Functional and structural abnormalities of the skin microcirculation in hemodialysis patients

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Background
The changes that occur at the level of the skin microvessels reflect changes at other microvessels including the cardiac microvessels. Several disease states seem to alter skin microvascular function and structure such as diabetes, hypertension, and hypercholesterolemia. Many of these disease states are frequently encountered in hemodialysis (Hdx) patients. The process of Hdx itself is also associated with vascular abnormalities. It was thus the aim of our study to examine the structure and function of skin microcirculation in Hdx patients.

Materials and methods
Sixty patients were examined: 20 patients on regular Hdx, younger than 60 years old, with no diabetes, hypertension, or hypercholesterolemia, 20 patients on regular hemodialysis with coexisting hypertension (Htn-Hdx), and 20 young healthy volunteers. The skin microcirculation was assessed using the laser Doppler fluxmetry and the capillaroscope.

Results
Results showed significant differences in the laser Doppler fluxmetry measurements between the Hdx group and the Htn-Hdx group compared with the control group, with no significant differences in the capillaroscope study.

Conclusion
The study of skin microcirculation in Hdx patients indicated the presence of functional abnormalities without significant structural changes.

Keywords:
capillaroscopy, endothelial dysfunction, hemodialysis, laser Doppler fluxmetry

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Introduction

The study of skin microcirculatory abnormalities represents a safe and easy tool to assess vascular abnormalities. Using laser Doppler fluxmetry (LDF) and capillaroscopy, many studies found a positive correlation between skin microcirculatory dysfunction and other vascular diseases [1,2] and the risk of development of heart disease [3,4]. The aim of our study was to examine skin microcirculation in hemodialysis (Hdx) patients and compare this with a group of young healthy adults as a control. LDF is commonly used for the study of the functional abnormalities of the skin microcirculation, [5], whereas the capillaroscope is used for direct visualization of structural capillary abnormalities [6]. We will use both techniques to evaluate skin microcirculation in Hdx patients.

Materials and methods

Clinical and laboratory assessment

The study was approved by the ethics committee of our institution. All participants provided informed written consents before the start of the study. Patients were recruited from the dialysis units in Cairo University. Patients and control participants were all subjected to a thorough assessment of history, clinical examination, and the following laboratory investigations: fasting blood glucose (FBG), postprandial blood glucose (PPBG), serum calcium (Ca), phosphorus (P), and parathormone (PTH).

Forty Hdx patients were chosen who were on regular Hdx for 5–10 years. All received hemodialysis with bicarbonate containing dialysate bath three times weekly; the duration of dialysis was 4 h/session and the interdialytic weight gain ranged from 3 to 5 kg. Patients were studied the day between the dialysis sessions. They all used the same type of membrane filters (FX 8; Fresenius Medical Care, Bad Homburg, Germany) (low flux dialyser, membrane material; polysulfone, sterilization: steam, effective surface area: 1.4 m^2, maximum transmembrane pressure (TMP): 600 mmHg).

These patients were divided into two groups.

Group A

Hdx included 20 patients: nonsmokers, less than 65, FBG less than 100 mg%, PPBG less than 140 mg%, systolic blood pressure (SBP) less than 140 mmHg, diastolic blood pressure (DBP) less than 90 mmHg,

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cholesterol less than 200 mg%, and with a normal ankle–brachial index (ABI). All were not on any medications other than calcium, vitamin D, iron, or erythropoietin. Thirteen patients were anuric. The average glomerular filtration rate in the rest of the patients was 6.7 ml/min. Their ECG and cardiologic assessment did not indicate any coronary artery disease. None had collagen vascular disease.

Group B

Hemodialysis with coexisting hypertension (Htn-Hdx) this group included 20 patients with hypertension (SBP≥140 and/or DBP≥90) of at least 10 years' duration, with or without diabetes and hypercholesterolemia. Those who received nitrates were excluded from the study. Six patients were smokers. Those who were included in the study had a normal ABI. Fifteen patients were anuric. The average glomerular filtration rate in the rest of the patients was 5.53 ml/min. For hypertension, these patients were maintained on calcium channel blockers, β-blockers, or angiotensin converting enzyme inhibitor (ACEI).

