

# Effects of Compression Stockings on Elevation of Leg Lymph Pumping Pressure and Improvement of Quality of Life in Healthy Female Volunteers: A Randomized Controlled Trial

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## Abstract

**Background:** Lymph is pumped through the collecting lymphatic vessels by both intrinsic and extrinsic forces. The intrinsic pump relies on spontaneous lymphatic contraction, which generates the pumping lymph pressure ( $P_{lp}$ ). Among healthy people with daily leg edema, a considerable number of cases are accompanied with low leg  $P_{lp}$ . Herein, a double-blinded controlled trial was conducted in healthy female volunteers with reduced leg  $P_{lp}$  to compare the effectiveness of a 15–29 mmHg compression stocking (Stocking A) and a 8–16 mmHg stocking (Stocking B) on elevating  $P_{lp}$ .

**Method and Results:** Among 219 healthy female volunteers who underwent measurement of leg  $P_{lp}$ , 80 participants (36.5%) had unilateral or bilateral legs with  $P_{lp} < 20$  mmHg (122 legs with  $P_{lp} < 20$  mmHg and 38 legs with  $P_{lp} \geq 20$  mmHg). These 80 participants were assigned to wear either Stocking A ( $n=40$ ) or Stocking B ( $n=40$ ) for 16 weeks. Leg  $P_{lp}$  was measured using indocyanine green fluorescence lymphography and an occlusion cuff technique while sitting. At 16 weeks, both Stockings A and B resulted in significantly elevated leg  $P_{lp}$ , with the effect on elevating  $P_{lp}$  being superior for Stocking A. Only Stocking A resulted in decreased prevalence of leg edema and improved Short Form-36 scores.

**Conclusion:** Compression stockings may represent a therapeutic option to elevate leg  $P_{lp}$  and ameliorate leg edema, thereby leading to improved quality of life in healthy females with low leg  $P_{lp}$ .

## Introduction

LYMPHATIC VESSELS ARE RESPONSIBLE for transporting lymph from the tissues back to the bloodstream, while maintaining the balance of body fluids, macromolecules, lipid, and immune regulators. After uptake by the initial lymphatic vessels, lymph is pumped through the collecting lymphatic vessels by both extrinsic and intrinsic forces.<sup>1,2</sup> While the extrinsic forces result from the contractions of the adjacent skeletal muscles, pulsation of arteries, and central venous pressure fluctuations, the intrinsic lymph pump relies on the spontaneous contraction of lymphatic muscles to generate the pumping lymph pressure ( $P_{lp}$ ).<sup>3,4</sup>

Although the importance of  $P_{lp}$  has been reported, very limited numbers of human studies regarding  $P_{lp}$  have been performed, owing to the fact that weakened  $P_{lp}$  is not necessarily associated with serious or deadly diseases, and, more importantly, that there is a lack of noninvasive methods to measure  $P_{lp}$  in the human extremities, which has hindered investigations of the physiological or pathological role of  $P_{lp}$  in human health.

Recently, we developed a novel method to measure human  $P_{lp}$  using indocyanine green (ICG) fluorescence lymphography and a transparent sphygmomanometer cuff.<sup>5</sup> This technique allows us to measure real-time  $P_{lp}$  in the arm or leg by only a subcutaneous injection of ICG. Using this technique,

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we previously found that human leg  $P_{lp}$  decreases along with aging in the general population. Among healthy volunteers, we also found that low leg  $P_{lp}$  was associated with lower quality of life due to intractable daily leg edema, so-called occupational edema.<sup>6</sup> These results prompted us to develop a therapeutic method to improve low  $P_{lp}$  for otherwise healthy people.

To achieve this goal, we investigated the effects of compression stockings on the improvement of  $P_{lp}$  by performing a randomized controlled trial. The effects of compression stockings on chronic venous insufficiencies such as varicose veins, deep vein thrombosis (DVT), and post-DVT syndrome have been well studied to demonstrate its efficacy. On the other hand, for lymphedema patients, although therapy with compression stockings is widely accepted as a first choice of treatment,<sup>7</sup> unlike the effect for venous insufficiency, little is currently known about how the compression stockings work on the lymph vessels.<sup>8</sup> Particularly, for healthy people with low  $P_{lp}$ , the effect of compression stockings on lymph propulsion is unknown. Therefore, the purpose of this study was to examine whether compression stockings can elevate low leg  $P_{lp}$  in otherwise healthy people.

## Materials and Methods

### Design and ethics

The study was a prospective, double blind, parallel-group (two groups), randomized controlled trial. The Ethics Committee of Hamamatsu University School of Medicine approved this study, which was performed in accordance with the Declaration of Helsinki of 1975, as revised in 2008. Written informed consent was obtained from all participants. The study protocol is registered at the UMIN Clinical Trials Registry (UMIN-CTR; ID: UMIN000009148).

