Review

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Posted Date: 2 April 2024

doi: 10.20944/preprints202404.0078.v1

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Nailfold Capillaroscopy: A Comprehensive Review on Its Usefulness Not Only in Clinical Diagnosis, but Also in Unhealthy Dietary Lifestyle Improvements

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Abstract: Since the 1970s, the usefulness of nailfold capillaroscopy (NFC) in the diagnosis of rheumatological disorders such as systemic sclerosis has been well known, and further studies also showed that NFC can detect non-rheumatic diseases such as diabetes, glaucoma, dermatitis, Alzheimer disease, and so on. In the past decade, the morphological changes in the nailfold capillary have been also reported in the unhealthy lifestyle habits such as smoking, inappropriate diets, sleep shortage, and even psychological stress which presents slow blood flow. Therefore, study in the relationships between the morphology of nailfold capillaries and lifestyle habits has high potential to understand the unhealthy state, or even predict the pre-disease condition. So, simple, inexpensive, and non-invasive methods such as NFC are constantly needed for routine health checkups. Thus, we undertook a systematic search in PubMed database, and summarized the studies reporting the assessment of morphological NFC in order to undertake a comprehensive review on the usefulness of NFC not only in clinical diagnosis, but also in unhealthy dietary lifestyle improvements. Here in this review paper, we finally summarized the dietary and lifestyle health promotion strategy judging from NFC- and the other relating-measurement from the viewpoint of healthy microvascular blood flow and endothelial function.

Keywords: nailfold capillaroscopy (NFC); health checkups; capillary morphology; dietary lifestyle; health claims; microcirculation; dietary flavonoids

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1. Introduction

Nailfold capillaroscopy (NFC) is a simple, non-invasive, highly sensitive, safe, reliable, and inexpensive tool, that is designed to assess multiple features of the nailfold capillaries, including blood flow, density, and different kinds of abnormal morphology. It can provide visual inspection for microcirculation in our body. Since the 1970s, NFC has gained recognition in the field of diseases that affect microcirculation, especially in many rheumatological disorders, such as connective tissue diseases (CTD); i.e., rheumatic diseases like systemic sclerosis (SSc), systemic lupus erythematosus (SLE), inflammatory myositis, rheumatoid arthritis (RA), and so on. Poor lifestyle and dietary habits can also cause cardiovascular diseases, cancer, diabetes, and Alzheimer's disease, and other lifestyle-related diseases. Healthy life style, including moderate exercise and reducing psychological stress, smoking, and alcoholic intake, can prevent diseases. As a matter of fact, full articles published from 1980 to 2023 retrieved from PubMed using the search word "nailfold capillaroscopy" are represented in Figure 1 that is paralleled well with previous paper [1].

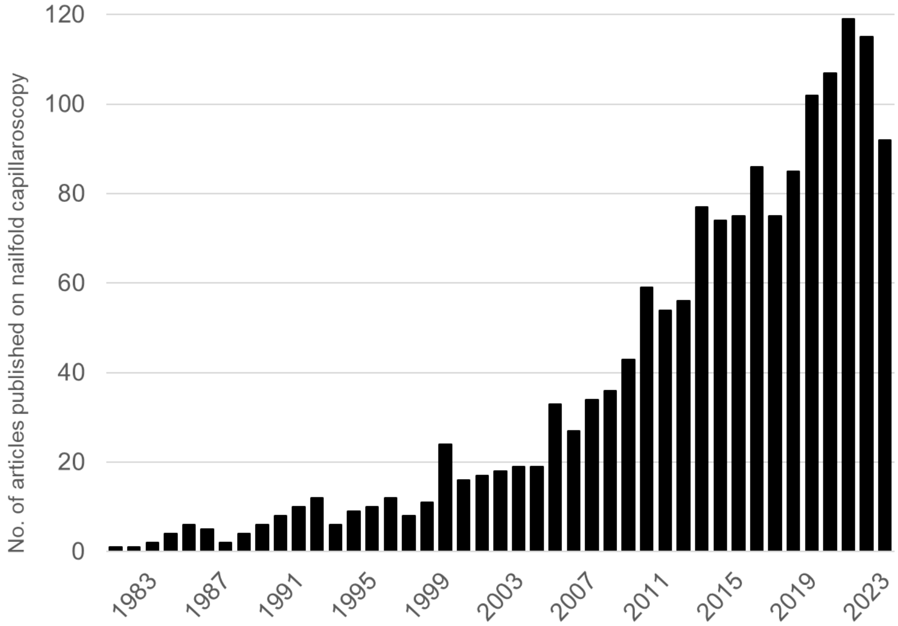

Figure 1. Number of articles published on nailfold capillaroscopy < Full articles published from 1980 to 2023 were retrieved from PubMed using the search word "nailfold capillaroscopy". (*2023: Up to October) >.

The 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc counts 2 out of the minimum 9 points needed for the pathology classification for NFC SSc-specific findings ([2], 2013). The inclusion of the capillaroscopic evaluation in the SSc classification criteria was based on its role in early SSc diagnosis; later the capillaroscopy indications expanded ([3–6]. Moreover, standardization guidelines for capillaroscopy practice for Raynaud's phenomenon (RP) and SSc were published by the EULAR study group on microcirculation in rheumatic diseases and the scleroderma clinical trials consortium group on capillaroscopy recently ([1], 2020).

NFC's usefulness in the diagnosis of SSc is well known, and in other rheumatic conditions such as other connective tissue diseases, e.g., vasculitis, and arthritis, the nailfold video-capillaroscopy (NVC) anomalies are often included in a scleroderma like pattern. The utility of NFC in non-rheumatic disease (NRD) has not been well studied, therefore recent Italian extensive research [7] was performed using PUBMED and GOOGLE SCHOLAR databases to identify studies using published papers relating non-rheumatic diseases between 1990 and 2019. Various diseases, such as diabetes, glaucoma, dermatology, sickle cell disease (SCD), interstitial lung disease (ILD), idiopathic pulmonary hypertension (i-PAH), Alzheimer disease (AD), Rett syndrome (RS) cause microvascular damage, that can be detected by capillaroscopy. NFC allows to evaluate the measurements of individual capillaries (length, shape, and diameter of each capillary loop, the number of capillaries), hemorrhage, avascular area, angiogenesis, and the dynamic parameters (blood flow velocity, using a software program) [8]. Actually, studies published in the last decades have demonstrated the importance of this innovative technique in these diseases (diabetes mellitus, glaucoma, essential hypertension, psoriasis (dermatology), cardiovascular disease, chronic kidney disease (CKD), Alzheimer's disease) [9]. For example, one of the systematically reviewed papers concluded that NFC findings such as reduced capillary density and length, dilated capillaries, micro-hemorrhages, tortuosity, ectasic loops, avascular areas or ramified capillaries, aneurysms are not infrequent, even in patients with no underlying CTD. A summary of the included studies with all significant differences in capillaroscopic findings between patients and controls is provided in that paper [9] and above-mentioned Dima's paper ([3]). Recent studies conclude that capillaroscopy provides key data for the determination of vascular damage in diabetic patients and thus, allows the evaluation of the

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progression of the disease [9], making this technique a potential future utility in the microvascular disease evaluation. Maldonado et al. demonstrated that the use of capillaroscopy in patients with diabetes allows the identification of capillaroscopic abnormalities, possibly including a characteristic pattern in this group of patients consisting of tortuous, cross-linked capillaries, avascular zones and ectasias, also the study showed an association between microangiopathies seen at the ophthalmoscopy and the presence of ramified capillaries and avascular zones seen at the nailfold level [10,11].

