

## Case Report

# Influences of Pinpoint Plantar Long-Wavelength Infrared Light Irradiation (Stress-Free Therapy) on Chorioretinal Hemodynamics, Atherosclerosis Factors, and Vascular Endothelial Growth Factor



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## ABSTRACT

**Background:** We previously reported that pinpoint plantar long-wavelength infrared light irradiation (stress-free therapy; SFT) is useful for alleviating insulin resistance and improving intracranial blood flow in patients with type 2 diabetes mellitus. This study was undertaken to evaluate the influences of SFT on chorioretinal hemodynamics (retinal artery and vein blood flows) as well as atherosclerosis-related factors (TG, LDL-C) and VEGF in patients with dyslipidemia.

**Methods:** Four patients with dyslipidemia received 15-minute irradiation with a stress-free apparatus (far-infrared wavelength, 30 mW). Using laser speckle flowgraphy, associations of chorioretinal blood flow with peripheral atherosclerosis-inducing factors/VEGF levels before and after irradiation were analyzed.

**Results:** Chorioretinal blood flow increased, while TG/LDL-C levels decreased, after irradiation. VEGF tended to rise in cases with pre-irradiation baseline levels at the lower limit but tended to decrease in cases in which baseline levels had exceeded the normal range.

**Conclusion:** SFT was suggested to enhance chorioretinal circulation and to normalize VEGF, thereby possibly contributing to amelioration of atherosclerosis-inducing factors. Abnormalities in chorioretinal hemodynamics are known to be highly involved in the pathophysiology of diabetic retinopathy and age-related macular degeneration, and anti-VEGF antibody has been used for treating these conditions. The necessity of risk management, involving chorioretinal blood flow, has been pointed out when dealing with central retinal vein occlusion, diabetes mellitus, ischemic cerebral/cardiac disease, dementia and so on. SFT is therefore a potential complementary medical strategy which can be expected to contribute to normalization of chorioretinal blood flow and atherosclerosis-inducing factors/VEGF levels, and thereby to the prevention of lifestyle-related chronic diseases.

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## 1. Introduction

It has been reported in recent years that the risks for vascular dementia (VD) and Alzheimer disease (AD) onset are high in patients with diseases such as dyslipidemia, hypertension and diabetes mellitus (DM).<sup>1,2</sup> It is also known that insulin resistance and hyperinsulinemia, which are problems associated with type 2 DM, can induce low insulin levels in the central nervous system which are closely associated with the onset of AD through reduction of cerebral blood flow, accumulation of amyloid- $\beta$ , phosphorylation of tau protein and so on.<sup>3</sup> In addition, diabetic retinopathy is known to be associated with abnormal vascular endothelial growth factor (VEGF) expression and AD.<sup>4</sup>

We previously reported that pinpoint plantar long-wavelength infrared light irradiation (stress-free therapy; SFT) suppresses the stress reaction mediated by cortisol and contributes to alleviation of insulin resistance and elevation of intracranial blood flow in patients with type 2 DM.<sup>5–8</sup> We have additionally demonstrated that SFT activates the immunoresponsive CD19<sup>+</sup> CD24<sup>hi</sup> and CD38<sup>hi</sup> B-reg cell groups and induces the expression of IL-10 on lymphocytes.<sup>9</sup>

The present study was undertaken to evaluate the influence of SFT on chorioretinal hemodynamics (retinal artery and vein blood flows) as well as its influences on atherosclerosis-inducing factors (triglycerides; TG, low-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; HDL-C), and VEGF in patients with dyslipidemia.