### Participants

The participants were recruited at the University Hospital of Hamamatsu University School of Medicine. Potential volunteers were found by advertising the project locally and with poster boards in the most frequented areas of the University Hospital. Females who were older than 30 years old were invited to participate in the study. After preliminary screening by inquiring about the exclusion criteria, subjects with no serious allergies or history of leg injury or surgery were included in the study. Additional exclusion criteria included current use of compression stockings, medical history of deep vein thrombosis, radiation therapy to the abdomen or legs, leg varicose veins (C2,3,4,5: CEAP classification), prescription of anti-cancer agents, and current pregnancy.

To confirm that the participants were healthy, not only a medical interview, but also a blood test was performed in every participant. If the blood test showed any abnormal values, the subjects were excluded from the study. A standard questionnaire including complaints of leg edema, body weight, and height (to calculate body mass index), smoking status, and co-morbid diseases (e.g., hypertension, diabetes mellitus, and hyperlipidemia) was administered. Previous smokers were defined as people who had smoked for more than 10 years during their life.

All participants received information about the study and provided written informed consent to participate before inclusion.

### Measurement of leg lymph pumping pressure ( $P_{lp}$ )

After screening for eligibility and the physical examination, the investigator measured the subjects' bilateral leg  $P_{lp}$  using ICG fluorescence lymphography and a standard sphygmomanometer cuff, as previously reported.<sup>5</sup> Briefly, while the participant was seated, a custom-made transparent sphygmomanometer cuff (17 cm in length) connected to a standard mercury sphygmomanometer was wrapped around the participant's lower leg just below the popliteal fossa. A larger cuff (18 cm in length) was used if the subject had thick legs. Using a 27-gauge needle, 0.3 mL of ICG (Diagnogreen 0.5%; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was subcutaneously injected into the dorsum of each participant's foot. The ICG signal was observed in real-time using a near-infrared camera system (PDE<sup>TM</sup>; Hamamatsu Photonics K.K. Hamamatsu, Japan).<sup>9,10</sup> After the ICG was injected, the transparent cuff was inflated to 60 mmHg, then gradually deflated, lowering the pressure in 5 mmHg increments.  $P_{lp}$  was defined as the value of the cuff pressure when the ICG fluorescence signal exceeded the upper border of the cuff.

### Manufacture of stockings

We manufactured two kinds of knee-length, elastic stocking (Stocking A and Stocking B), with different interface pressures, but identical appearance (Toray Opelontex Co., Ltd., Osaka, Japan). The pressure of each stocking was measured at eight sites of the leg using the pressure measuring system for stocking and badges (Model AMI3037-SB; AMI Co., Tokyo, Japan). This system can measure pressure on the human body through clothing such as socks.<sup>11</sup>

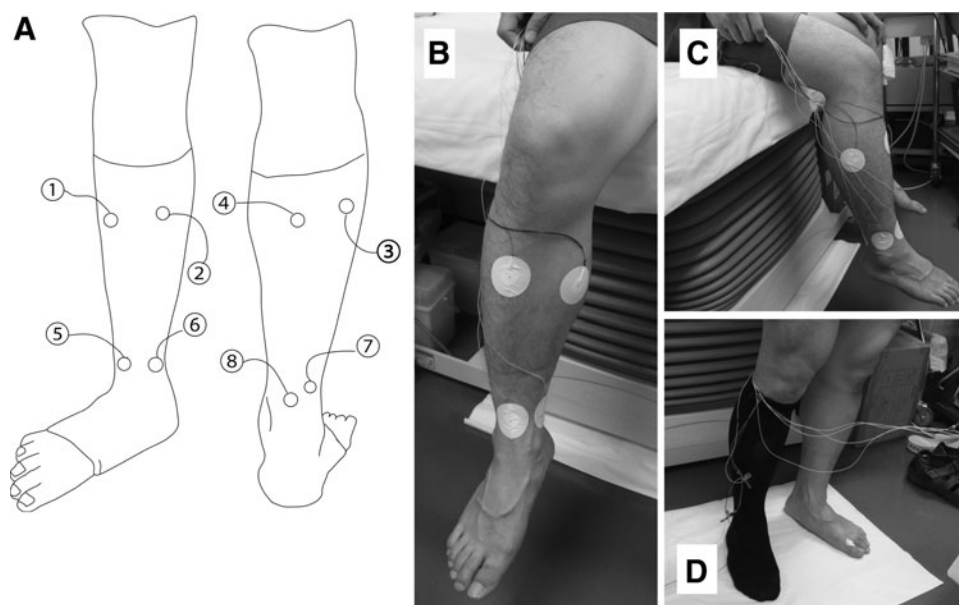
The sensors were placed on the following eight sites at each leg: the anterior, interior, lateral, and dorsal sites of both at the calf with its maximum diameter, and at the ankle at the level of transposition of the medial gastrocnemius muscle into the Achilles tendon (Fig. 1). The exerted pressure distributions by Stockings A and B are shown in Table 1. Both stockings' exerted pressure levels were as follows: Stocking A: 18–29 mmHg at the ankle and 15–23 mmHg at the calf, Stocking B: 8–13 mmHg at the ankle and 10–16 mmHg at the calf. Stocking A was made from polyurethane doubly covered with nylon, and was tubular knitted. Stocking B was made from textured nylon without covering, and was tubular knitted.

