

# Nailfold capillary abnormalities are associated with type 2 diabetes progression and correlated with peripheral neuropathy

Po-Chi Hsu, MD<sup>a,b</sup>, Pei-Yung Liao, MD<sup>c</sup>, Hen-Hong Chang, MD, PhD<sup>d,e</sup>, John Y. Chiang, PhD<sup>f,g</sup>, Yu-Chuen Huang, PhD<sup>h,i,\*</sup>, Lun-Chien Lo, MD, PhD<sup>b,j,\*</sup>

## Abstract

Diabetes mellitus (DM) is associated with a state of chronic hyperglycemia with a highly increased risk of vascular complications. The current study aimed to investigate microcirculation abnormalities in patients with type 2 DM and those with pre-DM using nailfold videocapillaroscopy (NVC) and evaluate the possible correlation with microvascular complications.

A total of 115 patients with type 2 DM, 41 patients with pre-DM, and 37 healthy subjects without diabetes were enrolled. All subjects underwent NVC to evaluate capillary density, length, morphology, distribution, presence of enlarged loops or hemorrhages, and blood flow. NVC score was used to quantitate the aforementioned characteristics.

Patients with type 2 DM showed significantly increased alterations including reduced capillary length (29.6%), irregular distribution (35.7%), and abnormal morphology (59.1%), while the corresponding NVC scores were comparable to those of control subjects. In addition, subjects with pre-DM had a significantly higher NVC score and greater alterations in distribution (26.8%) and morphology (48.8%) than control subjects. NVC score was positively correlated with diabetic peripheral neuropathy (DPN) and the number of microvascular complications.

NVC identified a high frequency of microcirculation abnormalities in subjects with pre-DM or type 2 DM compared to those in the control group. NVC score was also capable of detecting microvascular complications in patients with type 2 DM and was correlated with DPN and the number of microvascular complications.

**Abbreviations:** DM = diabetes mellitus, DPN = diabetic peripheral neuropathy, HbA1c = hemoglobin A1c, NVC = nailfold videocapillaroscopy.

**Keywords:** diabetic peripheral neuropathy, microcirculation, nailfold videocapillaroscopy, pre-diabetes, type 2 diabetes mellitus

## 1. Introduction

As population growth, aging, and the prevalence of obesity and inactivity have continued to increase rapidly, diabetes mellitus (DM) has become a major burden of adult public health.<sup>[1–3]</sup> DM increases the risk of adult disability and premature death and creates a tremendous socioeconomic burden due to micro- and macrovascular complications.<sup>[3]</sup> The long-term microvascular

complications of diabetes include retinopathy, nephropathy, and neuropathy.<sup>[4,5]</sup> Several risk factors, such as duration of diabetes and degree of glycemic control, are involved in the clinical course of micro- and macroangiopathy. Thus, clinicians should focus closely on vascular complications in patients with diabetes.

Nailfold videocapillaroscopy (NVC) is a noninvasive diagnostic method that is used to evaluate the microcirculation and identify microvascular patterns in many rheumatic diseases,

Editor: Yung-Hsiang Chen.

*Funding/support:* This study was supported in part by China Medical University Hospital, Taiwan (DMR-106-130), CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan, and also supported by Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), and Department of Chinese Medicine and Pharmacy (MOHW105-CMAP-M-114-133402) from Ministry of Health and Welfare, Taiwan.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Graduate Institute of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, <sup>b</sup> Department of Chinese Medicine, Changhua Christian Hospital, <sup>c</sup> Department of Endocrinology, Changhua Christian Hospital, <sup>d</sup> School of Post-Baccalaureate Chinese Medicine, College of Chinese Medicine, and Research Center for Chinese Medicine and Acupuncture, China Medical University, <sup>e</sup> Department of Chinese Medicine, China Medical University Hospital, Taichung, <sup>f</sup> Department of Computer Science and Engineering, National Sun Yat-sen University, <sup>g</sup> Department of Healthcare Administration and Medical Informatics, Kaohsiung Medical University, Kaohsiung, <sup>h</sup> School of Chinese Medicine, College of Chinese Medicine, China Medical University, <sup>i</sup> Department of Medical Research, China Medical University Hospital, Taichung, <sup>j</sup> Graduate Institute of Statistical and Informational Science, National Changhua University of Education, Changhua, Taiwan.

