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ORIGINAL ARTICLE

Far-infrared therapy improves ankle brachial index in hemodialysis patients with peripheral artery disease

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Abstract

Ankle brachial index (ABI) is a diagnostic tool for peripheral artery disease (PAD), which is an important issue in hemodialysis (HD) patients. We enrolled 198 maintenance HD patients in this study. PAD is defined as ABI ≤ 0.90. Only PAD patients received far-infrared (FIR) therapy using the WS TY101 FIR emitter for 40 min during each HD session, three times weekly for 6 months. The ABI was measured at the bilateral lower extremities for 4 times [pre-dialytic timing (0 min) and 40 min after the initiation of HD session at both day 0 and 6 months after the FIR therapy]. The primary outcome is the change in ABI. There were 51 out of 198 patients with PAD. In comparison with the period without FIR therapy in the 51 PAD patients, 6 months of FIR therapy significantly improved the ABI of the right/left side for 0 min (from 0.77 ± 0.19 to 0.81 ± 0.20, $p = 0.027$/0.79 ± 0.20 to 0.81 ± 0.17, $p = 0.049$), 40 min during HD (from 0.73 ± 0.23 to 0.83 ± 0.19, $p < 0.001$/from 0.77 ± 0.21 to 0.83 ± 0.18, $p < 0.001$), and the incremental change between 0 and 40 min (from − 0.04 ± 0.14 to 0.05 ± 0.13, $p = 0.007$/from − 0.05 ± 0.13 to 0.03 ± 0.11, $p = 0.012$), respectively. In conclusion, the application of FIR therapy for 40 min, three times weekly for 6 months, has improved the ABI of both lower extremities, thus providing a new strategy of PAD treatment in HD patients.

Keywords Ankle brachial index (ABI) · Far-infrared (FIR) therapy (FIRAPY) · Hemodialysis (HD) · Peripheral artery disease (PAD) · End-stage renal disease (ESRD)

Introduction

There is a higher prevalence of peripheral artery disease (PAD) among patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) in comparison with the general population. The prevalence of PAD is as high as 37.9% according to the 2016 United States Renal Data System (USRDS) annual data report [1]. Numerous patients on dialysis have been suffering or have possibly been suffering from PAD, which results in intermittent claudication, painful extremities, chronic foot ulcers (poor healing), and may finally lead to non-traumatic lower-extremity amputation [2–4]. Moreover, the complications of PAD often lead to decreased activity and therefore patients are more prone to be bed-ridden, resulting in a vicious cycle, which may further increase the incidence of other cardiovascular diseases and mortality [5–7]. In order to effectively screen patients with symptomatic or asymptomatic PAD, the ankle brachial index (ABI) is adapted to be a precise non-invasive marker both in the general population and ESRD patients [8, 9]. The optimal ABI threshold to diagnose PAD is controversial as it may affect its sensitivity and specificity. Studies have shown that an ABI ≤ 0.90 exhibited a high specificity but a relatively lower sensitivity in detecting > 50% arterial stenosis identified by imaging methods, but the sensitivity may be as high as 100% when ABI ≤ 1.0 was used [8]. Other than its function in screening and diagnosing of PAD, a reduced ABI of less than 0.9 also showed a significant correlation with higher mortality among patients undergoing HD [10–12]. In theory, therapies targeting PAD may improve arterial disease and potentially affect the incidence of cardiovascular diseases and mortality. Unfortunately, there are very few

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effective therapeutic options to help patients improve the distal circulation, lessen the discomfort and disability, and preserve the affected limbs. Traditional medical strategies aiming to prevent or treat PAD such as cessation of smoking, exercise, and medications including cilostazol, antiplatelet agents, lipid lowering agents, and pentoxifylline do not have enough medical evidence necessary to support its claims to benefit dialysis patients with PAD [13]. Cilostazol was suggested to improve long-term arterial patency after percutaneous transluminal angioplasty (PTA) in dialysis patients [14, 15]. Bypass surgical revascularization may not be an appropriate surgical approach in these patients because of poor distal perfusion. Research also showed that surgery did not improve survival [16, 17]. Although PTA would be beneficial for these patients, repeated invasive procedures may have a significant impact on their quality of life [18–20].