In addition to this NFC measurement, we expanded the dietary habit survey into microcirculation measurement by other methods because there have been few papers published concerning the NFC and dietary habits. Therefore, we finally summarized the dietary and lifestyle recommendation for peripheral artery disease (PAD) prevention from the viewpoint of microvascular blood flow.

2. Normal Capillaroscopy Pattern in Healthy Subjects

We undertook a systematic search in PubMed database and scientific website surveys, and selected the studies reporting quantitative and/or qualitative assessment of morphological NFC in order to undertake a comprehensive review on the usefulness of NFC not only in clinical diagnosis, but also in unhealthy dietary lifestyle improvements. We concentrated the latter case category because there have been few published papers in the healthy subject category up to now. Even though we selected not only "randomized controlled trial studies" but also other pilot studies, our search strategy identified 243 original and 84 review articles from 1999 to 2023, and only 8 and no articles were retrieved from the viewpoint of dietary habitual lifestyle in the original and review paper category respectively. Therefore, we focused on 8 original papers basically in the present paper to generalize the NFC application for the life-style improvement. Surveyed results of recently published NFC papers in the present study are shown in Figure 2.

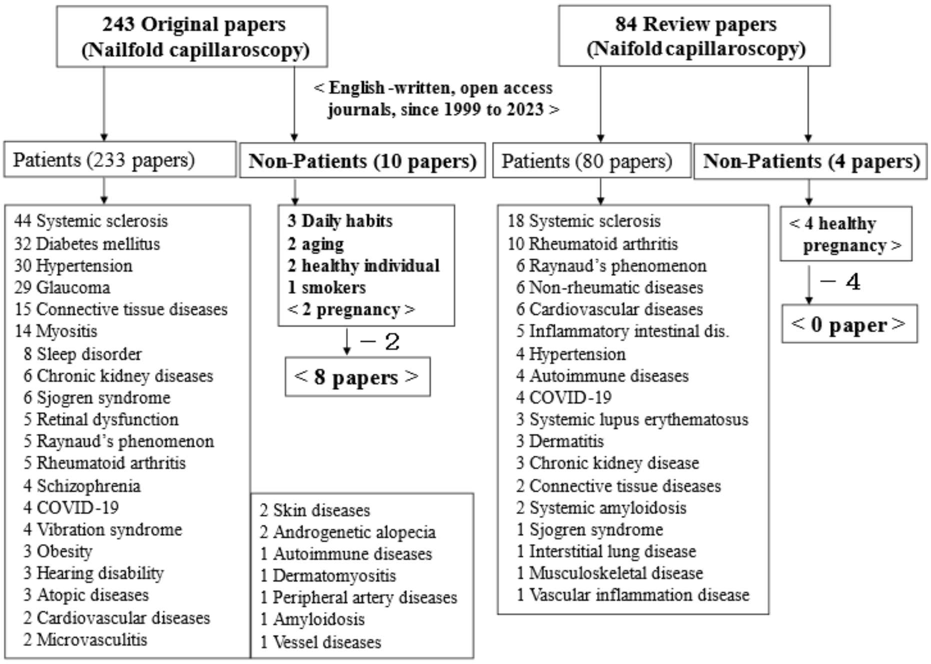

Figure 2. Surveyed results of recently published nailfold capillaroscopy papers (1999 to 2023).

Dima, A, et al. totally summarized the qualitative NFC assessment in healthy subjects as follows that shows homogeneous capillaries distribution in the field examined. Most frequently, the capillaries are stand perpendicularly to the nail edge [12,13]. The terminal row of capillaries is arranged in parallel fashion and grant a full-length description of the capillary [13] with U-shaped

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[14]. Under the rows of capillaries, the subpapillary venous plexus might be seen and appears of greater diameter [15]. The arterial afferent loop is thinner than the venous efferent one [12]. Besides the hairpin shape, other two discrete abnormalities, nonspecific variations are recognized for the normal pattern: tortuous (the loops undulate but do not cross) and crossing (loops crossed once or twice) capillaries that together with the hairpin shape are considered normal [1]. Besides these three shapes (hairpin, tortuous, crossing) all the other are defined as abnormal morphologies [1]. Ingegnoli, F., et al. described the morphological aspects of the capillaries as hairpin shaped loop, loops with one cross, loops with more than two intersections, as well as meandering loops and proposed three main capillaroscopic patterns for normal variations found in healthy subjects, namely first one "normal" with 2–5 U-shaped loops/mm and maximum 2 tortuous loops/mm; the second one, named also "perfect normal" which consists of more or equal than 5 U-shaped loops–/mm, and the third one, "unusual normal" consisting in at least any of the following: one meandering, one bushy loop, one microhemorrhage, or more than 4 crossed loops/mm [16]. Therefore, unusual capillaries like intercrossed, tortuous, elongated, or disorganization of the capillaries might occur even in subjects without underlying SSD (scleroderma spectrum disorders) [15]. Counting the number of capillaries reported to distance (per mm) is important for defining normality [16]. Different authors defined various limits for the normal capillary density; like 9–14 (average 10) capillaries/ mm [5], 7–10 capillaries/ mm [16], 9–13 capillaries/ mm [17], 6–14 capillaries/mm [15], 7–12 capillaries [18]. A recent standardization of the EULAR study group for microcirculation in rheumatic diseases stated that more than 7 capillaries/ mm define normal density [1] (see Table 1). Similarly, the reports for capillaries loops diameter or length are not uniform. The ectasia was initially defined as having 4–9 times higher, while the giant capillaries more than 10 times higher than normal diameter [12]. Further, the normal diameter of the afferent branch of 6–19 μm and 8–20 μm for the efferent branch, with diameters of more than 50 μm defining the mega/ giant capillaries, [12,15,17]. By consensus, it was recently established that a diameter of maximum 20 μm for normal diameter and 50 μm for ectasia [1]. The loop length is representing the visible part of the capillaries and normal ranges were reported by some authors of 200–250 μm [15], but also up to 500 μm [16,17], while elongated capillaries have length of more than 300 μm, 500 μm or even 700 μm [19]. Microhemorrhages might be seen in healthy individuals in case of local trauma in which its position is closer to the nail and not related to a giant capillary recently collapsed [12]. Overall characteristics of nailfold capillaroscopic morphology in healthy subjects were summarized in Table 2 [13,14,16,17].

Table 1. Normal capillaroscopic pattern in healthy subjects.

Parameter	Description
Skin transparency	Allows a good visualization of the capillaries
Subpapillary venous plexus	Visible in up to 30% of healthy individuals
General view	Homogeneously sized, regularly arranged
Capillary orientation	Straight, parallel fashion, usually perpendicular to the nailfold
Capillary density	Number of capillaries over 1 mm nailfold, more than 7 capillaries/mm
Capillary morphology	Inverted "U", hairpin shape, but also tortuous and/ or crossing capillaries (nonspecific variations)
Capillary length	less than 300 mm
Capillary diameter	less than 20 mm for each loop (afferent, apical, efferent)
Pericapillary edema	Absent
Hemorrhages	Absent (occasionally observed after microtrauma)
Giant capillary	Absent
Neoangiogenesis	Absent
Blood flow characteristics	Dynamic, no stasis

After Dima, A., et al. [3]; Kayser, C., et al. [12]; Chojnowski, M.M., et al. [6]; Cutolo, M. [4]; and Smith, V., et al [1].