## 2. Methods

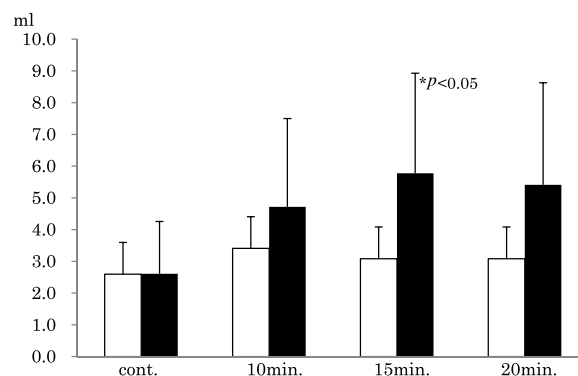
This study involved 4 untreated patients with dyslipidemia (3 men and 1 woman; mean age,  $54.8 \pm 13.5$  years) and 4 healthy volunteers (2 men and 2 women; mean age,  $48.8 \pm 9.7$  years; undergoing only placement of a probe without irradiation) serving as SFT controls.

Irradiation for SFT was applied to 4 points in total, including the point of intersection of the vertical line of the medial malleolus with the line joining the first and second metatarsal bones of the planta, the right and left orbital foramens and the depressed point one finger breadth above the center of the line joining the medial ends of the eyebrows (the latter 3 points were selected in view of increases in chorioretinal blood flow), as shown in Fig. 1.



**Fig. 1 – SF therapy apparatus and points of irradiation**

Left: SF therapy apparatus, Middle: Point of intersection of a vertical line of the medial malleolus with the line joining the first and second metatarsal bones of the planta, Right: Right and left orbital foramens and the depressed point one finger breadth above the center of the line joining the medial ends of the eyebrows (3 points).



**Fig. 2 – Changes in blood flow in healthy volunteers**

□: Placebo (only placement of a probe without irradiation).  
 ■: SF therapy. mean  $\pm$  SD, N = 10.

The maximal effect was obtained via 15 minutes-treatment. Changes in blood flow to the facial artery were analyzed using a laser Doppler flow meter (Advance ALF 21) in a similar manner as our previous report (Laser Therapy 24,1:27-32).

Each subject was instructed to remain still in the supine position for 15 minutes and then received 15-minute irradiation with an SFT apparatus (Controlled medical device certificate No. 224AFBZX00075000; probe diameter 20 mm, far-infrared wavelength 9000 to 12000 nm, output power 30 mW) (Fig. 1). Preliminarily, we have confirmed that maximal effect is obtained via 15 minutes-treatment (Fig. 2).

Changes in chorioretinal circulation (retinal artery and vein blood flows) after SFT from those before this therapy were analyzed on the basis of the data obtained by laser speckle flowgraphy (LSFG-NAVI) measurement conducted under identical conditions, with circadian rhythm influences, etc., taken into account. Blood, 5 cc, was collected via the cubital vein under identical conditions (time of collection, etc.) for determination of peripheral blood VEGF levels by electrochemiluminescence immunoassay (ECL) and analysis of TG, HDL-C and LDL-C by enzymatic methods (performed by Showa Medical Science Corporation). Three SFT sessions were applied to each participant at a frequency of once per week.

### 2.1. Statistical analysis

ANOVA was applied and multiple comparisons were performed using Tukey - Scheffé tests, with a significance level of  $p < 0.05$  (Fig. 2).

### 2.2. Ethical considerations

We explained to the subjects verbally and in writing the objectives and safety of the study. We also provided assurance that “subjects will not be treated disadvantageously by withdrawing their consent to cooperate in the study after the study has started” and “information obtained in this study will not be used other than in research presentations (information identifying names, etc. will not be disclosed)” and obtained their consent. The study was conducted after obtaining approval from the ethics review board of Ryotokuji University (approval No. 2304 and 2519).

## 3. Results

In all 4 patients with dyslipidemia, LDL-C had been higher than normal before SFT ( $151.3 \pm 4.9$  mg/dl) and decreased to  $131.5 \pm 9.1$  mg/dl after SFT. TG was  $309.3 \pm 154.4$  mg/dl before SFT and decreased to the normal range after SFT ( $154.8 \pm 30.5$  mg/dl) (Table 1). HDL-C showed no marked change, remaining within the normal range. VEGF rose after SFT in cases in which levels before SFT had not exceeded the upper limit of the normal range of 38.3 pg/ml, while it tended to decrease after SFT in cases in which levels before SFT had exceeded the normal range.

