	4 (10.0%)	6 (15.0%)	0.922
	Polycystic kidney disease	7 (17.5%)	8 (20.0%)	
	Obstructive Uropathy	6 (15.0%)	4 (10.0%)	
	Chronic glomerulonephritis	2 (5.0%)	4 (10.0%)	
	Chronic pyelonephritis	7 (17.5%)	5 (12.5%)	
	Analgesic abuse	5 (12.5%)	4 (10.0%)	
	Unknown	9 (22.5%)	9 (22.5%)	
Duration of dialysis		4.95±3.80	4.13±2.09	0.233
BMI		22.78±1.93	22.53±1.84	0.555
Type of vascular access	AVF	33 (82.5%)	33 (82.5%)	1.000
	AVG	7 (17.5%)	7(17.5%)	
AVF site	Radio-cephalic AVF	21 (63.6%)	21 (63.6%)	1.000
	Brachio-cephalic AVF	12 (36.4%)	12 (36.4%)	
Smoking	Yes	10 (25.0%)	11 (27.5%)	0.799
	No	30 (75.0%)	29 (72.5%)	

Table 2: comparison of baseline studied parameters among studied groups

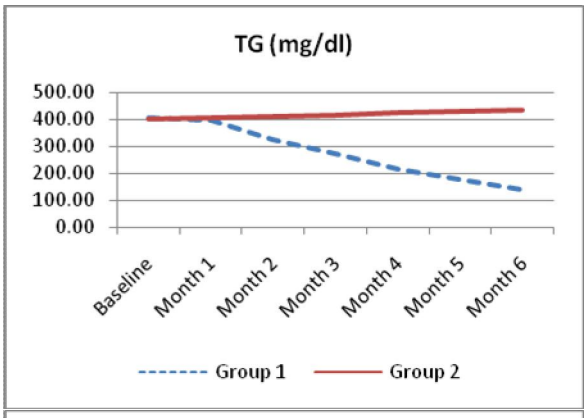
Baseline parameters	Group 1	Group 2	*P* value
TG (mg/dl)	403.40±89.57	401.83±76.30	0.933
Cholesterol (mg/dl)	264.13±47.12	294.35±28.77	**0.001**
LDL (mg/dl)	232.15±36.25	191.90±51.42	**0.000**
HDL (mg/dl)	89.80±30.43	90.98±25.51	0.852
URR (%)	71.58±7.33	69.30±2.29	0.067
Hb (gm/dl)	9.37±1.11	9.04±0.87	0.151
S.Ca (mg/dl)	9.05±0.38	9.04±0.40	0.932
$S.PO_4$ (mg/dl)	4.36±0.17	4.38±0.17	0.606
iPTH (pg/ml)	45.00±8.55	42.38±9.06	0.186
Access blood flow rate (ml/min)	746.25±54.76	711.25±68.40	0.014

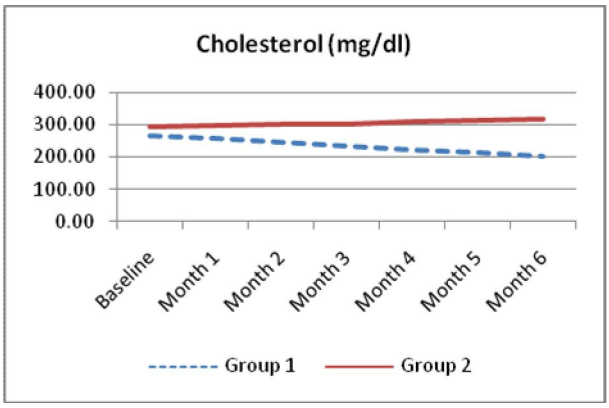
Table 3: Comparison of degree of change in studied parameters among studied groups

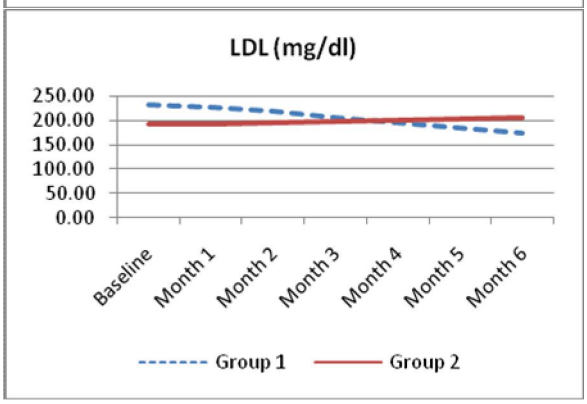
	Group 1	Group 2	*P* value
ΔTG (mg/dl)	265.30±78.98	34.20±45.17	**0.000**
%ΔTG	-64.84±6.90	9.74±14.26	**0.000**
Δ Cholesterol (mg/dl)	-62.73±35.31	21.15±16.42	**0.000**
%Δ Cholesterol	-23.31±10.84	7.21±5.73	**0.000**
Δ LDL (mg/dl)	-58.53±31.50	13.50±9.88	**0.000**
%Δ LDL	-23.93±9.54	7.37±5.00	**0.000**
Δ HDL (mg/dl)	1.80±7.80	-2.65±3.53	**0.002**
%Δ HDL	2.50±8.21	-2.43±4.41	**0.001**
Δ URR (%)	2.43±3.60	-0.98±0.80	**0.000**
%Δ URR	3.57±5.37	-1.41±1.16	**0.000**
Δ Access blood flow rate (ml/min)	-36.25±74.24	53.75±69.23	0.279
%Δ Access blood flow rate	-4.92±10.25	-7.77±10.28	0.218