Table 2. Summary of nailfold capillaroscopy (NFC) morphology in normal healthy subjects

Authors and Published Year	NFC morphology
Ingegnoli, F., et al. 2013, *Microvasc. Res.*, **90**, 90–95. [16]	Based on the cluster analysis three major "normal" morphologic capillaroscopic patterns were depicted: 1) the "normal" pattern mainly with 2 to 5 U-shaped loops/mm and ≤2 tortuous loops/mm; 2) the "perfect normal" pattern with ≥5 U-shaped loops/mm; and 3) the "unusual normal" with at least 1 meandering or bushy loop, or at least 1 microhemorrhage, or with N4 crossed loops/mm. Regarding the loop measurements, the majority of subjects had a median of 7 capillaries/mm with a median length of 198 μm.
Faggioli, P., et al. 2015, *Italian J. of Med.*, **9**, 234-242. [17]	Under physiological conditions the normal pattern is characterized by: 1) the orderly arrangement of the capillaries to comb; 2) density of 9-13 mm (maximum 3 per dermal papilla); 3) 6-9μm diameter afferent branch, efferent branch 8-21μm (>50 micron: megacapillaries); 4) length 200-500 μm.
Tavakol, M.E., et al. 2015, *Biomed. Res. Int.*, **2015**, 974530. [14]	Nailfold capillary density appears to be similar in healthy adults and healthy children across Europe. European authors found the mean capillary density in healthy children to be in the range of 5–7.3 compared to 7.3–10.3 in healthy adults. Brazilian authors showed slightly higher capillary counts, ranging from 6–7.3 capillaries per millimeter in children to 9.11–10.1 capillaries per millimeter in adults.
Emrani, Z., et al. 2017, *Microvasc. Res.*, **109**, 7–18. [13]	Density of finger capillaries in healthy control subjects were summarized by collecting 17 articles published from 1990 to 2016 as follows. The average capillary density was 8.45 ± 1.32/mm for individuals aged 40 or less and 8.71 ± 1.40 for individuals older than 40 years of age in healthy subjects*. Moreover, the average capillary densities in healthy males and females were found to be 8.83 ± 1.50 and 8.60 ± 1.26/mm, respectively.** < *Ingegnoli, F., Herrick, A.L., 2013. Nailfold capillaroscopy in pediatrics. *Arthritis Care Res.* **65**, 1393–1400. **Hoerth, C., Kundi, M., Katzeschlager, R., Hirschl, M., 2012. Qualitative and quantitative assessment of nailfold capillaries by capillaroscopy in healthy volunteers. *Vasa*, **41**, 19–26. >

3. Nailfold Capillary Patterns Correlate with Age, Gender, Lifestyle Habits

Poor lifestyle and dietary habits can cause cardiovascular diseases [20], cancer [21], diabetes [20], and Alzheimer's disease [23], and other lifestyle-related diseases. Healthy lifestyle, including moderate exercise and reducing psychological stress, smoking, and alcoholic intake, can prevent diseases. For routine health checkups, simple, inexpensive, and non-invasive methods are constantly needed. Actually, the morphological changes in the nailfold capillary have been reported in the unhealthy lifestyle habits such as smoking [24], sleep shortage, and even psychological stress presents slow blood flow [25]. Therefore, study in the relationships between the morphology of nailfold capillaries and lifestyle habits has high potential to understand the unhealthy state, or even predict the pre-disease condition [26,27]. Therefore, several papers described that the normality or normal range of the nailfold capillaries has been investigated in healthy individu- als in terms of nailfold capillary morphology [16,26–29]. Here, we selected 4 papers relating to dietary habits, out of 8 "non-patient" papers.

< Example 1: Nailfold capillaroscopy (NFC) of healthy individuals: --- An observational study [26] >

 doi:10.20944/preprints202404.0078.v1

The morphology and capillary density in the nailfold capillaries of healthy individuals were studied and analyzed. The study concludes that various capillary morphology findings such as tortuosity, dilated, meandering, bushy capillaries, and decreased plexus visibility can be present in non-clinical individuals with BMI greater than 25 that was statistically significant (*p*-value 0.0222, in "Plexus" capillary visibility); and "Tortuous" capillary (*p*-value of 0.0002) and "Receding" capillary (*p*-value 0.0229) were more frequently seen in the aged group greater than 41 years (Table 3). They have also suggested that those appearance in more than two fingers should be considered for it to be pathological.

Table 3. Result of various morphological characteristics.

Nailfold capillary	Dilated	Neoangio-genesis	Meandering	Tortuous	Ramified	Plexus Visibility	Micro hemorrhage	Receding	Angulated
Male (72)	25	29	34	29	4	29	4	23	9
%	34.72	40.27	47.22	40.27	5.55	40.27	5.55	31.94	12.5
Female (78)	25	29	33	39	6	26	4	24	13
%	32.05	37.17	42.3	50	7.69	33.33	5.12	30.76	16.66
P	0.8624	0.8247	0.549	0.3026	0.8442	0.3797	0.9074	0.8768	0.6244
BMI*<24.9 (84)	30	38	42	36	5	38	4	24	15
%	35.71	45.23	50	42.85	5.95	45.23	4.76	28.571	17.85
BMI* >25 (66)	20	20	25	32	5	17	4	23	7
%	30.3	30.3	37.87	48.48	7.57	25.75	6.06	34.84	10.6
P	0.6007	0.0909	0.1879	0.6016	0.9474	0.0222**	0.7253	0.5187	0.3108
20-40 years (78)	22	31	34	23	3	32	5	17	11
%	28.2	39.74	43.58	29.48	3.84	41.02	6.41	21.79	14.1
41-60 years (72)	28	27	33	45	7	23	3	30	11
%	38.88	37.5	45.83	62.5	9.72	31.94	4.61	41.66	15.27
P	0.225	0.9092	0.911	0.0002**	0.2654	0.3254	0.8074	0.0229**	0.9699

* BMI = Body Mass Index, ** significant difference. < From Gorasiya, AR, et al.: *Indian J. Dermatol*., 13, 600-605, 2022 [26] > .

< Example 2: Application of NFC for the lifestyle management [27] >

Nakajima, T., et al. have evaluated the relationship between nailfold capillary pattern and lifestyle habits and coldness of the fingertips which may exhibit microcirculation disorder linked with pre-disease. Their study was undertaken in order to evaluate the correlation between pattern of nailfold capillaries and lifestyle habits (I), clinical experimental design for the broad study (II), and follow-up study (III). In the broad study, both men and women participated, and data were collected as questionnaires for lifestyle habits, fingertip temperatures, and images using NFC. In the follow-up study, women participants addressed the improvement in lifestyle habits after the first test, and data were re-analyzed after 1–2 weeks.

Since the fourth finger may get less damage by physical stress than the second and third fingers, the fourth finger of the left hand was selected for observation, and for any participant who had a problem with fourth finger used the fourth finger on their right hand. Nailfold capillaries were observed under a light microscope (Kekkan-Bijin, AT Co., Ltd., Osaka, Japan; region of observation 500 μm × 700 μm; magnification 320×) after application of mineral oil to reduce light reflection. Capillary images were captured using Capillary Analysis System (At Co., Ltd.). The images of nailfold capillaries were numerically analyzed for four parameters: diameter, length, width, and distance. The mean value of these parameters for each individual was used for statistical analysis. Area and sums of capillary lengths were measured using Capillary Analysis System. Representative images of nailfold capillaries showing straight and long loops, twisted or bushy loops, and non-dense and small loops are shown in Figure 3.