\* Correspondence: Lun-Chien Lo, Department of Chinese Medicine, Changhua Christian Hospital, No.135 Nanxiao St., Changhua 500, Taiwan (e-mail: 126478@cch.org.tw); Yu-Chuen Huang, School of Chinese Medicine, China Medical University, No. 91, Hsueh-Shih Rd., Taichung 404, Taiwan (e-mail: yuchuen@mail.cmu.edu.tw).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2016) 95:52(e5714)

Received: 12 June 2016 / Received in final form: 10 November 2016 / Accepted: 25 November 2016

<http://dx.doi.org/10.1097/MD.0000000000005714>

particularly systemic sclerosis and related disorders.<sup>[6–8]</sup> NVC is used to evaluate the morphology, distribution, density, and blood flow of nailfold dermal papillary capillaries. However, diabetic microangiopathy is a frequent and often early complication that mainly involves the retinal and renal microcirculations. Few previous studies demonstrated the presence of abnormalities in nailfold microcirculation and capillary morphology in patients with diabetes.<sup>[9–11]</sup> However, NVC has been shown to qualitatively and quantitatively identify microcirculation abnormalities in diabetic patients, and changes detected using NVC showed a positive correlation with diabetic retinopathy.<sup>[12,13]</sup> However, their microvascular characteristics and correlation with glycemic control and classical microvascular complications have not been systematically investigated. This study had 3 aims: 1st, to investigate the nailfold capillary abnormalities in patients with type 2 DM or pre-DM versus control subjects; 2nd, to compare the NVC characteristics in patients with type 2 DM according to disease duration and glycated hemoglobin (hemoglobin A1c [HbA1c]) level; and 3rd, to determine whether NVC score was correlated with diabetic microvascular complications.

## 2. Patients and method

### 2.1. Ethical approval

This was an observational cross-sectional and clinical pilot cohort study (protocol identification number NCT02564913 at <http://www.clinicaltrials.gov>). All candidates underwent a standardized interview process. The participants were introduced to the study purpose, procedures, potential risks, and benefits. Subsequently, they signed the informed consent form. The trial protocol was approved by the Institutional Review Board of Changhua Christian Hospital, Changhua, Taiwan (institutional review board reference number: 111106).

### 2.2. Patients

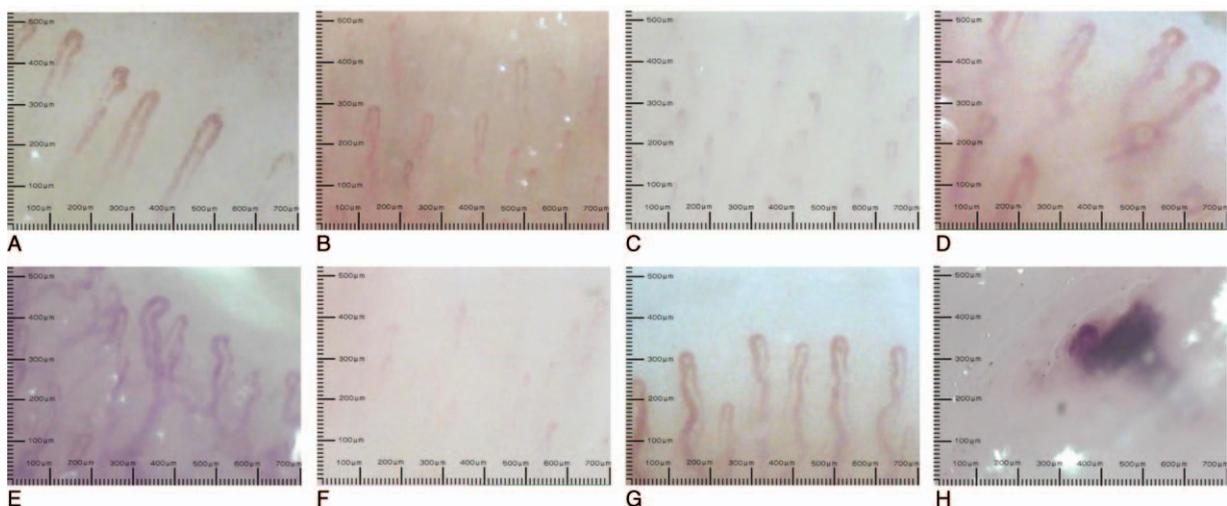
The participants in this prospective cross-sectional study were recruited from January 2012 to December 2013 from the outpatient clinic of endocrinology and Chinese medicine at