Far-infrared (FIR) therapy (FIRAPY) was shown to improve endothelial function and reduce the frequency of some cardiovascular diseases such as coronary artery disease, congestive heart failure, ventricular arrhythmia [21, 22]. FIR therapy was also confirmed to increase access blood flow and improve unassisted patency of arteriovenous fistula (AVF) among dialysis patients [23]. Infrared radiation could be classified into 3 classes according to the different ranges of wavelength: IRA (near infrared) where the wavelength is between 0.7 and 1.4 μm, IRB (middle infrared) where the wavelength is between 1.4 and 3 μm, and IRC (far infrared) where the wavelength is between 3 and 100 μm [24]. FIR can conduct heat energy and also improve microvascular circulation in skin tissues [25]. Skin perfusion pressure (SPP) was identified to be a prognostic factor where low SPP was an independent risk factor in predicting both lower limb survival and the prognosis of dialysis patients [26]. Aside from the thermal effect, FIR therapy was also shown to inhibit intimal hyperplasia, decrease oxidative stress, suppress inflammation, and improve endothelial function [27–30]. Thus, we hypothesize that FIR therapy may improve the blood flow and patency of peripheral artery, as well as improve the function of AVF. The clinical benefit of utilizing FIR therapy on peripheral arterial lesions in dialysis patients still needs to be clarified. The present study was conducted to evaluate the immediate and long-term effects of FIR therapy on the ABI of HD patients where PAD and ESRD coexists.

Materials and methods

Study population

The study was conducted at Taipei Veterans General Hospital in Taiwan. All the patients who received maintenance HD in the HD unit were inquired for participation in this study. The exclusion criteria are as follows: patients under 18 or above 90 years of age, dialysis vintage of less than 1 month, dialysis frequency of less than three times per week, contraindication for ABI examination (e.g. previous operation for breast cancer with lymph node dissection, arteriovenous access over bilateral upper extremities, etc.), bed-ridden or non-ambulatory status, and history of distal limb amputation due to trauma, ischemia, or uncontrolled infection.

There were 198 patients who consented to the preliminary baseline measurement of the ABI. All patients received the scheduled HD three times per week either before or during the studied period with the standard dialysis setting to achieve dialysis adequacy of $Kt/V \geq 1.7$ and to maintain relative hemodynamic stability. Besides, the least dosage of unfractionated heparin was administered to prevent blood clot formation within the dialysis route and vascular access but also to avoid increasing bleeding tendency.

Study protocol

A total of 194 patients underwent ABI measurements using the VP1000 (Colin Co. Ltd., Komaki, Japan). These patients were then divided into 3 groups according to the ABI baseline results: $ABI \leq 0.9$, $ABI > 0.9$ but < 1.4, and $ABI \geq 1.4$. There were 51 patients that had a baseline $ABI \leq 0.9$ and were then enrolled for the study.

At month 0, the enrolled patients underwent ABI measurements both at the start of HD (ABI_1) and 40 min after the start of HD (ABI_2). After that, the patients received FIR therapy for 40 min, three times per week, for 6 months. The therapy involved bilateral thighs being treated for 20 min, followed by bilateral calves for 20 min. During the treatment, the top radiator was set at a height of about 25 cm above the surface of the legs. The WS™ TY101 FIR emitter (Far IR Medical Technology Co., Ltd., Taipei, Taiwan) was used for the therapy, with the wavelength of the machine ranging between 3 and 25 μm (a peak at 5–6 μm). After a treatment period of 6 months, the enrolled patients received ABI measurements again both at the start of HD (ABI_3) and 40 min after the start of HD with FIR therapy (ABI_4). The study protocol is illustrated in Fig. 1.

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGH IRB No. 98-10-13) and all the investigations were conducted in accordance to the Declaration of Helsinki. The clinical factors of the enrolled patients including age, gender, dialysis vintage, comorbidities [history of diabetes mellitus (DM), hypertension, coronary artery disease (CAD), stroke, PAD], and medications [use of cilostazol, aspirin, clopidogrel, pentoxiphylline, lipid-lowering agents (statins), angiotension receptor blockers, and angiotensin converting enzyme inhibitors (ACEIs/ARBs)] were recorded. The biochemical test results were obtained at the start of a scheduled HD