Group C

The control group included 20 young healthy volunteers, nonsmokers, less than 65, FBG less than 100 mg%, PPBG less than 140 mg%, SBP less than 140 mmHg, DBP less than 90 mmHg, cholesterol less than 200 mg%, with a normal ABI. The study population included 60 patients, 50 men and 10 women, age range 27–60 years.

Assessment of the macrocirculation

An ABI measurement was performed to exclude macrovascular disease before the microcirculation was assessed. The ABI is the ratio of the SBP in the ankle to that in the arm. It is normally above 0.96. Values less than that represent peripheral arterial occlusive disease. A normal ABI ensures a healthy macrovasculature [7].

Assessment of microcirculation

Laser Doppler fluxmetry

Assessment of skin blood flow was performed using the LDF Periflux 4001 master/4002 Satellite Perimed Sweden. Measurements were performed after complete physical and mental rest for at least 20 min. The study was carried out in room temperature maintained at 24°C; the probe was held on the dorsum of the foot by a double-sided adhesive tape supplied by the manufacturer. Special care was taken to support the fiberoptic cable and to maintain the body stationary. Apparatus calibration was performed according to the guidelines of the manufacturer.

First, a registration of baseline flow (2 min) was performed, recording the basal flux. Then, arterial occlusion was performed with a suprasystolic pressure using a pneumatic cuff of a sphygmomanometer for 3 min at the ankle level, thus recording flow after occlusion [the biological zero (BZ)]. Following the release of pressure, the highest flux value measured was recorded, the peak flux. Because the output could not easily be translated into absolute values of blood flow, the magnitude of the changes in skin perfusion was calculated as the ratio between the peak and the mean baseline perfusions. Thus, the ratio between the peak flux and the basal flux was calculated by the apparatus as the percent change [8].

Reactive hyperemia is defined as a temporary increase in blood flow after the release of temporary occlusion of arterial inflow. The postischemic phase of the reactive hyperemia test is recorded by the LDF as an increase in the signal to a peak (maximum flow after occlusion) and then reverts to the resting value. This response to a provocative test is determined by the microvascular neural, myogenic, and endothelial activity. Consequently, reactive hyperemia was considered a good estimate of microvascular function [8].

The nailfold capillaroscope

The capillaroscope was used for direct visualization of the nailfold capillaries. Two fingers were tested in each patient: the middle and ring fingers of the hand. The nailfold was lubricated with paraffin oil and the area was examined thoroughly under the microscope. Four sequential microscopy fields were recorded (while the focusing level was adjusted systematically) and the capillaries were counted and examined while playing back the video. Several parameters can be examined in the nailfold capillaries. In our study, we examined the capillary density and the presence or absence of abnormal capillary forms. Capillary density was calculated as the average density in the two fingers. Density was measured as the number of capillary loops in 3 mm [9]. Abnormal capillary forms included enlarged or giant capillaries, the presence of capillary hemorrhage, and abnormalities in the organization of the normal capillary array [10]. The microscope used was the dynamic capillaroscopy (KK Technology, Honiton, UK).

Statistical analysis

Data were statistically described in terms of mean ± SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the

study groups was performed using the Student *t*-test for independent samples. The correlation between various variables was assessed using the Pearson moment correlation equation for linear relation in normally distributed variables and the Spearman rank correlation equation for non-normal variables. *P* values less than 0.05 were considered statistically significant. All statistical calculations were carried out using the computer program SPSS, version 15 (SPSS Inc., Chicago, Illinois, USA) for Microsoft Windows.

Results

Description of the clinical and lab data

Table 1 shows the clinical and lab data in the three groups. Table 2 shows the LDF data in the three groups.

Analysis of the LDF data

The basal flux

There was no statistically significant difference in the basal flux values between the Hdx group and the control group ($P = 0.145$), (Table 3). There was a statistically significant difference between the Htn-Hdx group and the control group ($P = 0.002$) (Table 4 and Fig. 1).