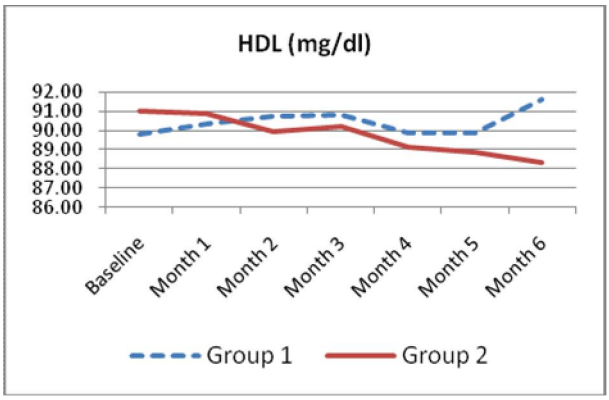
Table 4: Correlation between change in blood flow and change in serum lipid parameters

	Group 1 [r value (*P* value)]	Group 2 [r value (*P* value)]
Δ Access blood flow (ml/min)		
Δ TG (mg/dl)	0.411 (**0.008**)	0.235 (0.144)
Δ Cholesterol (mg/dl)	0.160 (0.324)	0.097 (0.550)
Δ LDL (mg/dl)	0.376 (**0.017**)	-0.280 (0.080)
Δ HDL (mg/dl)	-0.073 (0.656)	-0.377 (0.**016**)
%Δ Access blood flow		
%Δ TG	0.103 (0.527)	0.238 (0.139)
%Δ Cholesterol	0.033 (0.838)	0.125 (0.441)
%Δ LDL	0.310 (0.052)	-0.020 (0.901)
%Δ HDL	-0.173 (0.286)	-0.434 (**0.005**)









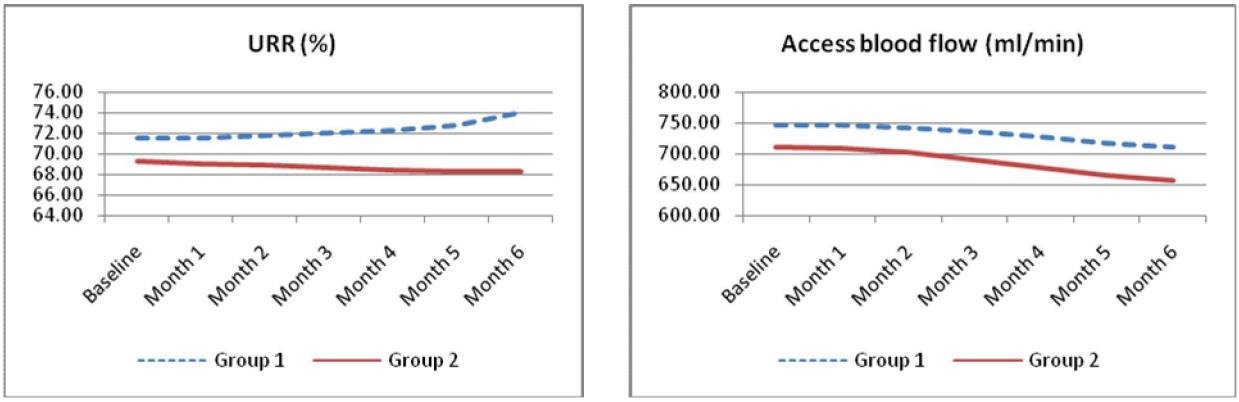


Figure 1: Showing the changes of monthly level of different studied parameters throughout the study duration among the studied groups

4. Discussion

Vascular access dysfunction is a common problem in patients undergoing hemodialysis. It follows that maintaining vascular access patency is important. Several drugs were reported to improve vascular access patency rates as antiplatelet, statins and anticoagulants.[5]

In the present we observed decease in blood flow of AVF and AVG in both groups, but this change of access blood flow not statistically significant different between both groups. Although there was significant increase in URR among group 1 in comparison to group 2, this might indicates better function of vascular Access. Angiography was mandatory in 8 (10%) of total patients 3 of them with 20% stenosis in group 1 and 5 with stenosis 30% in group 2, but there was no statistically significant difference between Omega -3 fatty acid group and control group as regard need of Angiography and presence of stenosis.