The healthy volunteer group ( $n = 4$ ) showed no changes in HDL-C, LDL-C, TG or VEGF levels (Table 2).

In the analysis of fundus chorioretinal circulation (retinal artery and vein blood flows), the laser speckle flowgraphy (LSFG-NAVI) images revealed enlargement of the red area (showing fundus chorioretinal blood flow) and increases in vascular diameter and blood flow (the areas marked with white circles) (Fig. 3). Mean chorioretinal blood flow as determined by LSFG-NAVI (Fig. 3) showed no change over time in the healthy volunteer group (mean,  $20 \pm 4.5$  ml), while the same parameter in the dyslipidemia group was markedly increased after SFT ( $20.3 \pm 6.2$  ml after the first session,  $30.9 \pm 14.6$  ml after the second session) as compared to the relatively low level recorded prior to SFT ( $16.3 \pm 4.7$  ml) (Fig. 4). Fig. 5.

**Table 1 – Changes in the four patients with dyslipidemia**

sex age	HDL-C		LDL-C		TG		VEGF	
	pre	post	pre	post	pre	post	pre	post
M 38	44	44	155	140	239	152	80.1	33.9
F 54	56	52	153	131	253	161	12.8	34.7
M 71	78	59	144	119	539	190	81.7	37.7
M 68	52	55	153	136	206	116	124.4	51.1
ave. 54.8	57.5	52.5	151.3	131.5	309.3	154.8	74.8	39.4
SD. 13.5	14.5	6.4	4.9	9.1	154.4	30.5	46.1	8.0

Each base line is as follows. HDL-C:40-90 mg/dl, LDL-C:70-140 mg/dl, TG:30-140 mg/dl, VEGF:38.3 pg/ml.

**Table 2 – Changes in the four volunteers**

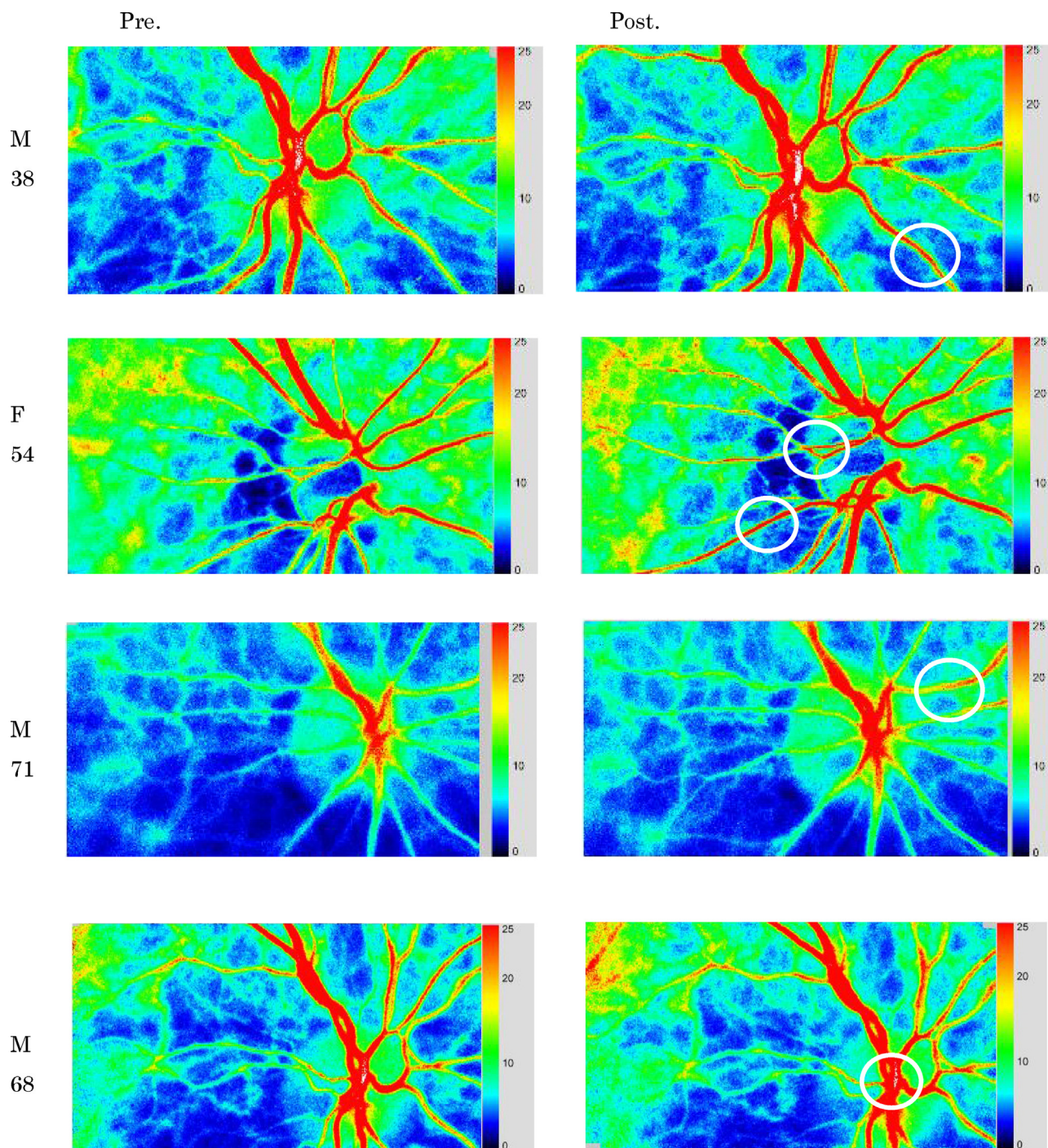
sex age	HDL-C		LDL-C		TG		VEGF	
	pre	post	pre	post	pre	post	pre	post
F 57	90	90	114	121	115	99	35.1	33.7
M 54	64	67	67	85	56	47	10.1	28.1
F 35	74	76	108	115	41	42	31.2	37.3
M 49	70	63	98	83	110	110	31.1	36.2
ave. 48.8	74.5	74.0	96.8	101.0	80.5	74.5	26.9	33.8
SD. 9.7	11.1	12.0	20.9	19.8	37.5	35.0	11.3	4.1