The peak flux

There was a statistically significant difference in the peak flux values between the Hdx group and the control group ($P = 0.006$) and between the Htn-Hdx group and the control group ($P < 0.001$) (Tables 3, 4 and Fig. 1).

The percent change

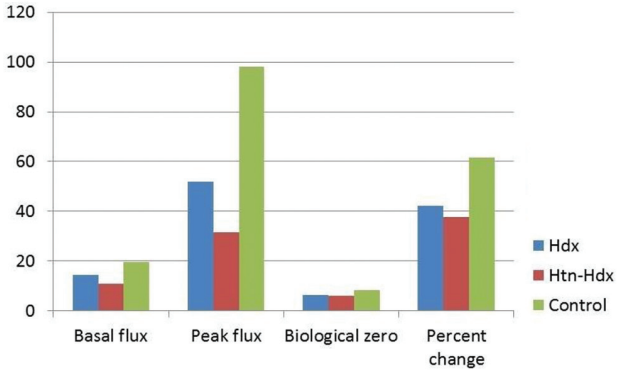
There was a statistically significant difference in the percent change values between the Hdx group and the control group ($P = 0.002$) and between the Htn-Hdx group and the control group ($P = 0.001$) (Tables 3, 4 and Fig. 1).

The biological zero

There was no statistically significant difference in the BZ values between the Hdx group and the control group ($P < 0.153$) or between the Htn-Hdx group and the control group ($P = 0.144$) (Tables 3, 4 and Fig. 1).

The significant results in the components of the reactive hyperemia test, that is the peak flux and the percent change indicate the presence of microvascular dysfunction (ED) in the Hdx group and as well in the Htn-Hdx group compared with the control group.

Figure 1



LDF results in the three groups. Hdx, hemodialysis; Htn-Hdx, hemodialysis with coexisting hypertension; LDF, laser Doppler fluxmetry.

Table 1 Clinical and lab results in the three groups studied

Item	Hdx group	Htn-Hdx group	Control group
Age	40 ± 15	44.26 ± 6.42	44.2 ± 6.42
SBP	119.5 ± 14.28	170 ± 24.49	117.0 ± 7.88
DBP	75.86 ± 8.12	100 ± 8.87	70.86 ± 6.12
BMI	20.2 ± 2.46	21.47 ± 1.89	21.47 ± 1.89
FBG (mg/dl)	86.7 ± 8.74	79.3 ± 8.87	82.7 ± 7.84
PPBG (mg/dl)	112 ± 8.2	125 ± 8.27	111 ± 9.31
BUN (mg/dl)	25.2 ± 3.03	23.5 ± 3.27	10.9 ± 3.23
Creatinine (mg/dl)	7.5 ± 1.06	8.07 ± 0.17	0.9 ± 0.27
Uric acid (mg/dl)	12.57± 0.755	10.12 ± 1.3	5.3 ± 1.01
Hb (g/dl)	9.95 ± 1.41	10.9 ± 0.81	12.6 ± 0.53
Ca (mg/dl)	9.28 ± 1.24	7.76 ± 0.47	8.84 ± 0.44
P (mg/dl)	7.07 ± 0.87	6 ± 0.21	4.01 ± 0.3
PTH (pg/ml)	455.5 ± 265.8	40.4 ± 14.9	34.85 ± 15.49

BUN, blood urea nitrogen; Ca, calcium; DBP, diastolic blood pressure; FBG, fasting blood glucose; Hb, hemoglobin; Hdx, hemodialysis; Htn-Hdx, hemodialysis with coexisting hypertension; P, phosphorus; PPBG, postprandial blood glucose; PTH, parathormone; SBP, systolic blood pressure.

Analysis of the results of the lab data

There was a statistically significant difference in the levels of uric acid, hemoglobin, phosphorus, and PTH values between the Hdx and the control group ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively) (Table 5).

There was a statistically significant difference in the levels of uric acid and hemoglobin between the Htn-Hdx and the control group ($P = 0.032$ and 0.003, respectively) (Table 6).