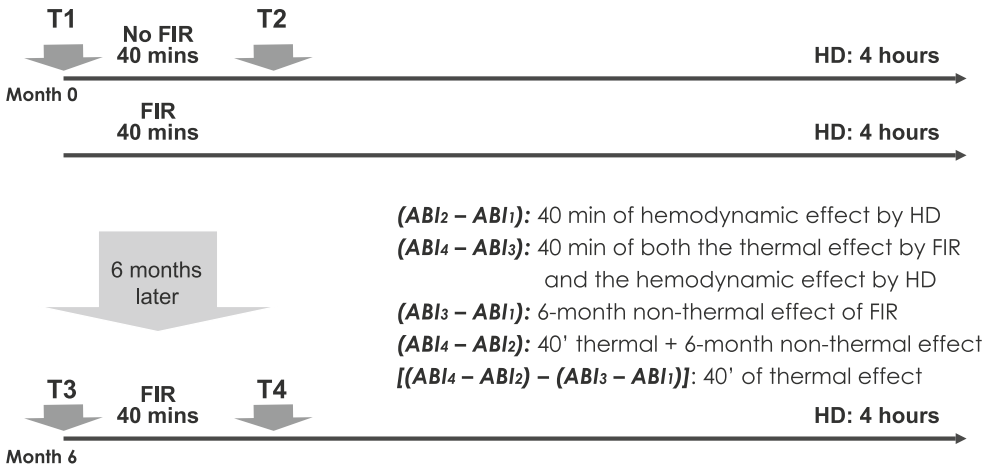

Fig. 1 Study Protocol: at month 0, ABI_1 and ABI_2 were recorded both at the start of HD and 40 min after (without FIR therapy), respectively. At month 6, ABI_3 and ABI_4 were recorded at the start of HD and 40 min after (with FIR therapy), respectively. *FIR* far-infrared

session, including albumin, cholesterol, uric acid, creatinine, fasting glucose, calcium, phosphate, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, high-sensitivity C-reactive protein (hs-CRP), hematocrit, and intact parathyroid hormone (i-PTH). The symptoms of PAD including intermittent claudication before and after FIR therapy, occurrence of foot ulcers, critical limb ischemia needed for angioplasty or bypass surgery, and hospitalization period were also recorded.

Statistics

The data management and statistical analysis were performed using IBM SPSS Statistics version 19.0 (IBM Corporation, New York, USA) for Windows. Distributions of continuous variables were expressed as mean (± standard deviation) and the categorical variables were expressed as percentage (%). All data were tested for normal distribution before using the *t* test and the differences between ABI results were determined by the paired *t* test. A significant value of $p < 0.05$ was set.

Results

Within the 194 patients underwent ABI measurements, there were 51, 129, and 14 patients with $ABI \leq 0.9$, $0.9 < ABI < 1.4$, and $ABI \geq 1.4$, respectively. The basic characteristics of these patients are shown in Table 1. There were 51 patients who completed the 6-month therapeutic course of FIR therapy and none of the patients withdrew from this study. The baseline demographic and clinical characteristics are shown in Table 2. The average age was 70.7 ± 11.9 years and the dialysis vintage was 68.5 ± 68.4 months. There were 24 patients with DM, 42 patients with hypertension,

Table 1 Baseline characteristics of the patients received ABI examination

	$ABI \leq 0.9$	$0.9 < ABI < 1.4$	$ABI \geq 1.4$
Number	51	129	14
Age (years)	70.7 ± 11.9	63.2 ± 10.4	72.8 ± 12.3
HD Vintage (months)	68.5 ± 68.4	72.3 ± 65.9	77.4 ± 58.4
DM [*n* (%)]	24 (47%)	51 (39.5%)	6 (42.9)
Time (months)	113.5	91.4	107.8
Insulinotherapy	9/24 (37.5%)	12/51 (23.5%)	2/6 (33.3%)
Time (months)	52	46	58.8
Etiology of ESRD			
DM	23	49	6
HTN	7	20	2
GN	14	38	3
Other	7	22	3

ABI ankle brachial index, *HD* hemodialysis, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *HTN* hypertension, *AKI* acute kidney failure, *GN* glomerulonephritis

18 patients with CAD, and 17 patients with PAD prior to enrollment in the study. There were 18 patients on cilostazol, 27 patients on aspirin, 13 patients on clopidogrel, 20 patients on pentoxyphylline, 2 patients on statins, and 41 patients on ACEIs/ARBs. The medical and HD prescriptions were continued as usual and were only modified if a change in individual hemodynamics or biochemical figures occurred.