Changhua Christian Hospital, Changhua, Taiwan. Participants in the type 2 DM group were diagnosed with DM based on criteria recommended by the American Diabetes Association and required to have a fasting plasma glucose of  $\geq 7$  mmol/L or an HbA1c of  $\geq 6.5\%$ , as measured on 2 separate occasions. People with pre-DM have a fasting glucose level of 5.6 to 7 mmol/L (impaired fasting glucose) or a 2-hour plasma glucose level of 7.8 to 11.1 mmol/L after an oral glucose tolerance test (impaired glucose tolerance) on 2 separate occasions.<sup>[14,15]</sup> Participants in the control group had a normal fasting glucose level ( $< 5.6$  mmol/L). Exclusion criteria were cancer, active liver disease, current pregnancy, active infection, and cerebrovascular disease.

All participants underwent a medical history collection, clinical examination including measurement of blood pressure (mmHg) and body mass index ( $\text{kg}/\text{m}^2$ ); and routine biochemistry testing including HbA1c (%), fasting blood glucose (mmol/L), triglycerides (mmol/L), total cholesterol (mmol/L), high-density lipoprotein cholesterol (mmol/L), and low-density lipoprotein cholesterol (mmol/L).

### 2.3. Nailfold videocapillaroscopy

The NVC was performed on a microscope coupled with a digital video camera (DMX960, x320; Digilens Co., Taiwan). The same operator blinded to the patients' clinical diagnoses performed the NVC examination according to a standardized and validated methodology on the 4th finger of each participant's left hand.<sup>[16]</sup> Each patient was acclimatized for 20 minutes at a room temperature of 24°C prior to the NVC examination.<sup>[6]</sup> We examined 2 fields: capillaries in the distal row of the nailfold and hemorrhages near the distal row. The following morphological measurements were considered: alterations in capillary length (normal length [normal values are 200–500  $\mu\text{m}$ ], increased length, or reduced length), distribution (ordered, comma-like, irregular, or severely deranged), morphology (hairpin, tortuous, ramified, or bushy capillaries), capillary density (10–30/ $\text{mm}^2$ , 8–10/ $\text{mm}^2$ , or  $< 8/\text{mm}^2$ ), diameter (normal, enlarged loop, or giant loop), hemorrhages (absent, in a few areas, or diffuse), and flux abnormalities (normal, slow, or discontinuous).<sup>[8,12]</sup>



**Figure 1.** Representative characteristics of nailfold videocapillaroscopy alterations: (A) normal pattern of capillary vessels; (B) reduced capillary length; (C) irregular capillary distribution; (D) abnormal capillary morphology; (E) abnormal capillary morphology (severe alteration); (F) reduced capillary density; (G) enlarged capillary loop; and (H) hemorrhage.

**Table 1**  
**Naifold videocapillaroscopy (NVC) score was used to quantitate NVC characteristics according to several criteria\*.**

Characteristics	0	1	2	3
Capillary length	Normal (200–500 $\mu\text{m}$ )	Increased (>500 $\mu\text{m}$ )	Reduced (<200 $\mu\text{m}$ )	Variable
Capillary distribution	Ordered	Comma-like	Irregular	Severe derangement
Capillary morphology	Normal	Tortuous	Ramified	Severe alteration
Capillary density	10–30/mm <sup>2</sup>	8–10/mm <sup>2</sup>	<8/mm <sup>2</sup>	–
Capillary dimension (diameter)	Normal (8–14 $\mu\text{m}$ )	Enlarged loop (>20 $\mu\text{m}$ )	Giant loop (>50 $\mu\text{m}$ )	–
Hemorrhages	Absent	In few areas	Diffuse	–
Subvenous plexus	Visible	Partially visible	Not appreciable	–
Flux	Normal	Slow	Discontinuous	Sludge phenomenon
edema/exudates	Absent	In few areas	Diffuse	–
Fundus	Transparent	Reduced transparency in few areas	Reduced transparency in all areas	–

\*The scoring criteria are modified from the report by Barchetta et al.<sup>[12]</sup>

Representative images of the NVC alterations are shown in Fig. 1. NVC score was used to quantitate NVC characteristics.<sup>[12]</sup> The scoring criteria are shown in Table 1.