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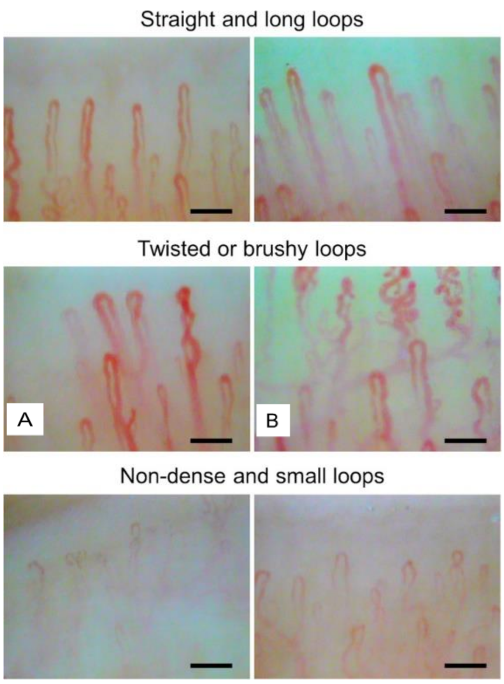

Figure 3. Representative images of nailfold capillaries. The straight and long loops were commonly correlated with being healthy (A, B). Twisted or bushy loops (C, D), and non-dense and small loops (E, F) were commonly correlated with being unhealthy. < From: Nakajima, T, et al.: Nailfold capillary patterns correlate with age, gender, lifestyle habits, and fingertip temperature. PLOS ONE, 17, e0269661 2022 [27] >.

They summarized significantly correlated parameters of nailfold capillary morphology and lifestyle habits included the same group of principal component analysis. That is, capillary area negatively correlated with the coldness of fingertips in men aged 20–39 years; the width negatively correlated with falling asleep in men aged 20–39 years; and positively and negatively correlated with the frequency of smoking and intense exercise in men aged over 40 years, respectively (Figure 4, Lower). Additionally, in women, capillary length negatively correlated with the frequency of drinking alcohol in those aged 20–39 year; and the dot plot indicated a tendency of small length of capillary loops in the high scoring group of drinking alcohol (Figure 4, Upper).

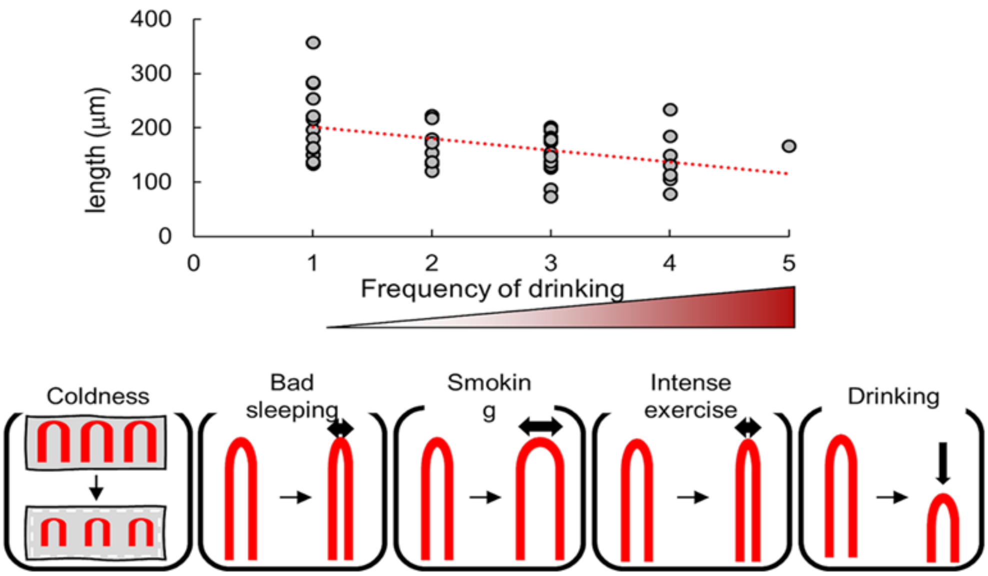

Figure 4. Structures of nailfold capillaries correlated with lifestyle habits. Upper: Representative dot plot showing length of the loop of nailfold capillaries negatively correlated with the frequency of

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drinking. Dashed line: least-squares line. Lower: Schematic representation of the correlation between the nailfold capillary structure and lifestyle habits. < Cited from: Nakajima, T, et al.: Nailfold capillary patterns correlate with age, gender, lifestyle habits, and fingertip temperature. *PLOS ONE*, 17, e0269661, 2022 [27] >.

Nakajima, T., et al.'s study might be the first report indicating a correlation between the morphology of nailfold capillaries and lifestyle habits in a non-clinical population. They are indicating that the morphology of nailfold capillaries correlated with coldness of fingertips, falling asleep, smoking, and intense exercise which were involved in car-cardiovascular phenotypes. Therefore, they concluded that the simple, inexpensive, and non-invasive method using NFC can be employed for routine health checkups everywhere even at a bedside.

< Example 3: LPS supplement improved capillary vessel and blood HbA1c level [28] >

Lipopolysaccharide (LPS) is known as an endotoxin that causes serious inflammation when it is released in the blood stream during the infection of Gram-negative bacteria. On the other hand, LPS is a substance that is universally present in the environment. It is reported also that it is not toxic when orally or trans-dermally administered, and it contributes to the activation of innate immunity [30]. From that viewpoint, one example of dietary supplement study has been reported by Nakata, Y., et al. in 2017 [28]. They used dietary supplement containing LPS in their randomized double-blind, parallel-group trial study. Used LPS was derived from Gram-negative bacteria *Pantoea agglomerans* (LPSp) (201.5 μg/tablet as LPS), and nailfold capillaroscopy measurement was applied to judge the effectiveness of this dietary supplement.

LPS is present in the environment by attaching to edible plants of floating in the air, and it has been recently revealed that the human immune system is controlled by ingesting LPS in the environment from diet or by breathing naturally [31]. Since LPS has been found in Chinese medicines and edible plants, Inagawa et al. [32] focused on the physiological actions of naturally ingested LPS, and the safety and effect of oral and transdermal administration were investigated.

One tablet of this LPSp supplement was composed of 25 mg of fermented wheat extract that contains 10 mg/g of LPSp (measured value was 201.5 ± 22.8 μg/tablet by ELISA). Fifty-two subjects were used in this study included males and females aged 20 years or older and 74 years or younger, and subjects were within the range of normal hematological values before the start of the study excluding oxidized LDL, IgA, and CRP (Mild abnormalities in the "Japan Society of Ningen Dock Criteria [Revised on 1 April 2014]"). For the control (n =26), the supplement replaced the LPSp (n=26) with dextrin. They used the Capillary Observation System of At Co., Ltd. for vascular observ- ation; and the capillary vessel and bloodstream in the subungual space of the left ring finger were analyzed microscopically by using the capillary bloodstream assessment system. When the number of fingertip capillary vessels that can be confirmed within the specified field was assessed as an indicator, a significant increase in the number of fingertip capillary vessels was found in the LPSp supplemented group after 3 months compared with the control group (Table 4). According to the JDS (Japan Diabetes Society) criteria, 24 subjects in the LPSp supplemented group and 20 subjects in the control group were within the borderline at the baseline in HbA1c which is a glycation marker. Including the subjects with borderline, a significant decrease in blood HbA1c was found in the LPSp supplemented group after 3 months of ingestion. That study indicates that an increase in the number of capillary vessels and antiglycative effects by the oral ingestion of LPSp were found in the healthy subjects. Thus, it was suggested that orally ingested LPSp contributed to the maintenance of normal bloodstream.

Table 4. Number of fingertip capillary vessel was measured after 3 months ingestion of LPSp supplement or Control.