As an outcome measure of FIR therapy on PAD, the difference between ABI_3 and ABI_1 [$\Delta(ABI_3 - ABI_1)$] can be calculated to represent the non-thermal effects of FIR therapy for 6 months and showed a significant increase in the bilateral lower extremities (right: 0.04 ± 0.13, $p = 0.03$; left: 0.02 ± 0.13, $p = 0.05$) (Fig. 2). Theoretically, the difference between ABI_4 and ABI_2 [Δ ($ABI_4 - ABI_2$)] was affected by both the thermal effect of FIR therapy for 40 min and

Table 2 Baseline characteristics of the patients with ABI ≤ 0.9

	Mean/percentage	Min.	Max.
Age (years)	70.7 ± 11.9	45.0	89.0
HD Vintage (months)	68.5 ± 68.4	1	255
Comorbidities			
DM [*n* (%)]	24 (47%)		
HTN [*n* (%)]	42 (82%)		
CAD [*n* (%)]	18 (35%)		
Stroke [*n* (%)]	0 (0%)		
PAOD [*n* (%)]	17 (33%)		
Biochemistry			
Albumin (g/dl)	3.78 ± 0.32	2.9	4.6
Calcium (mg/dl)	9.22 ± 0.70	7.7	10.8
Cholesterol (mg/dl)	175.7 ± 37.4	128	274
Uric acid (mg/dl)	7.86 ± 1.80	4.4	13.1
Creatinine (mg/dl)	9.92 ± 1.81	5.20	13.23
Glucose (mg/dl)	137.8 ± 47.0	70	241
Phosphate (mg/dl)	4.74 ± 1.18	2.3	7.1
HDL (mg/dl)	37.9 ± 13.1	26.0	64.0
LDL (mg/dl)	88.5 ± 37.9	49.0	201.0
Triglyceride (mg/dl)	178.0 ± 154.2	35	851
hsCRP (mg/dl)	5.69 ± 7.41	0.05	21.80
Hematocrit (%)	30.2 ± 4.3	12.6	38.0
PTH (IU/L)	261.2 ± 336.3	11	1571
Medications			
Cilostazole [*n* (%)]	18 (35.3%)		
Aspirin [*n* (%)]	27 (52.9%)		
Clopidogrel [*n* (%)]	13 (25.5%)		
Pentoxiphylline [*n* (%)]	20 (39.2%)		
Statins [*n* (%)]	32 (62.7%)		
ACEIs/ARBs [*n* (%)]	41 (80.4%)		

DM diabetes mellitus, *HTN* hypertension, *CAD* coronary artery disease, *PAOD* peripheral arterial occlusive disease, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *hsCRP* high sensitivity C-reactive protein, *PTH* parathyroid hormone, *ACEIs/ARBs* angiotensin converting enzyme inhibitors and angiotensin-receptor blockers

the non-thermal effect of FIR therapy for 6 months. We could use the difference between Δ ($ABI_4 - ABI_2$) and Δ ($ABI_3 - ABI_1$) to represent the thermal effect of FIR therapy for 40 min during HD, and it also showed a significant increase in the bilateral lower extremities (right: 0.06 ± 0.13, $p = 0.01$; left: 0.04 ± 0.12, $p = 0.01$) (Fig. 3).

The $\Delta(ABI_2 - ABI_1)$ was affected by the hemodynamic effect of HD for 40 min and decreased in the bilateral lower extremities (right: −0.04 ± 0.14, $p = 0.03$; left: −0.05 ± 0.13, $p = 0.02$). FIR therapy overcame the hemodynamic effect and increased the ABI exhibited as $\Delta(ABI_4 - ABI_3)$ (right: 0.05 ± 0.13, $p = 0.01$; left: 0.03 ± 0.11, $p = 0.04$). The detailed results of the ABI are shown in Table 3.

There were 35 patients that had intermittent claudication as a symptom before receiving FIR therapy and the number decreased to 21 patients after FIR therapy for 6 months. 8 patients developed foot ulcers during the experimental period and 3 patients received percutaneous angioplasty for limb ischemia with unhealed foot ulcers after aggressive medical treatment. No patient needed bypass surgery for PAD. In addition, there were no adverse effects such as burn injury or skin irritation on the studied patients.