The capillaroscopy findings

There was no statistically significant difference in the parameters studied between the three groups. The average capillary density in the two fingers was 5.36 ± 1.95 in the Hdx group, 5.9 ± 3.29 in the Htn-Hdx group, and 4.28 ± 1.56 in the control group, with a P value of 1.000 and 0.894, respectively. There were no obvious abnormal capillary forms in any of the groups studied.

Table 2 LDF results in the three groups studied

Item	Hdx group	Htn-Hdx group	Control group
Basal flux	14.5 ± 6	11 ± 4.42	19.7 ± 9.7
Peak flux	52 ± 27.9	31.7 ± 20.6	98.2 ± 55
Biological zero	6.2 ± 3.8	6.18 ± 3.64	8.3 ± 5.2
Change (%)	42.13 ± 19.17	37.8 ± 17.8	61.7 ± 18.3

Hdx, hemodialysis; Htn-Hdx, hemodialysis with coexisting hypertension; LDF, laser Doppler fluxmetry.

Table 3 Analysis of the LDF data in Hdx and control groups

Item	Hdx			Control			Analysis								
	Mean	SD	*n*	Mean	SD	*n*	*d.f.*	SD-both	1/n1	1/n2	Sum	SE difference	*t*	Tails	*P* value
Basal flux	14.5	6	20	19.7	9.7	20	38	65.05	0.05	0.05	0.10	2.55	2.04	2	0.145
Peak flux	52	27.9	20	98.2	55	20	38	1901.71	0.05	0.05	0.10	13.79	3.35	2	0.006*
Biological zero	6.2	3.8	20	8.3	5.2	20	38	20.74	0.05	0.05	0.10	1.44	1.46	2	0.153
Change (%)	42.13	19.17	20	61.7	18.3	20	38	351.19	0.05	0.05	0.10	5.93	3.30	2	0.002*

Hdx, hemodialysis; LDF, laser Doppler fluxmetry; *Indicates a statistically significant difference.

Table 4 Analysis of the LDF data in the Htn-Hdx and control groups

Item	Htn-Hdx			Control			Analysis								
	Mean	SD	*n*	Mean	SD	*n*	*d.f.*	SD-both	1/n1	1/n2	Sum	SE difference	*t*	Tails	*P* value
Basal flux	11	4.42	20	19.7	9.7	20	38	56.81	0.05	0.05	0.10	2.38	3.65	2	0.002*
Peak flux	31.7	20.6	20	98.2	55	20	38	1724.68	0.05	0.05	0.10	13.13	5.06	2	0.000*
Biological zero	6.18	3.64	20	8.3	5.2	20	38	20.14	0.05	0.05	0.10	1.42	1.49	2	0.144
Change (%)	37.8	17.8	20	61.7	18.3	20	38	325.87	0.05	0.05	0.10	5.71	4.19	2	0.001*

Htn-Hdx, hemodialysis with coexisting hypertension; LDF, laser Doppler fluxmetry; *Indicates a statistically significant difference.

Table 5 Analysis of the clinical and lab data in the Hdx and control groups

Item	Hdx			Control			Analysis								
	Mean	SD	*n*	Mean	SD	*n*	*d.f.*	SD-both	1/n1	1/n2	Sum	SE difference	*t*	Tails	*P* value
Age	40	15	20	44.2	6.42	20	38	133.11	0.05	0.05	0.10	3.65	1.15	2	0.257
SBP	119.5	14.28	20	117	7.88	20	38	133.01	0.05	0.05	0.10	3.65	0.14	2	0.892
DBP	75.86	8.12	20	70.86	6.12	20	38	37.45	0.05	0.05	0.10	1.94	0.00	2	1.000
BMI	20.2	2.46	20	21.47	1.89	20	38	4.81	0.05	0.05	0.10	0.69	1.83	2	0.075
FBG (mg/dl)	86.7	8.74	20	82.7	7.84	20	38	61.47	0.05	0.05	0.10	2.48	0.00	2	1.000
PPBG (mg/dl)	112	8.2	20	111	9.31	20	38	86.68	0.05	0.05	0.10	2.94	0.00	2	1.000
BUN (mg/dl)	25.2	3.03	20	10.9	3.23	20	38	9.81	0.05	0.05	0.10	0.99	4.34	2	0.000*
Creatinine (mg/dl)	7.5	1.06	20	0.9	0.27	20	38	0.60	0.05	0.05	0.10	0.24	18.81	2	0.000*
Uric acid (mg/dl)	12.57	0.755	20	5.3	1.01	20	38	0.80	0.05	0.05	0.10	0.28	8.05	2	0.000*
Hb (g/dl)	9.95	1.41	20	12.6	0.53	20	38	1.13	0.05	0.05	0.10	0.34	7.87	2	0.000*
Ca (mg/dl)	9.28	1.24	20	8.84	0.44	20	38	0.87	0.05	0.05	0.10	0.29	1.90	2	0.065
P (mg/dl)	7.07	0.87	20	4.01	0.3	20	38	0.42	0.05	0.05	0.10	0.21	5.15	2	0.000*
PTH (pg/ml)	455.5	265.8	20	34.85	15.49	20	38	35444.79	0.05	0.05	0.10	59.54	7.07	2	0.000*