### Randomization

Participants with  $P_{lp} < 20$  mmHg in one or both legs were assigned to wear either Stocking A or Stocking B. The cut-off value ( $P_{lp} < 20$  mmHg) was set according to our previous study, which identified  $P_{lp} < 20$  mmHg as an indicator of poor  $P_{lp}$  among the general population.<sup>6,12</sup> After additional informed consent was provided by the assigned participants, randomization was generated using the random number function in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and was conducted remotely by researchers. The two types of compression stockings (Stocking A and Stocking B) were directly sent from the manufacturer (Toray Opelontex Co., Ltd.) to our hospital in an envelope with each participant's number.

### Intervention

Following the randomization, the participants were provided two stockings of either Stocking A or Stocking B. The



**FIG. 1.** Measurement of the exerted pressure by the compression stockings. (A) Locations of the eight sensor probes (①-⑧) of the pressure measuring system in each leg. (B, C) The sensor probes attached to the leg. (D) Measurement of exerted pressure by a compression stocking after the sensor probes have been attached to the leg.

participants were instructed to wear the compressive stockings on the bilateral legs daily, from morning to bedtime, during the 16-week study period. The follow-up included a visit at baseline, 8 weeks, and the end (16 weeks) of the study. At the day of the hospital visit, the participants were not allowed to wear the compression stockings from the morning until returning home, to ensure a blinded assessment. Therefore, at each hospital visit, the non-compression period by the stockings lasted from the night before visiting the hospital to the  $P_{lp}$  measurement on the day of the visit, meaning that it lasted somewhere between approximately 12 and 18 hours.

#### Outcome measures

The primary outcome, evaluated after 8 and 16 weeks of wearing the compression stockings, was defined as an elevation of leg  $P_{lp}$ . Secondary outcome measures included the symptom prevalence of leg edema and muscle cramp. Quality of life (QOL) was assessed using the Short-Form 36 (SF-36) by comparing between the beginning (baseline) and the end (16 weeks) of the study. The SF-36 was designed to provide

an assessment of generic health domains that are not specific to age, disease, or treatment groups. The SF-36 is a well-validated instrument that provides estimates of the following eight health concepts: physical functioning, role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning-emotional, and mental health. For each domain, questions are scored, coded, summed, and transformed on a scale from 0 (worst health) to 100 (best health).

#### Sample size and power calculations

The sample size was calculated with the formula for the two-group parallel randomized controlled design based on the means of samples, as follows:<sup>13</sup>

$$n = (u_{\alpha} + u_{\beta})^2 (1 + 1/\kappa) \sigma^2 / \delta^2$$

In our recent study, the standard deviation of  $P_{lp}$  was 9.5 in subjects with  $P_{lp} < 20$  mmHg, and the difference of the means scores between the two groups was 5.<sup>6</sup> Therefore, the overall standard deviation is estimated as 9.5 (i.e.,  $\sigma = 9.5$ ), and the overall mean difference between the two groups is estimated as 5 (i.e.,  $\delta = 5$ ).

As a parallel design, the sample in the study group and control group is equal (i.e.,  $k = 1$ ). Given the 5% significance level (i.e.,  $\alpha = 0.05$ ) and 90% power (i.e.,  $\beta = 0.1$ ), the result by the above formula is 56.7 legs for each group. Besides, a dropout rate of 10% was assumed; thus, a total sample size of 122 legs was required for the study. A sample of 80 participants (160 limbs) was ultimately sought to accommodate attrition over the 16-week study period.

#### Data analysis

The outcome data were analyzed with the statistic software Statistical Package for the Social Sciences (SPSS) v.13 (SPSS

TABLE 1. EXERTED PRESSURES OF COMPRESSION STOCKINGS (MMHG)

Censor probe location			Stocking A	Stocking B
Calf	anterior	①	22.8 ± 1.8	10.9 ± 1.8
	interior	②	15.3 ± 1.8	10.3 ± 1.9
	lateral	③	15.5 ± 1.7	10.5 ± 1.7
	dorsal	④	15.0 ± 3.4	15.9 ± 2.5
Ankle	anterior	⑤	29.4 ± 4.0	13.3 ± 2.9
	interior	⑥	18.1 ± 2.1	7.5 ± 1.2
	lateral	⑦	19.7 ± 4.8	10.0 ± 2.4
	dorsal	⑧	27.2 ± 3.7	10.2 ± 2.8

Inc., Chicago, IL, USA). The demographic and baseline assessment data of the Stocking A and Stocking B groups were compared and tested by the *t*-test (continuous variables) or  $\chi^2$  test (discrete variables). Two-way repeated measured analysis of variance was used to reveal the mean differences in the leg  $P_{lp}$  and, symptom prevalence of leg edema or cramp between the Stocking A and Stocking B groups. The Wilcoxon signed rank test was used to analyze SF-36 data between each group. Data are expressed as the mean  $\pm$  standard deviation. The level of statistical significance was defined as  $p < 0.05$ .