#### 2.4. Classification of diabetic microvascular complications

Common diabetic microvascular complications include retinopathy, neuropathy, and nephropathy. Diabetic retinopathy, a microvascular complication that can affect the retina as well as the macula, is a leading cause of visual impairment and blindness in patients with diabetes. A retinal examination was used to evaluate each patient for diabetic retinopathy according to the following diabetic retinopathy severity grading scale: no apparent retinopathy, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy.<sup>[17]</sup> Diabetic peripheral neuropathy (DPN), the most common complication of diabetes, is caused by impaired neural microvasculature.<sup>[4]</sup> Clinical examinations for DPN according to the Michigan diabetic neuropathy score include foot appearance, presence or absence of ulceration, and the evaluation of ankle reflexes and sensory responses to vibration, light touch, a pinprick, and the 10-g monofilament.<sup>[18,19]</sup> An early diagnosis of diabetic nephropathy can be made using a simple urine test to detect protein as an assessment of kidney function. Diabetic nephropathy has been categorized into 3 stages based on urinary albumin excretion values as follows: normoalbuminuria (albumin:creatinine ratio <30  $\mu\text{g}/\text{mg}$ ), microalbuminuria (30  $\mu\text{g}/\text{mg}$   $\leq$  albumin:creatinine ratio  $\leq$ 300  $\mu\text{g}/\text{mg}$ ), and macroalbuminuria (albumin:creatinine ratio  $\geq$ 300  $\mu\text{g}/\text{mg}$ ).<sup>[20]</sup>

#### 2.5. Data analysis

The statistical analysis of the data was performed using IBM SPSS Statistics 19 (IBM Co., NY). Tests included analysis of variance for continuous variables as well as Chi-square test or Fisher exact test for categorical variables as appropriate. Values of  $P < 0.05$  were considered statistically significant. Alterations of NVC characteristics were quantified as NVC scores, while differences between the type 2 DM group and control subjects or individuals with pre-DM and control subjects were evaluated using the median values for the Mann–Whitney *U* test. Spearman correlation was used to show the correlation among the NVC score, diabetic retinopathy severity grading scale, diabetic nephropathy stage, diabetic neuropathy examination score, and the number of microvascular complications.

### 3. Results

#### 3.1. Study subject characteristics

A total of 115 patients with a diagnosis of type 2 DM, 41 patients with impaired glucose tolerance, and 37 healthy controls without diabetes were enrolled in the study. The clinical characteristics of the patients with type 2 DM, patients with pre-DM, and healthy controls are shown in Table 2. The clinical characteristics of the patients with type 2 DM were as follows: mean age,  $61.6 \pm 10.1$  years; mean diabetes duration,  $11.1 \pm 8.2$  years; and mean body mass index,  $26.0 \pm 3.8$ . The patients with type 2 DM had significantly higher changes in HbA1c and fasting blood glucose levels but significantly lower changes in total cholesterol and low-density lipoprotein cholesterol levels than did those in the other 2 groups.

Results of the NVC measurements performed in the type 2 DM, pre-DM, and control groups are shown in Table 3. The patients with type 2 DM showed significantly higher frequencies of reduced capillary length (<200  $\mu\text{m}$ ) (29.6%), irregular capillary distribution (35.7%), abnormal capillary morphology (59.1%), and NVC score alteration compared to the control subjects. In addition, the pre-DM group had significantly higher frequencies of irregular capillary distribution (26.8%), abnormal capillary morphology (48.8%), and NVC score alteration than the control group.

The NVC characteristics of patients with type 2 DM according to HbA1c level (HbA1c  $\geq 7\%$  and HbA1c <7%) are shown in Table 4. The frequencies of reduced capillary length, irregular capillary distribution, abnormal capillary morphology, enlarged loop, and abnormal flux were increased in the subjects with HbA1c  $\geq 7\%$ . In addition, there was a significant increase in NVC score in the subjects with HbA1c  $\geq 7\%$ . However, NVC characteristics and scores did not vary significantly between patients with a type 2 DM disease duration  $\geq 10$  years and those with a disease duration <10 years (data not shown).