BUN, blood urea nitrogen; Ca, calcium; DBP, diastolic blood pressure; FBG, fasting blood glucose; Hb, hemoglobin; Hdx, hemodialysis; P, phosphorus; PPBG, postprandial blood glucose; PTH, parathormone; SBP, systolic blood pressure; *Indicates a statistically significant difference.

Table 6 Analysis of the clinical and lab data in the Htn-Hdx and control groups

Item	Htn-Hdx			Control			Analysis								
	Mean	SD	*n*	Mean	SD	*n*	*d.f.*	SD-both	1/n1	1/n2	Sum	SE difference	*t*	Tails	*P* value
Age	44.26	6.42	20	44.2	6.42	20	38	41.22	0.05	0.05	0.10	2.03	0.03	2	0.977
SBP	170	24.49	20	117	7.88	20	38	330.93	0.05	0.05	0.10	5.75	9.21	2	0.000*
DBP	100	8.87	20	70.86	6.12	20	38	58.07	0.05	0.05	0.10	2.41	12.09	2	0.000*
BMI	21.47	1.89	20	21.47	1.89	20	38	3.57	0.05	0.05	0.10	0.60	0.00	2	1.000
FBG (mg/dl)	79.3	8.87	20	82.7	7.84	20	38	70.07	0.05	0.05	0.10	2.65	1.28	2	0.207
PPBG (mg/dl)	125	8.27	20	111	9.31	20	38	77.53	0.05	0.05	0.10	2.78	5.03	2	0.000*
BUN (mg/dl)	23.5	3.27	20	10.9	3.23	20	38	10.56	0.05	0.05	0.10	1.03	2.53	2	0.016*
Creatinine (mg/dl)	8.07	0.17	20	0.9	0.27	20	38	0.05	0.05	0.05	0.10	0.07	2.38	2	0.000*
Uric acid (mg/dl)	8.12	1.3	20	5.3	1.01	20	38	1.36	0.05	0.05	0.10	0.37	2.23	2	0.032*
Hb (g/dl)	10.9	0.81	20	12.6	0.53	20	38	0.47	0.05	0.05	0.10	0.22	3.23	2	0.003*
Ca (mg/dl)	7.76	0.47	20	8.84	0.44	20	38	0.21	0.05	0.05	0.10	0.14	0.56	2	0.582
P (mg/dl)	5.9	0.21	20	4.01	0.3	20	38	0.07	0.05	0.05	0.10	0.08	0.12	2	0.903
PTH (pg/ml)	40.4	14.9	20	34.85	15.49	20	38	230.98	0.05	0.05	0.10	4.81	1.15	2	0.255

BUN, blood urea nitrogen; Ca, calcium; DBP, diastolic blood pressure; FBG, fasting blood glucose; Hb, hemoglobin; Htn-Hdx, hemodialysis with coexisting hypertension; P, phosphorus; PPBG, postprandial blood glucose; PTH, parathormone; SBP, systolic blood pressure; *Indicates a statistically significant difference.