## Results

### Baseline characteristics of the participants and study process

From November 2012 to May 2014, a total of 219 healthy female volunteers (aged 30–66 years, mean age  $45 \pm 15$  years) were recruited to the study. Among these, 80 participants had unilateral or bilateral legs with  $P_{lp} < 20$  mmHg (122

legs with  $P_{lp} < 20$  mmHg and 38 legs with  $P_{lp} \geq 20$  mmHg); these women were enrolled to the study and divided into the Stocking A ( $n = 40$ ) and Stocking B groups ( $n = 40$ ). Therefore, Stocking A was assigned in 62 legs with  $P_{lp} < 20$  mmHg, and 18 legs with  $P_{lp} \geq 20$  mmHg, while Stocking B was assigned in 60 legs with  $P_{lp} < 20$  mmHg, and 20 legs with  $P_{lp} \geq 20$  mmHg. Among the enrolled participants with low  $P_{lp}$ , none showed any morphological abnormalities of lymph perfusion, such as the dermal back flow sign, upon ICG fluorescence lymphography. During the 16-week follow-up, 3 participants in each group stopped wearing the stocking because they considered it tiresome to wear the stockings throughout the day. Therefore, the total dropout rate was 7.5%. The progress of the whole study is shown in Figure 2. No differences in the demographic characteristics and baseline measurement were found between the two groups, including the age, body mass index, smoking rate, prevalence rate of hypertension, diabetes mellitus, hyperlipidemia, and the numbers of legs with  $P_{lp} <$  or  $\geq 20$  mmHg (Table 2).

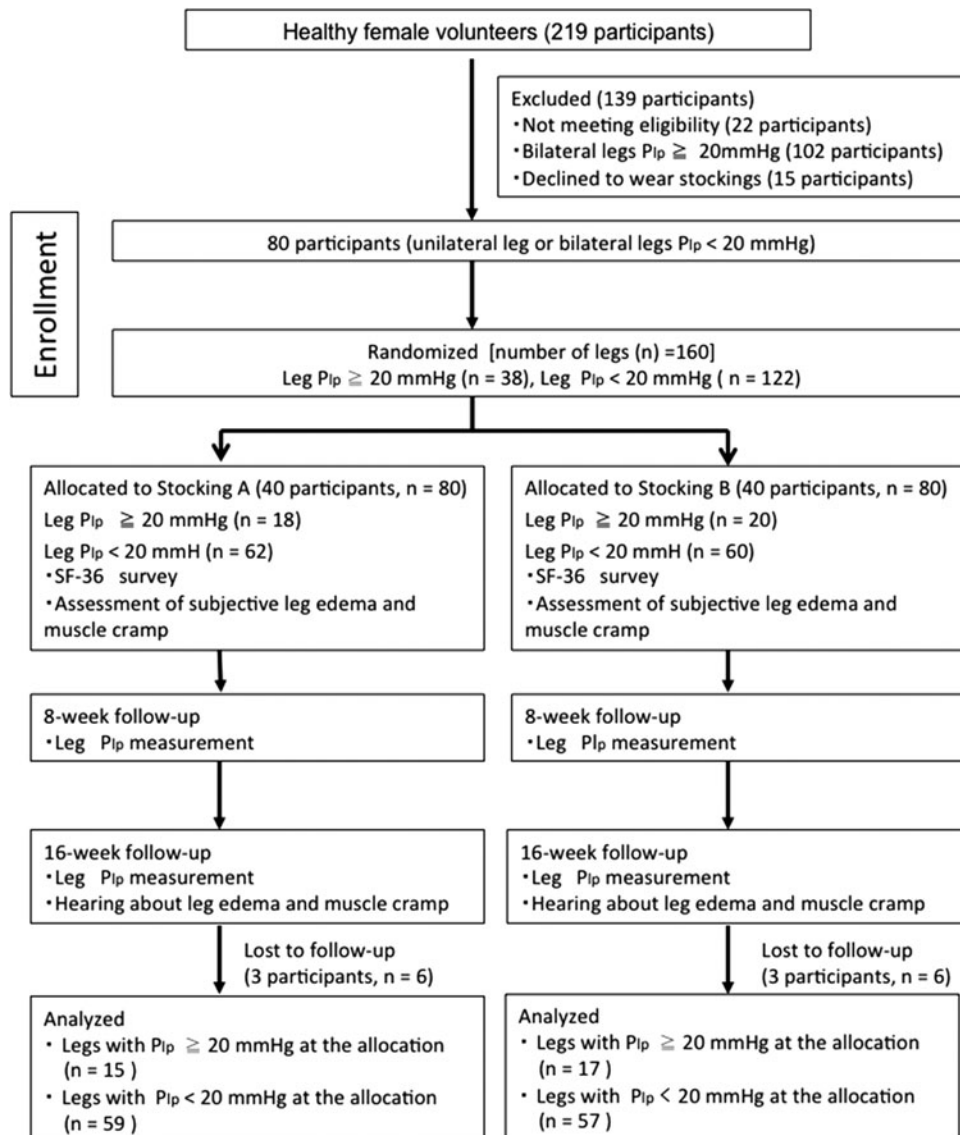


FIG. 2. Participant flow diagram.  $P_{lp}$ , lymphatic pumping pressure; SF-36, Short Form-36.