	Control (n=26)		**LPSp supplement (n=26)**	
Months (m)	0 m	+3 m	0 m	+3 m

Per field	4.92 ± 0.30	4.42 ± 0.25	4.65 ± 0.25	5.12 ± 0.27[1]
Relative value	1.0 ± 0.0	1.057 ± 0.17	1.0 ± 0.0	1.201 ± 0.10

Nailfold capillaroscopy was measured in the area near lunula of the left ring finger. [1] Control +3 m vs. LPSp supplement +3 m, $p < 0.05$ by Mann–Whitney U test. From: Nakata, Y., et al.: Effects of 3 months Continuous intake of supplement containing *Pantoea agglomerans* LPS to maintain normal bloodstream in adults. < Nakata, Y., et al.: *Food Sci. Nutr*., **2017**, 1-10. [28] >.

< Example 4: Fermented herbal decoction improves peripheral capillary [29] >

Another example relating to the effect of dietary factor on nailfold capillary morphology has been reported using fermented herbal decoction by Akazawa-Kudoh, S., et al. in 2018. Reduction in performance status of skin condition is one of the serious factors determining the prognosis of post-menopausal women. The purpose of their study was to investigate whether fermented herbal decoction (FHD) could improve the performance status of post-menopausal skin condition, inspecting capillary condition especially nail stem in the 4th finger of left hand. Commercially available 80 sorts of wild herbs were prepared and extracted by 100 ml of hot water (98°C) for 3 minutes to get 10 grams of grained roasted material. The fermentation was carried out by *Lactobacillus leuteria* for 5 days at 40°C, and each ratio of powdered sample, lactobacilli and water were 100:50:850 (prepared by ECHIGO YAKUSOU, Ltd. Niigata, Japan). After the centrifugation of 2000 x*g* for 10 minutes in a room temperature and supernatant was served for FHD. A randomized semi-clinical trial was conducted to assess the nailfold capillary length and its age-related value before and after (6 and 12 months) administration of FHD, which contained GABA (g-amino butyric acid) that was produced by the fermentation procedure mentioned above. After all, FHD both via oral and derma could improve the performance status of volunteer significantly ($p < 0.01$). That is, FHD could increase the regeneration of the capillary of nail stem; and actual increase of the number was observed in the capillary reconstitution in a group after 12 months rather than 6 months.

4. Nailfold Capillaroscopy (NFC) and Its Application for Peripheral Artery Diagnosis

Because there have been few papers published concerning the NFC and dietary habits, we expanded the dietary habit survey into microcirculation category measured by another methods that consists of a network of small blood vessels (small arteries, arterioles, capillaries, venules, and small veins) that establish a frontier with the interstitium and with lymphatic vessels, which maintain the homeostasis of tissues as well as of the entire cardiovascular system [33–35]. Small arteries and arterioles ensure the delivery of nutrients and oxygen to tissues with a given perfusion pressure and according to local demand. Waste products are extracted by venules, small veins, and lymphatics, the last of which also prevents the accumulation of interstitial fluid and the development of edema [36]. Considering from the important interface as a tissue interstitium, microcirculation also contributes to local tissue immunity by allowing the adhesion and infiltration of immune cells [37]. Finally, given its small caliber, microcirculation is a favorable site for the accumulation of hemostatic plugs. Under physiological conditions, the microvascular endothelium expresses a low level of adhesion molecules that limits the adhesion of leucocytes and platelets, therefore preventing inflammation and the occurrence of thrombotic phenomena. From this viewpoint, we summarized the paralleled relationship of abnormal NFC data and PAD (peripheral artery diseases)-relating conditions as shown in Table 5.

Table 5. Paralleled relationship of NFC (nailfold capillaroscopy) data and PAD (peripheral artery diseases)-relating condition.

Authors and Published Year	Title and Description
<Example 1 > Lundwall, K., et al., 2015	Paricalcitol, Microvascular and Endothelial Function in Non-Diabetic Chronic Kidney Disease: A Randomized Trial

< *Am. J. Nephrol.*, **42**, 265-273, 2015 > [38]	Endothelial function declined significantly over 3 months in patients with moderate CKD, and this decline could be ameliorated by VDRA (vitamin D receptor activator) treatment, possibly through increased capillary blood flow.
<Example 2 > Maranhao, P.A., et al., 2016 < *Microvasc. Res.*, **106**, 31-35, 2016 > [39]	Dynamic Nailfold Videocapillaroscopy may be Used for Early Microvascular Dysfunction in Obesity The authors could speculate that the derangement on microvascular hemodynamics occurs before the diagnosis of hypertension, diabetes and other metabolic syndromes. Therefore, NFC is the most appropriate technique to precociously assess microvascular dysfunction in obesity.
< Example 3 > Tian, J., et al., 2020 < *Front. Physiol.*, **11**, article 880; Sec. Vascular Physiology, 2020 > [40]	The Relationship Between Nailfold Microcirculation and Retinal Microcirculation in Healthy Subjects In healthy subjects, there was direct relationship between nailfold capillary and retinal microcirculation. Therefore, abnormalities seen in the NFC are associated with reduced retinal nerve fiber layer (RNFL) thickness and retinal vessel density (VD).
< Example 4 > Wijnand, J.G.J., et al., 2022 < *Eur. J. Endovascl Surg.*, **63**, 900-901, 2022 > [41]	Naiflold Capillaroscopy in Patients with Peripheral Artery Disease of the Lower Limb (CAPAD Study) NFC abnormalities can be used as markers for inflammation and endothelial dysfunction in PAD.
＜Example 5＞ Okabe, T., et al., 2023 < *Graefe's Archive Clin. & Exp. Ophthalmol.*, doi:10.1007/s00417- 023-06220-z., **2023** > [42]	Relationship between Nailfold Capillaroscopy Parameters and the Severity of Diabetic Retinopathy Alterations in NFC morphology, such as capillary shortening, may be closely correlated with the presence of DR (diabetic retinopathy) and PDR (proliferative DR).

< Example 1: The effect of vitamin D receptor activator treatment on capillary blood velocity (CBV) in CKD (chronic kidney disease) patients [38] >

This paper was included to the present review in spite of the non-healthy moderate CKD patients' case because of nutrients effectiveness on this disease. Before this paper, Dreyer, G., et al. [43], using ergocalciferol (=vitamin D2), in a double-blind randomized trial, showed that vitamin D supplementation improves microvascular endothelial function in the skin assessed by laser Doppler flowmetry after iontophoresis of acetylcholine in patients with CKD stages 3-4. Chitalia, N., et al. [44] using cholecalciferol and Zoccali, C., et al. [45] using paricalcitol (vitamin D receptor activator = VDRA) showed similar results on macrovascular endothelial function assessed by determining flow mediated vasodilatation (FMD) in the brachial artery. Here, we summarize Lundwall, K., et al.'s study [38] of double-blind placebo-controlled randomized trial, and they aimed to investigate whether low- or high-dose treatment with a VDRA can ameliorate sympathetic activation and macro- and microvascular functions assessed by several state-of-the art methods in non-diabetic patients with moderate CKD. Thirty-six patients with a mean age of 65 years and mean estimated glomerular filtration rate of 40 ml/min/1.73 m^2 were included. They found a significant decline in endothelial function after 3 months, except in the group receiving 2 μg of paricalcitol. The higher dose (2 μg) seemed to attenuate the decline in microvascular endothelial function compared with lower dose (1 mg), assessed by iontophoresis of acetylcholine ($p = 0.06$ for all groups, $p = 0.65$ for the 2 μg group) and for FMD ($p = 0.006$ for all groups, $p = 0.54$ for the 2 μg group). They also found a borderline significance ($p=0.05$) for improved CBV (capillary blood velocity) that was measured by NFC of the great toe in the treated group, 3 months after receiving 2 μg of paricalcitol. The higher dose (2 μg) seemed to attenuate the decline in microvascular endothelial function, assessed by iontophoresis of

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acetylcholine (p = 0.06 for all groups, p = 0.65 for the 2 μg group) and for FMD (p = 0.006 for all groups, p = 0.54 for the 2 μg group).