Each base line is as follows. HDL-C:40-90 mg/dl, LDL-C:70-140 mg/dl, TG:30-140 mg/dl, VEGF:38.3 pg/ml.

## 4. Discussion

The results of this study suggest that SFT, i.e. irradiation delivered to frontal points, reduces TG and LDL-C levels to within the normal ranges in patients with dyslipidemia, accompanied by increased chorioretinal blood flow and normalization of VEGF, raising the possibility of SFT contributing to the normalization of atherosclerosis-inducing factors. These observations may suggest that SFT has the potential to contribute to reducing the risk for VD and AD onsets associated with lifestyle-related chronic diseases (hypertension, DM, dyslipidemia, etc.). In this regard, hypercholesterolemia was previously demonstrated to be involved in the onset of AD mediated by vascular factors (atherosclerosis) and, furthermore, significant blood LDL-C elevation correlated with intracerebral amyloid- $\beta$  deposition based on an investigation of AD patients immediately after death.<sup>10</sup> In addition, since insulin resistance and hyperinsulinemia stimulate intracerebral amyloid- $\beta$  deposition and tau phosphorylation and because the onset of AD is associated with an intracerebral insulin shortage, AD is now viewed as “type 3 DM” or “intracerebral diabetes,” and a new disease entity termed “diabetes-related dementia” has, accordingly, been proposed.<sup>3,11</sup> SFT has already demonstrated efficacy in alleviating DM and dementia and is expected to be useful for preventing “diabetes-related dementia” by alleviating insulin resistance and increasing intracranial blood flow.<sup>7,8</sup>