TABLE 2. BASELINE CHARACTERISTICS OF ENROLLED PARTICIPANTS

	Stocking A group 40 participants	Stocking B group 40 participants	p value
Age (mean $\pm$ SD years)	53.7 $\pm$ 9.5	52.3 $\pm$ 10.6	0.54
Participants with bilateral leg $P_{lp}$ <20 mmHg (numbers of legs)	22 (44)	20 (40)	N.S
Participants with unilateral leg $P_{lp}$ $\geq$ 20 mmHg (numbers of legs)	18 (36)	20 (40)	N.S
Numbers of legs with $P_{lp}$ <20 mmHg	62	60	N.S
Numbers of legs with $P_{lp}$ $\geq$ 20 mmHg	18	20	N.S
Body Mass Index (kg/m <sup>2</sup> ; mean $\pm$ SD)	20.7 $\pm$ 4.1	21.7 $\pm$ 2.2	N.S
Previous smoking	5 (12.5%)	5 (12.5%)	N.S
Current smoking	2 (5.0%)	2 (5.0%)	N.S
Hypertension (%)	3 (7.5%)	4 (10.0%)	N.S
Diabetes mellitus (%)	0 (0.0%)	1 (2.5%)	N.S
Hyperlipidemia (%)	2 (5.0%)	7 (17.5%)	N.S
Workers in a standing position	30 (75.0%)	31 (77.5%)	N.S

N.S, nonsignificant;  $P_{lp}$ , Lymphatic pumping pressure.

#### Primary efficacy outcome—Elevation of leg $P_{lp}$

At 8 and 16 weeks, both Stocking A and Stocking B resulted in significantly elevated  $P_{lp}$  in legs with  $P_{lp}$  <20 mmHg at baseline. The elevation was significantly higher in the Stocking A group than in the Stocking B group (Fig. 3A). On the other hand, both stockings did not significantly change the  $P_{lp}$  in legs with  $P_{lp}$   $\geq$  20 mmHg at baseline (Fig. 3B).

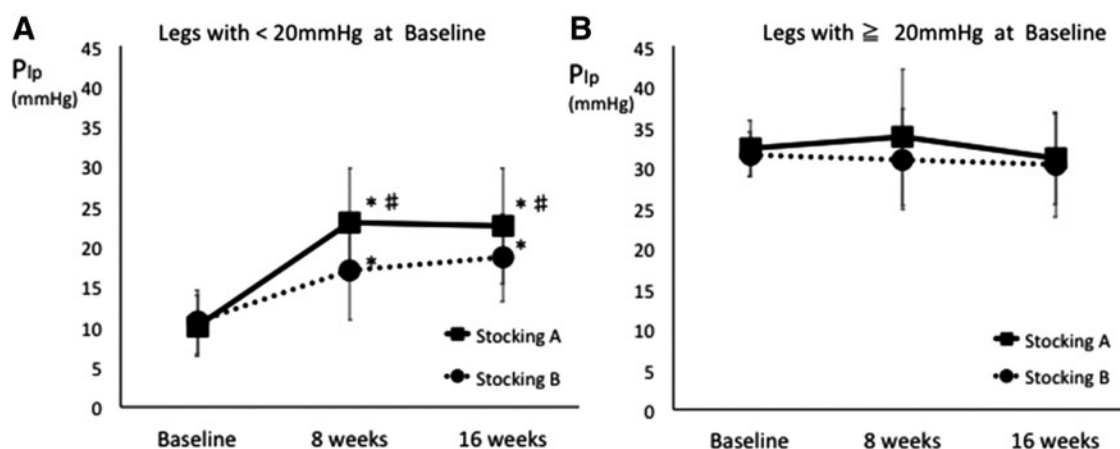
#### Secondary outcomes—Improvement of Quality of life (SF-36 scores) and leg symptoms

At the 16-week follow-up, significant differences were observed in body pain (BP) and vitality (VT) compared to at baseline in the Stocking A group (69.0  $\pm$  19 vs 79.5  $\pm$  20.6 in BP, 67.0  $\pm$  15.5 vs 72.3  $\pm$  18.4 in VT). However, no significant changes in the SF-36 scores were observed in the Stocking B group after 16 weeks in any SF-36 categories (Fig. 4). A medical interview regarding the presence or absence of leg cramp revealed that both Stockings A and B significantly