Discussion

The importance of studying the function and structure of the skin microcirculation emerged from the hypothesis that skin microvascular changes mimic changes in other vascular beds, including the coronaries [11,12]. The functional and structural abnormalities at the level of the microcirculation represent an easy access to the events occurring in the larger arteries [2] and the coronaries [3]. Such changes were found to correlate with the development of cardiovascular disease [4].

The skin microcirculatory changes in Hdx patients can be attributed to Hdx alone or to associated comorbidities such as diabetes, hypertension, and ischemic heart disease [13–18]. Our study included 40 patients on long-term maintenance Hdx; 20 patients were nonsmokers, did not have diabetes, hypertension, and hypercholesterolemia, and were less than 65 years old (Hdx). The other 20 patients were Htn-Hdx. Both were compared with a group of young healthy adults (control group).

The LDF and capillaroscope results in the Hdx group

The results of the LDF showed a statistically significant difference in the components of the reactive hyperemia test (the peak flux and the percent change values) between the Hdx group and the control group. This indicates the presence of microvascular functional abnormalities in the Hdx group.

Several previous studies have examined the microcirculatory function in response to stimulatory tests in Hdx patients. In nonhypertensive Hdx patients, a decreased vasodilation in the skin microcirculation in response to acetylcholine and sodium nitroprusside was found, but a preserved response in patients on conservative therapy. They concluded that Hdx treatment appears to accelerate the progression of atherosclerosis [19,20].

In other studies, using thermal stimuli as the provocative test, skin blood flow (SBF) was impaired in patients with stage 5 CKD on Hdx [21,22]. In a study by Kocak and colleagues, brachial artery flow-mediated dilatation (FMD) measurement was used for the assessment of endothelial function. Hdx patients were found to have endothelial dysfunction. The important finding in that study was the improvement in endothelial function after renal transplantation [23]. Similar results were found using different techniques such as the venous occlusion plethysmography. Passauer *et al.* [24] found that endothelium-dependent vasodilatation to acetylcholine was reduced in the Hdx group compared with the control group. Similarly, Pannier *et al.* [25] reported that the FMD response was impaired in Hdx patients and this decrease correlated with the duration of dialysis and the carotid intima media thickness. However, Cross and colleagues reported that, apart from hypertension, hyperlipidemia. and hyperglycemia, which are highly prevalent in Hdx patients, the uremic medium itself can cause microcirculatory dysfunction in these patients. They suggested that short-term elimination of uremic toxins may result in increased FMD of the brachial artery in Hdx patients, that is this endothelial dysfunction is normalized by Hdx [26].

Our results also showed that there was a statistically significant difference in the basal flux values between the Hdx group and the control group and between the Htn-Hdx group and the control group. This indicates that there is a significant impairment in flow even without the use of a provocative test. This is not in agreement with the study by Katalin *et al.* [22] who

reported that under basal conditions, no statistically significant difference was observed in forearm skin perfusion between CKD patients and control participants.

The results of the LDF can also be explained by underlying structural alterations in the skin microcirculation in Hdx patients. The capillaroscope examination in our study showed no statistically significant difference in capillary density or in the appearance of abnormal forms between the two groups. Unfortunately, not many studies have been carried out to evaluate the capillary morphologic changes in Hdx patients. Hirschl and colleagues studied the morphological and hemodynamic parameters of microcirculation, in the Hdx population, using quantitative capillaroscopy. He reported that the morphological microcirculatory parameters did not show any differences between the shunt arm and the contralateral side, but did not compare these with control participants [27].

The LDF and capillaroscope results in the Htn-Hdx group

The results showed a statistically significant difference in the components of the reactive hyperemia test as well between the Htn-Hdx group and the control group. This indicates the presence of microvascular functional abnormalities in the Htn-Hdx group. This finding has long been linked to the presence of hypertension [28–31]. The capillaroscope examination showed a statistically significant difference in the capillary density between the Htn-Hdx group and the control group.