Discussion

Previous studies using FIR therapy to improve AVF patency had shown that both the thermal and non-thermal effects of FIR radiation can increase access blood flow and AVF function [23]. In the present study, we aimed to evaluate if both the thermal and non-thermal effects of FIR therapy would also have an influence on PAD. The ABI at the start of HD after FIR therapy for 6 months (ABI_3) was only affected by the non-thermal effect of FIR radiation, without the influence that came from the thermal effect of FIR radiation and the hemodynamic effect of HD. The incremental change of ABI at the start of HD [$\Delta(ABI_3 - ABI_1)$] demonstrated that FIR radiation exerted a non-thermal effect on ABI, which was beneficial in HD patients with PAD. Aside from ABI_3, ABI_4 was affected by both the thermal and non-thermal effects of FIR therapy, with the addition of the hemodynamic effect of the 40-min HD. The difference between ABI_4 and ABI_2 [$\Delta(ABI_4 - ABI_2)$] removed the influence of the hemodynamic effect of HD and subtracting $\Delta(ABI_3 - ABI_1)$ from $\Delta(ABI_4 - ABI_2)$ further removed the non-thermal effect. Thus, an incremental change of $\Delta(ABI_4 - ABI_2) - \Delta(ABI_3 - ABI_1)$ demonstrated that the thermal effect of FIR therapy on ABI was beneficial to HD patients with PAD.

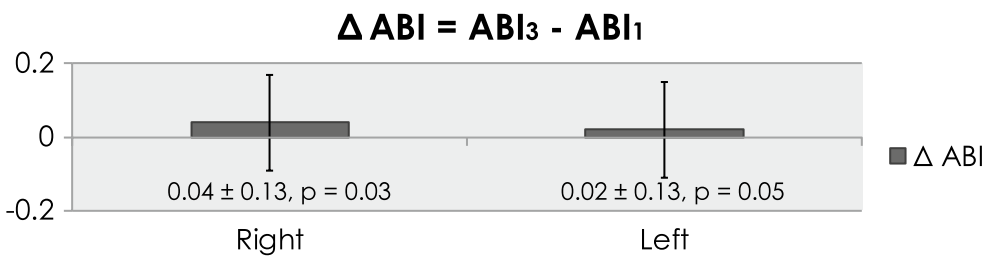

Fig. 2 Non-thermal effects of far-infrared therapy for 6 months: there was a significant increase in the ABI of the bilateral lower extremities after FIR therapy for 6 months. *ABI* ankle brachial index

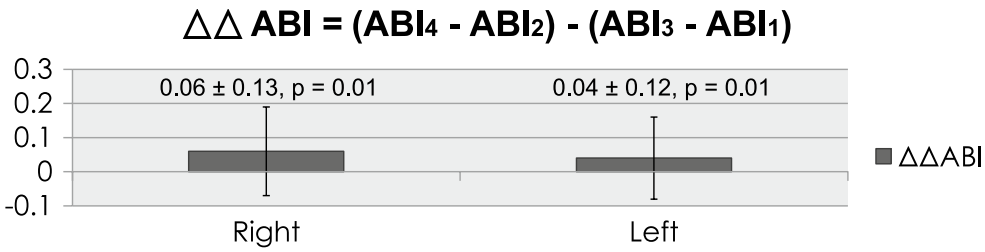

Fig. 3 Thermal effects of far-infrared therapy for 6 months: there was a significant increase in the ABI of the bilateral lower extremities after a single session of FIR therapy. *ABI* ankle brachial index

Table 3 Baseline ABI and change in ABI at different times

Parameters	Mean ± SD	Minimum	Maximum	*p* value
ABI_1 (right)	0.77 ± 0.19	0.49	1.13	0.027
ABI_3 (right)	0.81 ± 0.20	0.49	1.12	
ABI_1 (left)	0.79 ± 0.20	0.37	1.22	0.049
ABI_3 (left)	0.81 ± 0.17	0.37	1.05	
ABI_2 (right)	0.73 ± 0.23	0.32	1.14	< 0.001
ABI_4 (right)	0.83 ± 0.19	0.59	1.22	
ABI_2 (left)	0.77 ± 0.21	0.32	1.18	< 0.001
ABI_4 (left)	0.83 ± 0.18	0.39	1.14	
$ABI_2 - ABI_1$ (right)	− 0.04 ± 0.14	− 0.42	0.20	0.025
$ABI_4 - ABI_3$ (right)	0.05 ± 0.13	− 0.28	0.31	0.008
$ABI_2 - ABI_1$ (left)	− 0.05 ± 0.13	− 0.39	0.15	0.015
$ABI_4 - ABI_3$ (left)	0.03 ± 0.11	− 0.32	0.55	0.044
$ABI_3 - ABI_1$ (right)	0.04 ± 0.13	− 0.22	0.38	0.027
$ABI_3 - ABI_1$ (left)	0.02 ± 0.13	− 0.23	0.42	0.049
$(ABI_4 - ABI_2) - (ABI_3 - ABI_1)$ (right)	0.06 ± 0.13	− 0.07	0.71	0.007
$(ABI_4 - ABI_2) - (ABI_3 - ABI_1)$ (left)	0.04 ± 0.12	− 0.12	0.62	0.012