A comparison of NVC characteristics in type 2 DM patients without versus with microvascular complications is shown in Table 5. The frequencies of reduced capillary length, irregular capillary distribution, abnormal capillary morphology, enlarged loop, hemorrhage, and abnormal flux increased in type 2 DM patients with microvascular complications. Patients with type 2 DM and microvascular complications showed a significantly reduced capillary length (<200  $\mu\text{m}$ ) and increased NVC score.

The correlations among NVC score, diabetic retinopathy severity grading scale, diabetic nephropathy stage, diabetic

**Table 2****Clinical and biochemical characteristics of subjects with type 2 DM, subjects with pre-DM, and control subjects.**

Characteristics	Type 2 DM n = 115	Pre-DM n = 41	Control n = 37	P
Gender				0.04
Male (n, %)	55 (47.8%)	17 (41.5%)	9 (24.3%)	
Female (n, %)	60 (52.2%)	24 (58.5%)	28 (75.7%)	
Family history of DM				0.08
No (n, %)	47 (40.9%)	18 (43.9%)	23 (62.2%)	
Yes (n, %)	68 (59.1%)	23 (56.1%)	14 (37.8%)	
Age, years	61.6 ± 10.1	58.2 ± 8.8	59.6 ± 11.3	0.18
Duration of diabetes, years	11.1 ± 8.2	—	—	
Microvascular complication				
Retinopathy	26 (22.6%)	—	—	
Nephropathy	36 (31.3%)	—	—	
Neuropathy	18 (15.7%)	—	—	
Systolic pressure, mmHg	121.5 ± 12.4	123.8 ± 10.0	124.0 ± 16.5	0.53
Diastolic pressure, mmHg	72.2 ± 3.7	73.7 ± 4.7	72.5 ± 4.6	0.19
BMI, kg/m <sup>2</sup>	26.0 ± 3.8	25.5 ± 3.7	23.1 ± 2.6	<0.01
HbA1c, %	7.2 ± 1.2	5.8 ± 0.4	5.6 ± 0.4	<0.01
fasting glucose, mmol/L	7.5 ± 1.8	5.9 ± 0.7	5.4 ± 0.6	<0.01
Cholesterol, mmol/L	9.5 ± 3.0	10.7 ± 2.4	10.6 ± 1.8	0.04
Triglycerides, mmol/L	7.5 ± 5.6	8.0 ± 3.9	5.2 ± 3.6	0.24
HDL cholesterol, mmol/L	2.5 ± 0.7	2.6 ± 0.5	2.8 ± 0.6	0.09
LDL cholesterol, mmol/L	5.3 ± 1.5	6.2 ± 1.7	6.6 ± 1.3	<0.01

P-values were performed by ANOVA test or Chi-square test. ANOVA = analysis of variance, BMI = body mass index, DM = diabetes mellitus, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

**Table 3****NVC measurements in the total group with type 2 diabetes, prediabetes, and control subjects.**

NVC characteristics	Control n = 37	Type 2 DM n = 115	P <sup>*</sup>	Pre-DM n = 41	P <sup>†</sup>
Reduced capillary length (<200 μm)	3 (8.1%)	34 (29.6%)	0.008	4 (9.8%)	0.799
Irregular capillary distribution	0 (0.0%)	41 (35.7%)	<0.001	11 (26.8%)	0.001
Abnormal capillary morphology	7 (18.9%)	70 (59.1%)	<0.001	20 (48.8%)	0.006
Reduced capillary density (<8/mm <sup>2</sup> )	0 (0.0%)	1 (0.9%)	0.569	0 (0.0%)	NA
Presence of enlarged loops	1 (2.7%)	9 (7.8%)	0.274	0 (0.0%)	0.474
Presence of hemorrhages	0 (0.0%)	1 (0.9%)	1.000	0 (0.0%)	NA
Presence of abnormal flux	7 (18.9%)	32 (29.6%)	0.205	3 (7.3%)	0.126
Presence of edema/exudates	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	NA
NVC score (median [25th, 75th])	1 (0, 1)	2 (1, 4)	<0.001 <sup>‡</sup>	1 (0, 2)	0.049 <sup>‡</sup>

P-values were performed by Chi-square test or Fisher exact test. DM = diabetes mellitus, NVC = nailfold videocapillaroscopy, NA = not available.