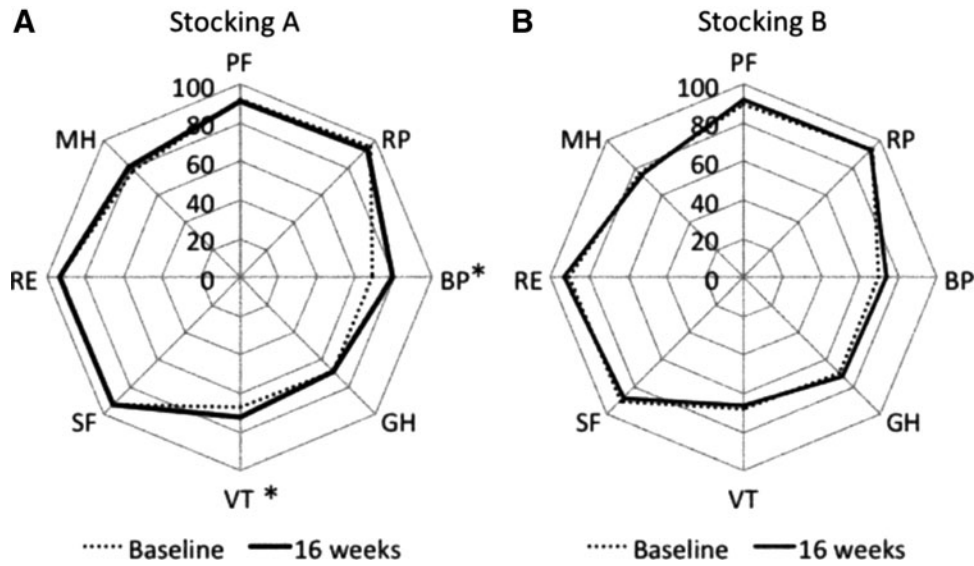
reduced its prevalence (from 78.2% to 54.8% in the Stocking A group, from 78.9% to 57.9% in the Stocking B group); however, there was no significant difference in the symptom prevalence between the two stocking groups (Fig. 5B). On the other hand, with regard to leg edema, only Stocking A significantly reduced the edema prevalence after 16 weeks, while Stocking B failed to ameliorate such symptoms, although the occurrence of the edema was subjectively reported from the participants (Fig. 5A).

#### Discussion

In this study, we have shown that continuously wearing compression stockings from morning to bedtime could recover leg lymph pumping in otherwise healthy females. This was the first randomized controlled study performed to evaluate any parameters related to lymphatic function other than limb volumes. It was aimed to examine the effectiveness of compression stockings on improving lymph pumping function in the



**FIG. 3.** Effects of compression stockings on the leg lymphatic pumping pressure ( $P_{lp}$ ). (A) Changes in the  $P_{lp}$  in legs with baseline  $P_{lp}$  <20 mmHg. Stocking A ( $n=62$  at baseline and 8 weeks,  $n=56$  at 16 weeks); Stocking B ( $n=60$  at baseline and 8 weeks,  $n=54$  at 16 weeks). (B) Changes in the  $P_{lp}$  in legs with baseline  $P_{lp}$   $\geq$  20 mmHg. Stocking A ( $n=18$  at baseline, 8 weeks, and 16 weeks); Stocking B ( $n=20$  at baseline, 8 weeks, and 16 weeks). \* $p$  < 0.05 compared to the baseline value; # $p$  < 0.05 vs. the  $P_{lp}$  values of Stocking B at the matched period.



**FIG. 4.** Comparison of Short Form-36 (SF-36)–Quality of Life (QOL) scores between the baseline and 16 weeks after wearing compression stockings. (A) Means of the SF-36-QOL survey scores in (A) the Stocking A group and (B) the Stocking B group. Stocking A group (40 participants at baseline, 37 participants at 16 weeks); Stocking B group (40 participants at baseline, 37 participants at 16 weeks). *Dotted line:* scores at baseline, *Solid line:* scores at 16 weeks. \* $p < 0.05$ . BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role functioning-emotional; RP, role functioning-physical; SF, social functioning; VT, vitality.

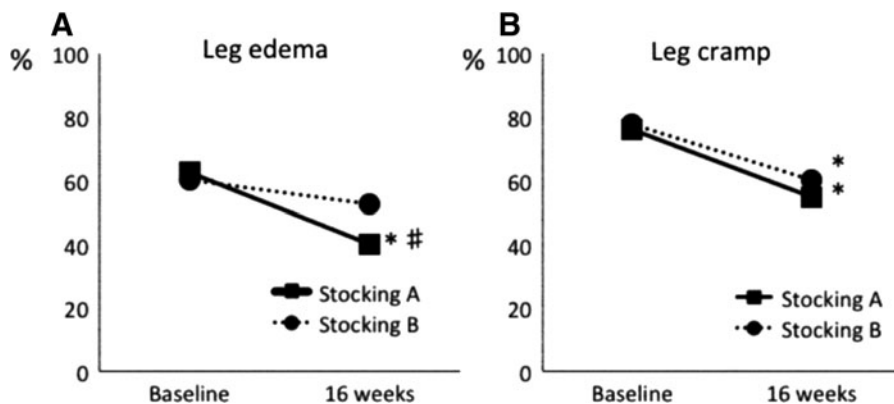
collecting vessels of the legs. The study also identified that compression stockings with an exerted pressure of approximately 20 mmHg (Stocking A) were superior to stockings with a pressure of approximately 10 mmHg (Stocking B).