ABI ankle brachial index

Atherosclerosis and the possible thrombosis that might follow after are some of the contributing causes of arterial ischemia and the formation of PAD. To overcome the impaired blood flow, the wall shear stress from increased laminar flow stimulate the endothelial cells and triggers the activity of endothelial nitrite oxide synthase (eNOS), which promotes the increase of vessel caliber [31]. In addition, it was hypothesized that fluid shear stress may cause arteriogenesis, which increases collateral circulation [32]. Several pathogenic mechanisms, which may originate from pre-existing cardiovascular disease, DM, uremic milieu, chronic inflammation, and occult infection in HD patients, interrupt the normal adaptation mechanisms and may trigger the formation of PAD [33]. In addition, transient ischemia of stenotic arteries during ultrafiltration and potential exposure of these vessels to high calcium- or sodium-containing dialysates also play an important role in the progression of PAD.

The thermal effect of a single session of FIR therapy may result in vasodilatation and increased blood flow, which overcomes the impaired perfusion of occlusive arteries. Besides, the hyperthermia resulting from FIR radiation might stimulate the expression of heat shock proteins 70 (Hsp70), heme oxygenase-1 (HO-1), IκBα, whereas it reduces the tumor necrosis factor α (TNFα)-induced translocation of p65 into the nuclei, leading to the down regulation of E-selectin and vascular cell adhesion protein-1 (VCAM-1) [34]. FIR therapy is different from traditional heat therapy wherein it exerts non-thermal effects possibly through mechanisms such as inhibiting intimal hyperplasia, decreasing oxidative stress, suppressing inflammation, and improving endothelial function [27–30]. FIR therapy could inhibit vascular endothelial inflammation via the stimulation of HO-1 mRNA and protein expression of NF-E2-related factor-2 (Nrf2)/antioxidant responsive element (ARE) complex in cultured HUVECs [29]. FIR therapy may also inhibit TNF-α-mediated expression of E-selectin, VCAM-1, intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and interleukin-8 (IL-8) in HUVECs as well as in human aortic endothelial cells (HAECs), all of which are crucial components that mediate leukocyte-endothelial interaction and induce the inflammatory response [29]. The aforementioned evidence indicate that FIR therapy might improve endothelial function to prevent stenosis of peripheral arteries.

The limitations of the study are as follows. First, the number of studied patients was small and the study was neither randomized nor blinded. Our study enrolled only patients in the study group because almost all of the HD patients in the HD unit received FIR therapy for dialysis vascular access [23, 35]. Potential bias may come from the systemic effects of FIR therapy other than the localized effects on ischemic arteries if these patients were enrolled in the control group. Based on the benefits of FIR therapy on vascular access for hemodialysis as demonstrated in our previous studies, withdrawing FIR therapy in the control group would be unethical and would have detrimental effects in HD patients. The application of FIR needs a specific machine that conducts heat. Therefore, the intervention cannot be blinded because the control group would not have the machine and the patients will not be able to differentiate the change in temperature. Second, using ABI as a diagnostic tool to survey ABI may miss a large portion of uremic patients with PAD because of normalized or extreme high ABI due to peripheral arterial calcification. These patients also manifested clinical features of PAD and possessed a high risk of developing cardiovascular comorbidities [36], which invalidates the ABI being a definite marker to determine the overall prognosis in all HD patients. Direct imaging techniques such as angiography or Doppler ultrasound which would be more accurate screening methods rather than ABI but were not performed in the present study. A further study utilizing Doppler ultrasound to specify the stenotic segments and to evaluate the effect of FIR may be needed to clarify its beneficial effect in HD patients with PAD and normal or high ABI. Thirdly, the dosage of anticoagulation was not controlled in this study but set with the least dose of unfractionated heparin to prevent coagulation developed during hemodialysis and to preserve the patency of vascular access. Whether the dose of anticoagulation would affect the change of ABI after FIR therapy or not may need further study to clarify this relationship.

In conclusion, our study demonstrated that FIR therapy produce potential beneficial effects in HD patients with PAD and a low ABI of less than 0.90, in presenting by the rise of ABI. Both the thermal and non-thermal effects of FIR therapy contribute to the increase in the ABI, which may also improve the prognosis of the patients. Whether or not the effects can be applied in patients with PAD and high ABI would need further clarification in future studies.

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Conflict of interest None.

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