< Example 2: Dynamic nailfold videocapillaroscopy must be used for early microvascular dysfunction in obesity [39] >

It has been hypothesized that obesity is the primary cause of microvascular dysfunction, which could be a pathway to increase blood pressure and decrease insulin sensitivity. Due to the high prevalence of this metabolic disorder in the world today, Maranhao, et al. investigated which is the most appropriate videocapillaroscopic method, between nailfold and dorsal finger, to assess microvascular function in obese patients since both techniques could be used for early detection as well as for follow-up. After all, their results strongly suggest that microvascular dysfunction consequent to obesity could be better detected by dynamic nailfold videocapillaroscopy than by dorsal finger videocapillaroscopy. They could speculate the derangement on microvascular hemodynamics occurs before the diagnosis of hypertension, diabetes and other metabolic syndromes. Therefore, they advocated that NFC is the most appropriate technique to precociously assess microvascular dysfunction in obesity.

< Example 3: The Relationship Between Nailfold Microcirculation and Retinal Microcirculation in Healthy Subjects [40] >

Tian, J., et al. evaluated whether the nailfold microcirculation is associated with retinal microcirculation in healthy subjects. That is, 50 subjects without systematic and ocular diseases were enrolled. Thickness of peripapillary retinal nerve fiber layer (RNFL), vessel density (VD) of radial peripapillary capillaries (RPCs), and superficial capillary VD in macular zone were measured with optical coherence tomography angiography (OCTA) in left eyes. Nailfold microcirculation, including capillary density, avascular zones, dilated capillaries, and hemorrhages was examined on the fourth digit of each subject's non-dominant (left) hand with NFC. They found out that nailfold capillary lower density and abnormalities are associated with reduced RNFL thickness and retinal VD. The results provide a theoretical foundation for relevant studies on ocular diseases with microvascular abnormalities and could contribute to pathogenesis understanding in the future. NFC and OCTA have the potential to identify risk factors and improve accuracy of the early diagnosis and treatment of ocular diseases, even systemic diseases with any microvascular component in clinical practice.

< Example 4: NFC and peripheral artery diseases (PAD) [41] >

NFC patterns and their related predictive value in patients with PAD have not been reported up to 2022. NFC patterns in patients with PAD are likely to be aberrant, therefore, it was hypothesized that NFC is feasible in patients with PAD attending outpatient clinics and NFC patterns are abnormal. Wijnand, J.G.J., et al. recently collected the data prospectively on three randomly selected days from patients visiting the outpatient clinic of a single vascular surgery unit between April and June 2018. All patients with a history of PAD (intermittent claudication [IC]; n=17) or chronic limb threatening ischemia [CLTI]; n=9) who consented to the procedure were eligible. Controls without a history of PAD or CLTI (n=10) were visitors accompanying the patients.

Their results showed that there were no significant abnormalities in quantitative measures, namely mean capillary diameter was within the normal reference value range [46], and mean capillary count per millimeter ± standard deviation was similar among healthy controls, IC, and CLTI groups. However, among the qualitative measures, both hemorrhages and non-specific qualitative abnormalities (ranging from disturbed capillary architecture, lower density, abnormal morphology, dilatation, areas of decreased vascularity, and atypical branching) were most prevalent in the IC group. Two observations, both prominent venous plexus (PVP) and mega-capillaries (MCs), occurred exclusively in CLTI patients. Biomarkers of endothelial dysfunction are present in CLTI [47]. In systemic sclerosis the extent of abnormalities on NFC has been linked to circulating biomarkers of

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inflammation and endothelial dysfunction [48], which have also been shown to be altered in CLTI. Those findings suggest that NFC abnormalities may also be used as markers for inflammation and endothelial dysfunction in PAD, although this needs to be confirmed in larger studies as they described.

< Example 5: Relationship between NFC parameters and the severity of diabetic retinopathy [42] >

Recently Okabe, et al. investigated whether non-invasive measurements of the NFC are associated with the presence and severity of diabetic retinopathy (DR) in patients with type 2 diabetes. Eighty-three eyes of 83 patients with type 2 diabetes were enrolled, and 63 age-matched non-diabetic subjects served as controls. Diabetic patients were classified by the severity of their DR: non-DR (NDR), non-proliferative DR (NPDR), and proliferative DR (PDR). They showed that 4 NFC parameters in the diabetic patients were significantly lower than in the controls (all $P < 0.001$); i.e., there was a statistically significant decrease in the NFC parameters along with the increasing severity of DR (number: $P = 0.02$; all others: $P < 0.001$). Logistic regression analysis revealed that combining the systemic characteristics of age, sex, systolic blood pressure, estimated glomerular filtration rate, Hb A1c level, and history of hypertension and dyslipidemia could indicate the presence of DR and PDR (the area under the receiver operating characteristic curve [AUC] = 0.81, $P = 0.006$; AUC = 0.87, $P = 0.001$, respectively). Furthermore, the discriminative power of DR was significantly improved ($P = 0.03$) by adding NFC length to the systemic findings (AUC = 0.89, $P < 0.001$). Finally, they concluded that alterations in NFC morphology, such as capillary shortening, may be closely correlated with the presence of DR (diabetic retinopathy) and PDR (proliferative DR).

5. The Role of Dietary or Nutritional Supplementation in Microcirculation

Finally, we focused on the role of dietary or nutritional supplementation in microcirculation summarized from recently published papers majorly in the USA and EU where the government-approved dietary supplement system preceded than other countries [49].

< Health claims in USA and Europe > [33,34]

Food supplements are manufactured from food, isolated nutrients, or food-derived compounds, which occur as powders, pills, potions, and other types of medication that are not commonly associated with food [50]. Due to the increasing interest shown in personal health, aging demographics, and successful personalized care products, the demand for food supplements has grown and is expected to continue [51]. Cardiovascular disease (CVD) is a significant public health concern worldwide and a leading cause of morbidity and mortality in developed countries [52,53]. In 2015, nearly one third of all deaths worldwide were caused by CVD according to the World Health Organization [54]. Therefore, the effects of cardiovascular risk and CVD on most food supplements have long since been investigated [51,55–57].

< American and European Legal Framework of Food Supplements >

There are different ways of classifying claims for food supplements in the USA and the EU. In the USA, there are three major categories, namely “nutrition content claims”, “structure/function claims”, and “health claims” [58]. In the EU, the three major categories are also defined as “nutrition claims”, “health claims”, and “reduction of disease risk claims” [59]. There is neither a consensus about nor overlaps between the two different classifications of USA and EU. Indeed, from the scope of Raposo, A., et al.'s review paper [33,34], it seemed adequate to consider only two types of claims, “nutritional claims” (which correspond to the EU “nutrition claims”, plus the “nutrition content claims” and “structure/function claims” in the USA) and “health claims” (which encompass the USA “health claims”, and “health claims” plus the “reduction of disease risk claims” in the EU).