\* Type 2 DM group compared with control group.

† Pre-DM group compared with control group.

‡ Mann-Whitney U test.

**Table 4****Comparison of NVC characteristics between the HbA1c <7% and HbA1c ≥7% groups in patients with type 2 diabetes mellitus.**

NVC characteristics	HbA1c <7 n = 61	HbA1c ≥7 n = 54	P
Reduced capillary length (<200 μm)	17 (27.9%)	17 (31.5%)	0.672
Irregular capillary distribution	20 (32.8%)	21 (38.9%)	0.495
Abnormal capillary morphology	32 (52.5%)	36 (66.7%)	0.122
Reduced capillary density (<8/mm <sup>2</sup> )	0 (0.0%)	1 (1.9%)	0.470
Presence of enlarged loops	3 (4.9%)	6 (11.1%)	0.302
Presence of hemorrhages	1 (1.6%)	0 (0.0%)	1.000
Presence of abnormal flux	13 (22.4%)	19 (38.0%)	0.077
Presence of edema/exudates	0 (0.0%)	0 (0.0%)	NA
NVC score (median [25th, 75th])	1 (0, 3)	2 (1, 4)	0.032 <sup>*</sup>

P-values were performed from Chi-square test or Fisher exact test. HbA1c = hemoglobin A1c, NVC = nailfold videocapillaroscopy, NA = not available.

\* Mann-Whitney U test.

**Table 5****Comparison of NVC characteristics between patients with type 2 diabetes mellitus without or with microvascular complications.**

NVC characteristics	DM without microvascular complications	DM with microvascular complications	P
	n=43	n=53	
Reduced capillary length (<200 μm)	9 (20.93%)	23 (43.40%)	0.020
Irregular capillary distribution	12 (27.91%)	25 (47.17%)	0.054
Abnormal capillary morphology	26 (60.47%)	34 (64.15%)	0.711
Reduced capillary density (<8/mm <sup>2</sup> )	0 (0.00%)	0 (0.00%)	NA
Presence of enlarged loops	2 (4.65%)	4 (7.55%)	0.688
Presence of hemorrhages	0 (0.00%)	1 (1.89%)	1.00
Presence of abnormal flux	12 (27.91%)	17 (32.08%)	0.638
Presence of edema/exudates	0 (0.00%)	0 (0.00%)	NA
NVC score (median [25th, 75th])	1 (1, 4)	3 (1, 4)	0.034*

P-values were performed from Chi-square test or Fisher exact test. DM=diabetes mellitus, NVC=nailfold videocapillaroscopy, NA=not available.

\*Mann-Whitney U test.

neuropathy examination score, and the number of microvascular complications are shown in Table 6. NVC score was significantly positively correlated with diabetic neuropathy examination score (Spearman correlation coefficient, 0.211;  $P=0.035$ ) and the number of microvascular complications (Spearman correlation coefficient, 0.211;  $P=0.039$ ).

#### 4. Discussion

A typical diabetic pattern in the nailfold capillary has not yet been described, even if NVC detected increased density; reduced length and irregular distribution of the capillary loops; abnormal morphological features; and the presence of exudates, edema, and flux abnormalities variably associated with DM.<sup>[12,13]</sup> Our study showed that patients with type 2 DM had significantly greater alterations in reduced capillary length (<200 μm), an irregular capillary distribution, an abnormal capillary morphology, and increased NVC score compared with those of the control subjects. These previous studies found that patients with DM presented with a higher frequency of abnormal capillary morphology than control subjects.<sup>[10,11]</sup> Furthermore, we aimed to quantitatively and qualitatively study the nailfold capillary abnormalities of subjects with pre-DM. In particular, we found that NVC was able to detect microvascular abnormalities in prediabetic subjects compared with control subjects. The results revealed that subjects with pre-DM had significant alterations of irregular capillary distribution, abnormal capillary morphology, and NVC score. Other studies that used NVC to study red blood cell velocity at rest and at its peak after 1 minute of arterial occlusion revealed microcirculation dysfunction in patients with obesity and metabolic syndrome, but the same findings were not

associated with impaired fasting glucose.<sup>[21,22]</sup> Thus, NVC could play a role in the characterization of diabetic microangiopathy and pre-DM among the NVC characteristics. We reported the nailfold capillary abnormalities based on a Taiwanese population, and these NVC characteristics were similar with those in patients of other ethnicities with diabetes.<sup>[12,13]</sup> Thus, we suggested that NVC abnormalities comprise a global phenomenon in patients with diabetes in different ethnic populations.