As the secondary endpoint of the trial, the elevation of the  $P_{lp}$  was associated with the improvement of QOL based on the SF-36 assessment. Previously, it has been considered difficult to design a randomized controlled study for assessing lymphatic function in the general population because either invasive maneuvers to directly approach the lymphatic vessels or radioisotope usage for lymphoscintigraphy were needed. In this trial, we highlighted  $P_{lp}$  as a parameter of lymphatic vessel contraction in the legs. The measurement method used is simple and minimally invasive, and is thereby easily accepted

by healthy volunteers; the only invasive element is the injection of ICG.

Historically speaking,  $P_{lp}$  was first measured in humans by Olszewski and Engeset almost half a century ago.<sup>14,15</sup> The authors inserted a pressure transducer into the prenodal lymphatics after skin incision. The same group later successfully performed the measurement of lymphatic contractility under various conditions such as exercising and standing, using the same technique. According to that study, the exerted pressure by pneumatic cuffs transmitted to the deep tissues and improved lymph flow in lymphedema patients’ legs.<sup>16</sup>

However, studies regarding lymph contraction in humans have failed to attract researchers’ attention due to, as mentioned above, the invasiveness of inserting a probe into the lymphatic



**FIG. 5.** Comparisons of prevalence of leg edema and cramp between the baseline and 16 weeks after wearing compression stockings (Stocking A and Stocking B). (A) Prevalence rate of leg edema complaints; (B) Prevalence rate of leg cramp complaints. Stocking A group (40 participants at baseline, 37 participants at 16 weeks); Stocking B group (40 participants at baseline, 37 participants at 16 weeks). *Solid line:* Stocking A group, *Dotted line:* Stocking B group; \* $p < 0.05$  compared to the baseline values, # $p < 0.05$  compared to the values of the Stocking A group at 16 weeks.

vessels. In 2010, we first reported our novel method of measuring human lymph pumping using ICG fluorescence lymphography and a transparent sphygmomanometer cuff.<sup>5</sup> This method enables us to measure leg lymph pumping almost non-invasively. Using this method, we have previously identified that leg  $P_{lp}$  decreases along with aging, and found that there are considerable populations with low  $P_{lp}$  (<20 mmHg) who complain of occupational edema despite their venous function being normal.<sup>6,12</sup> Based on these previous findings, we designed the present randomized controlled trial to examine the effectiveness of wearing compression stockings on improving lymphatic vessel contractions in otherwise healthy female volunteers with low leg  $P_{lp}$ .

Before starting the trial, we manufactured two types of compression stockings by referring to previous literature regarding the compliance of prolonged wear of compression stockings with various levels of exerted pressure, because we considered it important for subjects to continuously wear the compression stockings for a long time. According to the previous reports, the discontinuation rate of patients wearing Class I (10–20 mmHg at the ankle) compression stockings was approximately 5%–7%,<sup>17,18</sup> whereas the compliance was worse, with a discontinuation rate of approximately 15%–28%, when wearing stockings with exerted pressures of 30–40 mmHg at the ankle in patients with DVT.<sup>19,20</sup>

Commonly, wearing compression stockings is considered unacceptable by patients with mild symptoms. For people with low  $P_{lp}$  who are otherwise healthy, lower exerted pressure would hence be preferable, leading to a better compliance. Therefore, continuous wearing compression stockings with exerted pressure >30 mmHg or class II, III stockings are unrealistic for healthy people with occupational leg edema. In this study, we manufactured two types of compression stockings (i.e., Stockings A and B) with relatively low exerted pressure (7.5–25 mmHg at the ankle). As a result, the discontinuation rate of wearing the compression stockings during the trial was only 7.5% in both groups, which was similar to that in previous studies with class I stockings.<sup>17</sup> Accordingly, we believed that compression stockings with the exerted pressure distributions used in this study are acceptable for healthy people with occupational edema.

The effectiveness of compression stockings on treating chronic venous insufficiency has been well studied, for example, as for treatment of venous leg ulcers, leg edema due to DVT, and prevention of post-thrombotic syndrome in patients with DVT.<sup>21,22</sup> The scientific background of the effectiveness of compression stockings on the venous system originated from the study by Sigel et al.<sup>23</sup> The author demonstrated that wearing compression stockings significantly increased the velocity of blood flow in the femoral vein using Doppler ultrasonography. Since then, most current compression stockings have been designed to exert pressure on the legs similar to their report, and have been demonstrated to improve calf muscle pump function and reduce residual venous volume fraction using plethysmography.<sup>24,25</sup>

Because lymph is propelled from the extremities to the blood stream by not only intrinsic contraction but also extrinsic forces such as contractions of the skeletal muscles adjacent to the lymphatic vessels, the effectiveness of the compression stockings on improving calf muscle pumping on the veins may also help lymph propulsion by enhancing the extrinsic force.