Authorized health claims, approved by the FDA, USA, must comply with the so-called Significant Scientific Agreement (SSA health claims) or the Food and Drug Administration

Modernization Act (FDAMA health claims). However, only SSA health claims are allowed on food supplement labels [60]. When a food supplement does not fully satisfy the SSA but is still recognized for some scientific evidence that can support its intended claim, the FDA may recognize that claim as a “qualified health claim”. Thus, it is worth knowing which food supplements may have beneficial effects on microcirculation by considering that the health claims approved by the USA, the EU, or other governments positively affect consumer choices. Although it was impossible to find any health claims directly identified with the word microcirculation in the list of claims approved by the FDA [60], some of these claims may, in fact, have direct and indirect implications for microcirculation (Table 6). This "Authorized Health Claims" contains "Dietary saturated fat and cholesterol and risk of coronary heart disease", “Fruit, vegetables and grain products that contain (dietary) fiber, particularly soluble fiber, and risk of coronary heart disease”, "Soy protein and risk of coronary heart disease", and “Plant sterol/stanol esters and risk of coronary heart disease”. "Qualified Health Claims" contains "Whole grain foods with moderated fat content and risk of heart disease", “Substitution of saturated fat in diet for unsaturated fatty acids and reduced risk of heart disease”, "B vitamins and vascular disease", “Nuts and heart disease”, "Omega 3 fatty acids and coronary heart disease", “Monounsaturated fatty acids from olive oil and coronary heart disease”, and so on (See Table 6).

Table 6. List of authorized claims in the USA with direct or indirect impact on microcirculation.

Authorized Health Claims	**Qualified Health Claims**
Dietary saturated fat and cholesterol and risk of coronary heart disease	Whole grain foods with moderate fat content and risk of heart disease
Fruit, vegetables and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease	Saturated fat, cholesterol, and trans fat, and reduced risk of heart disease
Soluble fiber from certain foods and risk of coronary heart disease	Substitution of saturated fat in diet for unsaturated fatty acids and reduced risk of heart disease
Soy protein and risk of coronary heart disease	B vitamins and vascular disease
Plant sterol/stanol esters and risk of coronary heart disease	Nuts and heart disease
	Walnuts and heart disease
	Omega 3 fatty acids and coronary heart disease
	Monounsaturated fatty acids from olive oil and coronary heart disease
	Unsaturated fatty acids from canola oil and reduced risk of coronary heart disease
	Corn oil and corn oil containing products and a reduced risk of heart disease

< Raposo, A., et al.: The role of food supplementation in microcirculation. ---A comprehensive review. *Biology*, 10, 616-, 2021. (27 pages) [33, 34] >
* Fiber = dietary fiber

Regarding the EU [61,62], the list of non-authorized claims with the word microcirculation are shown in Table 7, which can be generically considered similar to those recognized by the FDA, USA. There are five claims with specific references to the word microcirculation that were not authorized given the EFSA’s previous assessment ([63–67]). This list contains “Dry isoflavones soy extract”, “Niacin”, "Bioflavonoids" and "Vitamin E acetate", and oligomeric procyanidins. For example, it is described that "Bioflavonoids" has a positive effect on microcirculatory tropism by favoring the processes that protect small venous vessels. It protects the body from the harmful action of free radicals and skin from ultraviolet rays [65]; and that "Vitamin E acetate" supports microcirculation and scalp oxygenation [66].

Table 7. List of nonauthorized claims in the EU with the word microcirculation.

Nutrient, Substance, Food, or Food Category	Claim	[Ref]=year
Dry isoflavones soy extract	Acts on hair bulb to support hair growth. Prevents hair from premature aging via antioxidant properties and microcirculation.	[63]=2011
Niacin (B Vitamin)	Activates scalp microcirculation.	[64]=2009
Bioflavonoids	It has a positive effect on microcirculatory tropism by favoring the processes that protect small venous vessels. It protects the body from the harmful action of free radicals and skin from ultraviolet rays.	[65]=2011
Vitamin E acetate (D,L alpha tocopherol acetate)	It supports microcirculation and scalp oxygenation.	[66]=2010
OPC Plus, containing 40 mg oligomeric procyanidins (OPC) and 40 mg berry blend per capsule	OPC Plus has been shown to increase microcirculation and may, therefore, reduce the risk of chronic venous insufficiency.	[67]=2020

< Dietary and lifestyle recommendation for peripheral artery disease (PAD) preven- tion [68] =2020 >

Peripheral artery disease (PAD) is defined as partial or complete stenosis of ≥≥ 1 peripheral arteries ([69,70], 2015 and 2008). PAD affects 3%-10% of the Western population and if remains untreated can have devastating consequences to patients and their families. Researchers belonging to Western countries (Greece, USA, UK, the Netherlands) published review paper entitled "Nutrition, dietary habits, and weight management to prevent and treat patients with PAD" in 2020 [68]. Their paper analyzed how healthy dietary habits can decrease PAD rates when applied in the general population, limited to artery disease and excluding renal, coronary cerebral, mesenteric, and aneurysms [70]. PAD prevalence ranges between 3%-10%, but it can be as high as 15%-20% among elderly ([71]). More than 65% of adults with PAD are overweight or obese, while 78% are characterized by deficiencies in vitamins and minerals [72]. Both suboptimal nutritional status and high fat mass have been associated with worsening of the ambulatory status and vascular health in patients with PAD and claudication [73]. Nutritional advice and weight management are of paramount significance in PAD management [74].

Sagris, M., et al. [68] summarized the dietary and lifestyle recommendations for PAD prevention. They pointed out that the habitual recommended consumptions of various nutrients and fruits, vegetables and anti-oxidants with other recommendation of lifestyle managements (regular physical activity, avoiding smoking). This recommendation includes increased consumption of omega-3 fatty acids, various B vitamins (folic acid, B6, B12), vitamin D, vitamin A, vitamin C, vitamin E; and minerals (zinc intake and sodium upper-limit). While further research attempts are anticipated, emphasis on proper nutrition, dietary interventions and weight management should be part of the PAD prevention and treatment as they described.

<Advancing beyond the "Heart-Healthy Diet" for PAD [71] =2015 >

PAD is a burdensome cardiovascular condition that results from chronic inflammatory insults to the arterial vasculature. Key risk factors include age, gender, type II diabetes mellitus, hypertension, hypercholesterolemia, hyperhomocysteinemia, smoking, lack of physical exercise and poor diet, the latter three being modifiable in the development and progression of PAD. A growing body of evidence indicates that imbalanced nutrient intake may contribute to the development and progression of PAD. In 2015 Nosova, E.V., et al. summarized nine categories of nutrients, as well as four diets endorsed by the American Heart Association (AHA) and American College of Cardiology (ACC) that may be prescribed to patients with or at risk for PAD [71]. They firstly explained the items of this National "Guidelines for Cardiovascular Disease". The 2013 AHA/ACC composite Task Force

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guidelines [75] address nutrition-focused risk reduction strategies for cardiovascular disease in a broad context, with the aim of improving public health. The guidelines endorse a “Heart Healthy Lifestyle" and they provide a general framework for incorporating healthy nutrition into lifestyle management to improve blood pressure and lipid control. They emphasize broad nutrient categories that are associated with better cardiovascular outcomes (eg. fruits and vegetables, whole grains, legumes, etc.), although an important limitation is that particular nutrients that may benefit patients with advanced cardiovascular disease are not explicitly identified. The most specific suggestions are embedded in recommendations for lowering low-density lipoprotein cholesterol (LDL-C): the task force advises obtaining a maximum of 5-6% of total calories from saturated fat, and minimizing intake of foods rich in trans-fats (found in milk, animal fats and some vegetable oils).