The challenge remains in identifying patients with DM who are at risk of developing microvascular complications.<sup>[23]</sup> Microvascular complications, including nephropathy, retinopathy, and neuropathy, are strongly related to both poor glycemic control and longer DM duration.<sup>[24]</sup> Here, we attempted to compare the NVC characteristics in patients with type 2 DM according to their diabetic duration and HbA1c level. The results revealed that the frequencies of capillary abnormalities were increased and NVC score was significantly increased in the subjects with HbA1c  $\geq 7\%$  compared to the subjects with HbA1c  $< 7\%$ . The results indicated that nailfold capillary abnormalities have been associated with vascular damage in patients with type 2 DM and poor glycemic control. On the other hand, there was no significant difference in NVC characteristics and scores according to disease duration. Therefore, we should consider other clinical and metabolic measurements to decrease bias. Capillary lengths were significantly reduced (<200 μm) and NVC score was increased in patients with type 2 DM and microvascular complications. Our study findings showed that type 2 DM with microvascular complications is indicative of significant microcirculation impairments. However, we did not compare each diabetic microvascular complication to determine severity in this study. Pseudo-3-dimensional vision-based nailfold morphological and hemodynamic analysis could potentially facilitate studies of microvascular complications and act as a significant index for a specific disease through the automatic analysis of a large number of microvascular images.<sup>[25]</sup> Therefore, NVC combined with pseudo-3-dimensional vision-based nailfold morphological and hemodynamic analysis could possibly be used to determine the severity of DM-related microvascular complications.

Our study demonstrated that NVC score was also capable of detecting microvascular abnormalities in patients with type 2 DM and was positively correlated with DPN and the number of microvascular complications. Microvascular abnormalities in the epineurial arteries and veins also revealed arteriosclerosis on the surface of the nerve and impaired blood flow in patients with DPN.<sup>[26,27]</sup> These microvascular changes were closely correlated with the presence of DPN. The other study surveyed nailfold

**Table 6**

**Correlations among nailfold videocapillaroscopy (NVC) score, diabetic retinopathy severity grading scale, diabetic nephropathy stages, diabetic neuropathy examination score, and the number of microvascular complications.**

NVC score	Spearman correlation coefficient	P
Diabetic retinopathy severity grading scale	0.081	0.422
Diabetic nephropathy stages (A/C ratio)	0.106	0.289
Diabetic neuropathy examination score	0.211	0.035*
Number of microvascular complications	0.211	0.039*

A/C ratio represents albuminuria/creatinine ratio.

\*Represents P-value < 0.05, correlation with NVC score.

capillary abnormalities in diabetic patients and revealed similar capillary characteristics and a correlation with diabetic retinopathy.<sup>[12]</sup> However, the previous study showed that more than half of the patients with DM suffered from one or more microvascular complications during >10 years of follow-up.<sup>[28]</sup> We tried to compare NVC characteristics of only 1 microvascular complication in patients with type 2 DM, but the sample size of patients with only 1 complication was too small to analyze. Future studies with a larger number of patients with a single microvascular complication would be valuable for evaluating NVC characteristics.

## 5. Conclusion

The current study revealed that NVC identified high frequencies of microcirculation abnormalities among subjects with pre-DM or type 2 DM. NVC score was positively correlated with DPN and the number of microvascular complications. The future application of NVC in patients with diabetes, pre-DM, and DM-related microvascular complications requires extensive investigation.

## Acknowledgments

The authors thank all participants in the study. The authors also thank China Medical University Hospital, Taiwan (DMR-106-130), CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan, and also supported by Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), and Department of Chinese Medicine and Pharmacy (MOHW105-CMAP-M-114-133402) from Ministry of Health and Welfare, Taiwan for the support.

