Applied nutritional investigation

Plasma albumin levels correlate with decreased microcirculation and the development of skin defects in hemodialyzed patients

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Abstract

Objectives: Difficulty healing wounds and skin defects is a frequent problem in patients on chronic hemodialysis (HD) because of malnutrition, inflammation, and atherosclerosis (MIA) syndrome. The aim of the present study was to estimate the influence of peripheral blood flow changes during HD on the development of foot defects and its relationship to plasma albumin levels.

Methods: Peripheral skin blood flow was measured using a laser Doppler line scanner in 10 different areas of the dorsal part of the instep and the toes of each foot before and during HD with ultrafiltration (897 ± 465 mL/procedure) in 31 HD patients (10 female, 21 male; age 36-79 y, body mass index = 28 ± 5.0). No skin defects or apparent acute disease or infection were detected in any patient at the time of laser Doppler line scanner measurement. The feet of the patients were clinically re-examined carefully over the next 18 mo.

Results: We found a significant and constant decrease of skin blood flow during the HD procedure (P < 0.001). Skin blood flow was significantly correlated with serum albumin level both before HD (r = 0.36, P = 0.05) and during HD (r = 0.47, P = 0.007). Skin defects developed in 11 patients, with significantly lower skin blood flow during the 18-mo follow-up period. A significantly larger number of patients who had normal perfusion remained defect-free in comparison to patients with critical perfusion (93% versus 38%, P = 0.002, Kaplan-Meier analysis).

Conclusion: Skin blood flow may be impaired in HD patients. The apparent malnutrition and inflammation in HD patients are likely responsible for the decreased skin blood flow and the development of the difficulty to heal skin defects and wounds.

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Introduction

Non-healing wounds, pressure ulcers, and skin defects are frequent in individuals with end-stage renal disease (ESRD) treated with chronic hemodialysis (HD). The etiology of these skin defects is complex. These are caused by premature atherosclerotic vascular disease, calciphylaxis (small vessel mural calcification leading to tissue ischemia and skin necrosis, with very high mortality [1]), malnutrition, and other factors. Decreased skin blood flow can also be an important factor because it contributes to the more frequent wounds in HD patients. Skin defects can increase inflammatory stress with negative consequences. In addition, HD patients are at an increased risk of atherosclerosis and cardiovascular disease. This risk is almost 30 times higher than the general population and remains 10–20 times higher even after stratification for age, gender, and the presence of diabetes mellitus [2], and it is the principal factor of high mortality in this group of patients.

Traditional risk factors such as obesity, hypertension, or hyperhomocysteinemia, which are associated with the increased risk of atherosclerosis and cardiovascular disease in the general population, also relate to high mortality in ESRD patients but in the opposite direction. This paradoxical association is called reverse epidemiology [3], which is a condition in which being overweight (body mass index >27.5) is associated with a better outcome than being normal or underweight [4]. Therefore, protein energy malnutrition in ESRD patients is a good predictor of atherosclerosis and mortality [5–7]. The reason for this reverse epidemiology is chronic illness and inflammation, followed by a decline in muscle mass. Thus, ESRD patients normally develop sarcopenia. A decrease in appetite from different causes can also lead to low fat mass, with a subsequent development of protein-energy wasting [3,8,9].
Peripheral arterial occlusive disease (PAOD) resulting from excessive atherosclerosis is also more common among patients with ESRD than the general population. Prevalence rates cited in the literature range from 17% to 48% [10]. The presence of PAOD substantially increases the risk of both morbidity (chronic ischemic ulceration, gangrene, and amputation) [11,12] and mortality among ESRD patients [13].

A temporal association of an increase in the incidence of foot ulcers and major limb amputation with the start of regular hemodialysis treatment has been published, and a possible relation to dialysis-induced hypoxemia due to the hypoperfusion of peripheral tissues has been advocated as a hypothetical explanation [14].

Our study was therefore based on the hypothesis that hemodialysis with ultrafiltration induces a decrease in skin blood flow, which can result in the formation of skin defects and subsequently in an increased risk of mortality. To estimate the influence of hemodialysis on blood flow in a large surface area of skin, we employed the distant laser Doppler line scanner (LDLS; Moor, Devon, UK) for HD patients.

To our knowledge, peripheral skin flow during hemodialysis has not been assessed in a large surface area of skin. Thus, we focused on both demonstrating skin perfusion and plasma albumin levels, which have recently been found to be the best predictor for 10-y mortality [15]. In this study, we primarily focused on the long-term outcome of patients with HD-induced peripheral skin flow changes.