The nutrients reviewed by their paper included omega-3 polyunsaturated fatty acids (n-3 PUFAs), B vitamins (folic acid, B6, B12), and anti-oxidants. The diet plans described include the DASH (Dietary Approaches to Stop Hypertension) diet, Mediterranean diet, low-fat diet, low carbohydrate diet, Dr. Dean Ornish’s Spectrum® Diet and Dr. Andrew Weil’s Anti-Inflammatory Diet, though these latter two Diets are not recommended by national guideline [76]. Considering from "Strength of Evidence" by their paper, n-3 PUFAs (poly-unsaturated fatty acids), fatty fish, and EPA + DHA must be beneficial for primary and secondary prevention of CVD. "Reduce saturated fat intake to 5-6% of total daily caloric intake" and "daily sodium intake restriction to 2.3 grams (~ 6 grams/day salt)" also must be beneficial for prevention of CVD. "Dietary fiber intake of 14 gram/1000 kcal, or 25 g for adult women and 38 g for adult men” are also recommended for CVD prevention. The obtained findings were summarized in their paper’s Tables; which was entirely beneficial, but partly non-effective in some items.

6. The Effects of Dietary Flavonoids on Microvascular Health

Before closing, it is worthy to mention the effect of dietary flavonoids on microvascular health; because over the past two-decades, various experimental and epidemiological studies have shown that the consumption of flavonoid-rich foods is associated with a reduced risk of CVDs [77,78]. Flavonoids are a large family of over 5,000 hydroxylated polyphenolic compounds that carry out important functions in plants, including attracting pollinating insects; combating environmental stresses, such as microbial infection; and regulating cell growth [79]. Their bioavailability and biological activities in humans appear to be strongly influenced by their chemical nature.

Vascular function has been shown to be linked with cognition and brain function, with increased cardiovascular health being associated with greater cognitive performance [80–82]. Furthermore, many of the risk factors associated with cardiovascular health are also risk factors for cerebrovascular health, such as hypertension, hypercholesterolemia, and diabetes, with CVD itself having been identified as a risk factor for vascular dementia, caused by a reduction in blood flow to the brain [83,84]. As Rees, A., et al. reported, various flavonoids have significant effects on increasing endothelial function and peripheral blood flow, and thereafter on decreasing the risk of CVD [85–90]. Rees, A., et al. summarized the effect of flavonoids on endothelial function from the viewpoint of "flow-mediated dilation" measurement. Acute or chronic ingestions of dark chocolate flavanols, chocolate polyphenols, cocoa flavanols, apple polyphenols, black tea catechins, were mostly effective to increase in FMD (flow-mediated dilation) of peripheral arteries [91–104].

< Biological effects of epicatechin and taxifolin [105] = 2021 >

Especially, Bernatova, I. and Liskova, S. emphasized 2 typical flavonoids: epicatechin and taxifolin which benefit peripheral blood flow and endothelial function. Both epicatechin and taxifolin are naturally occurring in various fruits, vegetables, and edible tree extracts. Epicatechin is present mainly in green tea, black tea, cacao, and cacao products (cocoa and chocolate). Cacao beans are supposedly the most abundant sources of EC [106,107]. Taxifolin can be found in red onions [108], apples [109], tomatoes, sorghum grain, white grapes, strawberries, mulberries [110], acai berries, peanuts, adzuki bean, pine seeds [111], thyme, and citrus fruits [112]. Taxifolin is also present in a high concentration in conifers such as French maritime bark, Siberian larch, Korean red pine, cedar deodar, Indian pine and Chinese yew, from which it can be industrially produced. Both epicatechin and taxifolin are also broadly available in various commercially available food supplements.

We briefly summarize the examples of the biological effects of (−)-epicatechin as well as (+)-taxifolin and/or (−)-taxifolin that were found in the experimental models and that may be relevant for the treatment of hypertension and viral infection through improvements of peripheral vascular function and anti-inflammatory activity as shown in Bernatova and Liskova's paper [105], and references of peripheral vascular function, cardioprotective- and anti-inflammatory effects were summarized in Table 8 [105,113–137]. References of cellular and molecular mechanisms underlying the biological effects of epicatechin and taxifolin are listed in Table 9 [105,113,117,121,126,128,138–150], and these two flavonoids are effective in ROS (reactive oxygen species) reduction, antioxidant enzymes activation, endothelial NO elevation, and NF-kB reduction.

Table 8. Summarized protective effects of (-)-epicatechin and (+)-taxifolin and/or (-)-taxifolin on cardiovascular diseases in animal models. [105].

Biological Effects	(-)-Epicatechin	(+)-Taxifolin and/or (-)-Taxifolin
Vascular	113, 114, 115, 116, 117, 118, 119, 120	121
Cardioprotective	122, 123, 124	125, 126
Antiinflammatory	127, 128, 129	130, 131
Antiaggregatory, antisthrombotic, or anticoagulant	113, 132, 133	134, 135, 136, 137
	< Reference number >	< Reference number >

Table 9. Summarized anti-oxidative and anti-inflammatory effects of (-)-epicatechin and (+)-taxifolin and/or (-)-taxifolin on endothelial function. [105].

Cellular and Molecular Mechanisms	(-)-Epicatechin	(+)-Taxifolin and/or (-)-Taxifolin
ROS scavenging	138, 139	140
Activation of antioxidant enzymes (SOD, CAT, GPx)	141, 142	126, 143
Elevation of endothelial NO	113, 117, 141, 144, 145	121
NF-kB reduction	128, 146, 147	148
Inflammasome reduction	no	149, 150
	< Reference number >	< Reference number >

7. Conclusion and Prospects

In the past decade, the morphological changes in the nailfold capillary have been reported in the unhealthy lifestyle habits such as smoking, inappropriate diets, sleep shortage, and even psychological stress which presents slow blood flow. Therefore, study in the relationships between the morphology of nailfold capillaries and lifestyle habits has high potential to understand the unhealthy state, or even predict the pre-disease condition. So, simple, inexpensive, and non-invasive methods such as NFC are constantly needed for routine health checkups. Thus, we undertook a systematic search in PubMed database, and summarized the studies reporting the assessment of morphological NFC in order to undertake a comprehensive review on the usefulness of NFC not only in clinical diagnosis, but also in unhealthy dietary lifestyle improvements.

Because there was a paralleled relationship of abnormal NFC data and peripheral artery diseases (PAD)-relating conditions, we summarized the health claims information from recently published papers in the USA and EU where the government-approved dietary supplement system preceded than other countries, in order to overview the role of dietary or nutritional supplementation in healthy microvascular blood flow and endothelial function.

Here in this review paper, we finally summarized the dietary and lifestyle health promotion strategy judging from NFC- and the other relating-measurement from the viewpoint of microvascular blood flow and endothelial function. However, the dietary interventional studies with

 doi:10.20944/preprints202404.0078.v1

flavonoids or other functional nutrients are still necessary to understand the whole mechanisms of flavonoids or nutrients actions in our body; hopefully using pre-symptomatic subjects with NFC monitoring.

Especially, recent researches suggest that not only essential nutrients, but also flavonoids and other functional food components are able to exhibit cardio- and neuro-protective effects, as demonstrated with improvements in both of peripheral blood flow and endothelial function, which benefit body health. However, the dietary interventional studies with flavonoids, nutrients, and other functional food components are still necessary to understand those mechanisms in our body; hopefully using pre-symptomatic subjects with NFC monitoring.

Author Contributions: Conceptualization, M.K. and D.T.; methodology, D.T., J.N., C.F.; software, J.N., C.F.; investigation, M.K., D.T., J.N., C.F.; resources, M.K., D.T.; writing—original draft preparation, M.K.; writing—review and editing, D.T., Y.O., H.S.; supervision, M.K., D.T., H.S.; project administration, D.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors thank the Capillary Laboratory and Social Implementation Consortium for their contribution to the manuscript charge payment.

Conflicts of Interest: The authors declare no conflicts of interest.

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