## References

- [1] Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362:1090–101.
- [2] Engelgau MM, Geiss LS, Saaddine JB, et al. The evolving diabetes burden in the United States. *Ann Intern Med* 2004;140:945–50.
- [3] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047–53.
- [4] Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther* 2008;88:1322–35.
- [5] Kitada M, Zhang Z, Mima A, et al. Molecular mechanisms of diabetic vascular complications. *J Diabetes Invest* 2010;1:77–89.
- [6] Gallucci F, Russo R, Buono R, et al. Indications and results of videocapillaroscopy in clinical practice. *Adv Med Sci* 2008;53:149–57.
- [7] Ruaro B, Smith V, Sulli A, et al. Methods for the morphological and functional evaluation of microvascular damage in systemic sclerosis. *Korean J Intern Med* 2015;30:1–5.
- [8] Chojnowski MM, Felis-Giemza A, Olesinska M. Capillaroscopy – a role in modern rheumatology. *Reumatologia* 2016;54:67–72.
- [9] Meyer MF, Pfohl M, Schatz H. Assessment of diabetic alterations of microcirculation by means of capillaroscopy and laser-Doppler anemometry. *Medizinische Klinik* 2001;96:71–7.
- [10] Gasser P, Berger W. Nailfold videomicroscopy and local cold test in type I diabetes. *Angiology* 1992;43:395–400.
- [11] Pazos-Moura CC, Moura EG, Bouskela E, et al. Nailfold capillaroscopy in diabetes mellitus: morphological abnormalities and relationship with microangiopathy. *Braz J Med Biol Res* 1987;20:777–80.
- [12] Barchetta I, Ricciari V, Vasile M, et al. High prevalence of capillary abnormalities in patients with diabetes and association with retinopathy. *Diabetic Med* 2011;28:1039–44.
- [13] Rajaei A, Dehghan P, Farahani Z. Nailfold Capillaroscopy Findings in Diabetic Patients (A Pilot Cross-Sectional Study). *Open J Pathol* 2015;5:8.
- [14] American Diabetes ADiagnosis and classification of diabetes mellitus. *Diabetes Care* 2008;31(Suppl 1):S55–60.
- [15] Nathan DM. Diabetes: advances in diagnosis and treatment. *JAMA* 2015;314:1052–62.
- [16] Mark C Hou, Hui-Min Wang, Cheng-Lung Tseng, et al. A computerized system of nail-fold capillaroscopy for dry eye disease diagnosis. *Multidim Syst Sign Process* 2012;23:515–24.
- [17] Wu L, Fernandez-Loaiza P, Sauma J, et al. Classification of diabetic retinopathy and diabetic macular edema. *World J Diabetes* 2013;4: 290–4.
- [18] Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010;33:2285–93.
- [19] Won JC, Park TS. Recent advances in diagnostic strategies for diabetic peripheral neuropathy. *Endocrinol Metab* 2016;31:230–8.
- [20] Basi S, Fesler P, Mimran A, et al. Microalbuminuria in type 2 diabetes and hypertension: a marker, treatment target, or innocent bystander? *Diabetes Care* 2008;31(Suppl 2):S194–201.
- [21] Kraemer-Aguilar LG, Laflor CM, Bouskela E. Skin microcirculatory dysfunction is already present in normoglycemic subjects with metabolic syndrome. *Metab: Clin Exp* 2008;57:1740–6.
- [22] Panazzolo DG, Sicuro FL, Clapauch R, et al. Obesity, metabolic syndrome, impaired fasting glucose, and microvascular dysfunction: a principal component analysis approach. *BMC Cardiovasc Disord* 2012; 12:102.
- [23] Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *Am J Med* 2010;123(3 Suppl):S3–11.
- [24] Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clin Diabetes* 2008;26:77–82.
- [25] Lo LC, Lin KC, Hsu YN, et al. Pseudo three-dimensional vision-based nail-fold morphological and hemodynamic analysis. *Comput Biol Med* 2012;42:873–84.
- [26] Tesfaye S, Harris N, Jakubowski JJ, et al. Impaired blood flow and arterio-venous shunting in human diabetic neuropathy: a novel technique of nerve photography and fluorescein angiography. *Diabetologia* 1993;36:1266–74.
- [27] Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. *Diabetes/Metab Res Rev* 2012;28(Suppl 1):8–14.
- [28] Huang CY, Tsai YT, Lai JN, et al. Prescription pattern of Chinese herbal products for diabetes mellitus in Taiwan: a population-based study. *Evid Based Complement Alternat Med* 2013;2013:201329.