However, in this study, the leg  $P_{lp}$  was measured in the sitting position without leg exercise; hence, the effect of compression stockings on enhancing the extrinsic force can be neglected. As a result, the mechanism of improving  $P_{lp}$  by compression stockings is completely speculative. In fact, even the mechanisms of lymphatic vessel contractions remain to be elucidated. In blood vessels, fluid shear stress promotes nitric oxide (NO) production by endothelial NO synthase, in which NO diffuses from the endothelium to smooth muscle cells to cause vessel relaxation via cyclic guanosine monophosphate (cGMP)-dependent protein kinase G (PKG) pathways.<sup>26</sup>

Several studies have tried to identify the basic mechanisms of lymphatic contraction using isolated lymphatic vessels or thoracic ducts of animals. According to these studies, lymphatic vessels appear to be more sensitive to wall shear stress (WSS) in terms of the NO production, as well as to contractions, compared to blood vessels.<sup>27–29</sup> On the other hand, compression stockings have been identified to raise the WSS in the superficial veins of the calf in human studies, and may also raise the WSS in the leg lymphatic vessels.<sup>30</sup> Recently, Gasheva et al. reported that the lymphatic vessels also possess cGMP-PKG pathways.<sup>31</sup> Thus, taken together, wearing compression stockings may raise the WSS in lymphatic vessels, thereby promoting NO production and modulating contractions via the cGMP-PKG pathway.

Another potential benefit of wearing compression stockings is to decrease capillary filtration.<sup>32</sup> Under physiological conditions, an increase of capillary filtration may be associated with enhanced intrinsic lymphatic pumping force. However, chronic elevation of the capillary filtration may collapse the pumping function of the lymph vessels due to overwork. Hence, by continuous wearing of compression stockings owing to the subsequent decreased filtration, the pumping function in the lymph vessels might recover.

In the general population, as in this trial, there are considerable numbers of people who complain of leg edema after working for prolonged periods in a sitting or standing position. Such people, who experience so-called occupational leg edema, usually do not have venous insufficiencies. Occupational leg edema has been considered to develop as a result of gravity raising the hydrostatic pressure and increasing the venous pressure in the legs, which in turn leads to extravasation of fluid from the venules, thereby causing edema.

Because both the venules and lymphatic system work together to drain fluid from the interstitium, lymphatic pumping failure may also contribute to occupational leg edema. Interestingly, calf-length compression stockings exerting a pressure of 10–20 mmHg, similar to that of the stockings used in this study, have been shown to be effective at preventing occupational edema.<sup>33,34</sup> These results might also reflect the effect of the compression stockings on improving  $P_{lp}$  in the leg lymphatic vessels, as indicated in this study.

The current study has a number of limitations. First, the study was conducted only in women. However, females appear to account for the majority of occupational leg edema cases,<sup>34</sup> and the current study was designed to assess a representative, general female population in Japan. With regard to the size of the patient population surveyed in the study, with only 80 participants, the sample size of the survey is clearly limited. Second, a control group without compression was not set in this study; hence, the natural course of  $P_{lp}$  in

subjects with  $P_{1p} < 20$  mmHg could not be assessed. Moreover, the effect of longer stockings such as thigh-length stockings thus remains unknown because only knee-length stockings were tested. Lastly, the durability of the improved  $P_{1p}$  after cessation of compression stocking use is also unknown. Accordingly, further studies are needed in the future to answer these questions.

In conclusion, wearing knee-high compression stockings for 16 weeks significantly raised the leg  $P_{1p}$  and improved QOL in healthy female volunteers with low leg  $P_{1p}$ . Comparison between two types of compression stockings with different exerted pressures revealed that stockings with 18–29 mmHg at the ankle and 15–23 mmHg at the calf are more effective than those with exerted pressures of 7.5–13 mmHg and 10.3–15 mmHg, respectively. Only the former type improved the prevalence of leg edema and the QOL significantly. Based on these findings, compression stockings may become a therapeutic option to elevate leg  $P_{1p}$  and to ameliorate leg edema, consequently leading to a better QOL in otherwise healthy people.

### Acknowledgments

The authors thank Tsuyako Ida, Makiko Kato, and Yuichi Ito of the Angiology Laboratory of Hamamatsu University School of Medicine for their assistance and support in this study. This work was supported by JSPS KAKENHI Grant number 26293310 (to NU) and in part by Toray Opelontex CO., Ltd.

### Author Disclosure Statement

Hamamatsu University School of Medicine holds a patent for “Lymphatic pressure-measuring system and method for controlling same” (PCT/JP2010/051706). Naoki Unno is an inventor listed in the patent. Hironori Uranaka and Tomohiko Marumo are employees of Toray Opelontex Co. Ltd., the vendor of polyurethane yarns used in the compression stockings in this study.

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