Dementia is known to advance if it is accompanied by multiple cardiovascular risk factors such as dyslipidemia and DM,<sup>13</sup> and an association between abnormal VEGF expression and AD has been recognized as a factor underlying these observations.<sup>4</sup> VEGF is a dimeric glycoprotein, inducing new vessel formation and neovascularization through stimulation of the division, migration, and differentiation of vascular endothelial cells and is also known to be involved in inflammatory cell migration and neuroprotection as an inflammatory cytokine which acts to increase vascular permeability, etc.<sup>14</sup> Thus, if VEGF is abundant in the macular capillaries, it can cause diabetic macular edema, possibly leading to reduced visual acuity. Furthermore, in patients with diabetic retinopathy and age-related macular degeneration, abnormal chorioretinal circulation is closely related to the pathophysiology of these diseases, and VEGF inhibitors such as bevacizumab (a molecular targeted drug) have been used

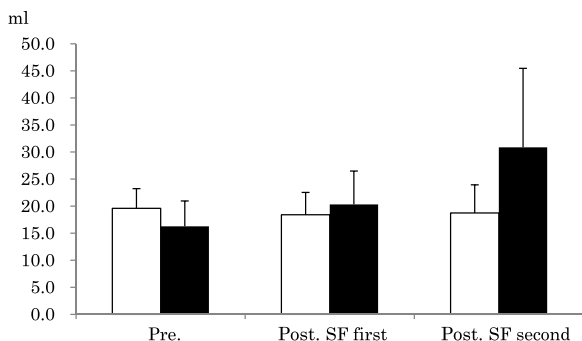


**Fig. 3 – Fundus blood flow images (four patients with dyslipidemia)**

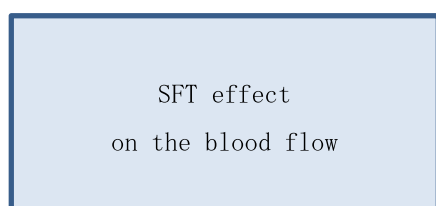
**Enlargement of the red area (indicating chorioretinal circulation, i.e., retinal artery and vein blood flows) and increases in vascular diameter and blood flow (marked with white circles) are visible. Pre.; before implementation of SF therapy. Post.; second time of SF therapy final.**

for treating these disorders. However, the necessity of risk management, especially in terms of fundus chorioretinal blood flow, when dealing with central retinal vein occlusion, DM, ischemic cerebral/cardiac disease, dementia and so on, has been recognized<sup>15</sup>). We may therefore say that SFT has the potential to serve as a non-drug strategy for preventing

cardiovascular risk factors and improving chorioretinal blood flow, thus raising the possibility of providing an adjunctive treatment for dealing with symptoms and risk factors accompanying the onset of DM. On the other hand, using only the laser speckle flowgraphy images, it was difficult to distinguish the artery and vein in this study.



**Fig. 4 – Changes in chorioretinal hemodynamics**  
 □ Four healthy volunteers receiving placebo treatment.  
 ■: Four patients with dyslipidemia. mean  $\pm$  SD.



- (1) Dilation of existing vessels  
(short-term viewpoints)
- (2) Collateral blood flow  
(long-term viewpoints)
- (3) Prevention of atherosclerosis  
(Normalization of VEGF levels,  
Reduction of TG/LDL-C levels)

**Fig. 5 – The physiological mechanism of the SFT effect.**

It is also important whether the effect of the SFT on retinal blood flow is just ‘temporary’ or ‘long lasting persistent’. To clarify them, we would like to continue further studies. Furthermore, in view of the involvement of inflammatory cytokines (e.g., IL-6 and TNF- $\alpha$ ) in DM,<sup>12</sup> SFT might have potential for contributing to the control of inflammation through activation of the immunoresponsive CD19<sup>+</sup> CD24<sup>hi</sup> and CD38<sup>hi</sup> B-reg cell groups as well as IL-10 expression on lymphocytes.<sup>9</sup> We plan to conduct a more detailed future study focusing on these possibilities, including the relationships of SFT responses with dietary and exercise-related factors.

In conclusion, our results suggest that SFT for dyslipidemia reduces TG and LDL-C levels, enhances chorioretinal blood flow and promotes the normalization of VEGF levels, thereby contributing to the normalization of atherosclerosis-inducing factors and, ultimately, the prevention of atherosclerosis.

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