Many studies also confirmed structural alterations detected by a capillaroscope in hypertensive patients [32]. In a similar study in hypertensive geriatric patients, Bonacci and colleagues reported a decrease in the number of capillary loops; they appear thin and lengthened, in the hypertensive patients, compared with the control group. Dilated and tortuous capillaries, arteriovenous sludge, and 'flea bite' juxtacapillary microhemorrhages were found more frequently in the patients with isolated systolic hypertension; they linked this to the atherosclerotic nature of that disease [33]. In a study by Noon and colleagues, capillary rarefaction had been described in the nailfold and forearm skin in hypertensive patients and appeared to be a structural rather than simply a functional defect. This structural rarefaction preceded the development of hypertension being present in the dermal vessels of young men who had a familial predisposition to high blood pressure. Similar findings have been described in the conjunctival microcirculation and in other tissues [34].

Kanishcheva and colleagues carried out a study to assess parameters of the nail bed capillary net of the hand in hypertensive and normotensive individuals in the 60–80 years age range. They concluded that in hypertensive patients aged 60–80 years, compared with normotensives of the same age, the size of the pericapillary zone of the nail bed was significantly larger because of interstitial hyperhydration of this area [35]. Van der Veldt *et al.* [36] reported, in their study, that the decrease in capillary density was related to the increase in SBP and DBP.

Significance of the lab parameters

There was a statistically significant difference in the levels of uric acid, hemoglobin, phosphorus, and PTH values between the Hdx and the control group and in the uric acid and hemoglobin between the Htn-Hdx and the control group.

These findings were supported by various trials. In a cross-sectional, single-center study, creatinine clearance correlated with the microvascular function scores [37]. Many studies concluded that microvascular functional abnormalities in CKD patients showed a positive correlation with the level of serum uric acid [38,39]. Several studies have reported that a phosphorus load increased the production of reactive oxygen species, decreased nitric oxide production, and inhibited endothelium-dependent vasodilation of animal aortic rings [40,41]. Control of serum phosphorus was associated with an improvement in microvascular function [42].

In a study by Choi and colleagues, Cinacalcet significantly decreased serum iPTH, calcium, phosphorus, and calcium × phosphorus product, with a significantly improvement in brachial FMD. The authors concluded that it might ameliorate microvascular dysfunction by decreasing oxidative stress and increasing serum nitric oxide production in Hdx patients with secondary hyperparathyroidism [43]. In a cross-sectional study by Bosworth and colleagues, it was found that a higher serum PTH concentration was associated with lower brachial artery flow-mediated vasodilation (FMD). These relationships may help explain the observed associations of elevated PTH with cardiovascular disease [44]. The relationship between hemoglobin, red blood cells, and microvascular dysfunction is an area of intense research. Red cell distribution width, a measure of erythrocyte size variability, was found to be a significant predictor of FMD in CKD patients, independent of diabetes, inflammation, anemia, and kidney function [45]. Solak *et al.* [46] showed an independent association of mean cell volume (MCV) and FMD in patients with CKD. In systemic hypoxia,

erythrocyte-derived H_2O_2 induces proinflammatory gene transcription in vascular endothelium [47,48].

Conclusion

We suggest that patients on maintenance Hdx, without any clinical manifestations of hypertension, diabetes, or dyslipidemia, still show abnormalities in LDF parameters consistent with microvascular dysfunction. This may be viewed as an early sign of impending clinically important cardiovascular disease in the Hdx population. Several interventions to improve microvascular function have been attempted, such as regular exercise [49], the use of antioxidants [50], ACEI, calcium channel blockers [31], and statins [51]. It remains to be determined whether these measures play a role in Hdx patients. Also, correction of the previous parameters such as hemoglobin, phosphorous, PTH, and uric acid levels may improve microvascular performance in this population.

It is worth noting, however, that the timing for performing the test for ED in HDx patients is important. Levels of mediators of ED, that is, the uremic toxins, decrease markedly after HDx, with an improvement in microvascular function. With reaccumulation or rebound of these toxins, the microvascular function becomes impaired again. Cross and colleagues showed that the plasma concentration of circulating inhibitors of microvascular function was reduced after Hdx and that Hdx improved FMD. These changes persisted for 5 h, but returned to baseline by 24 h [26]. Perhaps, this can explain the evident LDF measurements obtained in our study because our study was carried out on the day between dialysis sessions.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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