Lok *et al.,* in 2012 studied 201 participants were randomly allocated to receive fish oil capsules (four1-g capsules/d) or matching placebo on day 7 after graft creation with follow-up for 12 months after graft creation, the studied graft showed that the proportion with graft thrombosis or a radiological or surgical intervention to maintain graft patency did not significantly differ between fish oil and placebo recipients. However, fish oil recipients had a prolonged time without thrombosis, half the thrombosis rate, and a clinically meaningful reduction in frequency of radiological and surgical interventions.[23]

Fish oil has antithrombotic, anti-aggregatory, and antiproliferative actions,[24] fish oil may be effective in improving dialysis shunt patency rates.[1] Diskin *et al.,* in 1990 reported that four patients who consumed 3 g/d fish oil for 6 months had no outflow stenosis by duplex ultrasonography compared with two of three who were on placebo and did have outflow stenosis. However, there was no overall difference in graft survival.[25] Schmitz *et al.,* in 2002 randomly assigned 24 patients who underwent new arteriovenous graft placements to 3.2 g/d fish oil versus placebo. Patients were followed up to 1 year or until graft thrombosis developed. The overall patency rate in the fish oil group and the placebo group was 76 versus 15%, respectively. A trend toward an increase in venous outflow pressures was seen only in the placebo group. Compliance was confirmed by platelet membrane fatty acid measurements.[26] Thus, fish oil holds promise as an effective prophylaxis against shunt thrombosis. [1]

In patients with ESRD changes in lipid metabolism occur, creating a complex form of dyslipidemia. Moreover, The effect of lowering LDL on vascular access patency is unclear.[27]

In our study there was highly significant statistical decrease in total cholesterol, LDL levels and highly significant statistical increase in HDL level in group 1 received Omega-3 fatty acid compared to group2 over the six months period, and statistically significant correlation between the degree of decrease LDL and degree of increase blood flow of vascular access by Doppler study over 6 months. But no significant correlation between change of access blood flow and total cholesterol or HDL means of change.

Although changes observed in the serum lipid parameters among group 1 (decreased TG cholesterol, & LDL with increased HDL) was significantly different than the changes observed in group 2 (increased TG cholesterol, & LDL with decreased HDL), but this was not associated with the same changes in the vascular access blood flow.

Among 2353 SHARP trial participants who had functioning vascular access at randomization, allocation to simvastatin plus ezetimibe resulted in a 13% proportional reduction in vascular access occlusive events for simvastatin/ ezetimibe versus for placebo.[27] AURORA trial did not provide independent confirmation (vascular access occlusive

events: 352 [28.9%] for rosuvastatin versus 337 [27.6%] for placebo; RR, 1.06, 95% CI, 0.91 to 1.23; *P*=0.44).[28] After combining the SHARP & AURORA trials, the overall effect of reducing LDL-C with a statin based regimen on vascular access occlusive events was not statistically significant (707 [29.3%] with any LDL lowering therapy versus 725 [30.5%] with placebo; RR, 0.95, 95% CI, 0.85 to 1.05; *P*=0.29). [27]

Our results agreed with Goren *et al.,* 1991, Panzetta *et al.,* 1995& Ando *et al.,* 1999 who found a beneficial effect of Omega 3 fatty acid on cholesterol and LDL levels in hemodialysis patients .[29-31] but these results disagrees with the study done by Hombrouckx *et al.,* 1992which showed no change in total cholesterol level.[32] Furthermore, Rustemeijer *et al.,* 1988 & Bonanome *et al.,* 1996 studies which showed increase in total cholesterol level in patients received fish oil. [33, 34]

Svensson *et al.,* in 2008 showed that treatment with ω-3 fatty acids reduces serum triglycerides with the largest effect observed in non-fasting patients but does not significantly affect HDL cholesterol, LDL cholesterol, total cholesterol, Lp(a) or ApoB, so consumption of fish or treatment with n-3 PUFA might be part of a CVD prevention strategy in patients treated with chronic HD.[15]

Svensson *et al.,* also considered that the effect of ω-3 fatty acids on serum triglycerides might be important, not only as a result of the actual reduction in serum triglycerides but also from changing the uremic lipid profile towards a more normal and less atherogenic lipid profile.[15] It has previously been shown that elevated serum triglycerides are closely related to the presence of small dense LDL particles both in data from the general population [35] and in dialysis patients.[18]In our study there was no significant statistical difference between both groups as regard change of hemoglobin level ,calcium level or PTH level over the duration of the study.

5. Conclusion

Daily ingestion of Omega-3 fatty acids in patients with ESRD under regular hemodialysis leads to significant decrease in TG, total cholesterol level & LDL together with increase in HDL level. There was no significant effect on vascular access blood flow.

Disclosure

The results presented in this paper have not been published previously in whole or part.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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