Methods

Patients

We prospectively studied 31 clinically stable patients [21 male, 10 female, with a mean age of 59 y (range, 36–79)] who were on chronic hemodialysis for an average of 30 mo (range, 1–163 mo). The patients were randomly selected from a dialysis unit at the Faculty Hospital, Medical Faculty, Charles University in Hradec Králové, Czech Republic. All patients were without skin defects at the dialysis unit at the Faculty Hospital, Medical Faculty, Charles University in Hradec Králové, Czech Republic. All patients were without skin defects at the time of the LDLS skin perfusion measurement. Patients were asked not to drink coffee, black or green tea, or alcoholic beverages or to smoke within 6 h prior to the hemodialysis procedure, before and during which the skin perfusion was measured by LDLS. All measurements were done in the dialysis room at a stable temperature (24 ± 1 °C), where patients were resting for at least 20 min prior to the first (predialysis) measurement. The body temperature of the patients was normal and stable throughout the whole study procedure (36.1 ± 0.3 during the first measurement compared to 36.0 ± 0.3 during the second); No signs of local or general inflammation were noted.

Informed consent was obtained from all patients, and the study was conducted in accordance with the Helsinki Declaration. The ethical committee of the University Hospital and Medical Faculty in Hradec Králové approved the study.

Measurement of peripheral skin blood flow

The measurement of the peripheral skin blood flow was performed as previously described [16]. LDLS is a non-invasive device based on measuring the cutaneous blood flow by scanning the examined area using a laser beam. Skin blood flow to a 1- to 1.5-mm depth of skin was measured on the principle of backscattered light from moving red blood cells. The superficial skin plexus and its supplying blood vessels can be found at this depth. The advantage of this technique is that there is no direct contact of the device with skin; thus, the results are not influenced by local pressure. Moreover, LDLS yields information about two-dimensional skin microcirculation in a large surface area (15 × 12 cm).

The measurement time was less than 25 s, and therefore, all four extremities (both hands and both feet) were investigated within 5 min. The only task for the patient was to stay still during the required time interval. Data are computerized and expressed as a picture and a set of numerical data (in arbitrary perfusion units).

We also measured skin perfusion on the hands of 15 patients after inflating the cuff above systolic blood pressure (biological zero). We used the median of this value for each measured area as the cutoff for critical perfusion. We were not able to determine this value for feet because of the low compressibility of the vessels in the lower extremities that was likely due to calcification. Two-thirds of the patients had an ankle-brachial index higher than 1.3. The value acquired for the hands was therefore used for analysis on the feet. All measurements and evaluations were performed by the same investigator (E.M.).

Cutaneous blood flow was measured in 10 areas of interest (AI) of defined size on the dorsum of each foot (four AI at the dorsal part of the toes, six at the metatarsal part of the foot), and paired measurements of skin blood flow were performed. None of the AI changed throughout the measurement. The first measurement was performed just prior to the start of HD, and the second measurement was taken during the course of HD. The time of dialysis and the total ultrafiltration achieved was noted for each patient. The median interval between LDLS measurements was 65 min (interquartile range, 45–90), and the median ultrafiltration at the time of the second measurement was 730 mL (range, 500–1170), which equals 0.9 (0.6–1.3 percentage of predialysis body weight). In addition to the flux image, the LDLS makes two photographs (an LD photo image and a digital photograph) during the measurement; which can be used to help define the scan region. The cursor position on the LD photo corresponds to the cursor position on flux (measurement) image if opened in two windows in the LDLS analysis software, thus ensuring that the same AI are measured after a period of time.

In another set of LDLS measurements, we analyzed skin microcirculation changes during the HD procedure with the same technical parameters. Measurements were taken before hemodialysis and at the first, second, third, and fourth hour of the procedure (data from this study are used in Fig. 1).

The hemodialysis procedure

All HD procedures were isothermic [i.e., the temperature of all patients was kept constant using a blood temperature monitor (Fresenius, Bad Homburg, Germany) in active mode (ΔT = 0) and removing an average of 280 kJ [166; 369] per HD procedure] [17]. We used steam-sterilized polysulphone dialyzers with low flux, a two-needle system with a blood flow rate (QB) of 300 mL/min, bicarbonate dialysis solution with a flow rate of 500 mL/min, and a linear ultrafiltration rate. Dialysate purity was checked and fulfilled the European Best Practice Guidelines standards for ultrapure dialysis solutions [18]. No endotoxin was present in the dialysis solution. Therefore, the dialysis procedure itself could not induce an inflammatory response. The blood pressure, peripheral pulse, and
saturations were recorded before HD, immediately after the beginning of dialysis and then every hour and immediately after each LDLS measurement. Approximately 200 mL blood was required to fill the dialysis apparatus. This volume was replenished with saline. No hypotensive episodes according to the European Best Practice Guidelines for hemodynamic stability [19] were recorded, indicating that all patients were hemodynamically stable throughout the hemodialysis and measurement period.

### Follow-up

After the first measurement, the defect-free patients were closely followed every month for 18 mo. All new occurrences of foot skin defects, wounds, and peripheral gangrene and amputations were noted. Other cardiovascular events (myocardial infarction, stroke, and transitory ischemic attack) and death were also noted. Baseline skin blood flow in patients (LDLS results) was analyzed for possible associations with the new occurrence of skin defects, cardiovascular events, and mortality during the follow-up period.

### Biochemical analysis

Predialysis blood samples were collected monthly as part of the routine procedures. The averages computed from the previous 3 mo were used for analysis. Serum levels of albumin (S-Alb; colorimetric method with brom cresol green), TIBC (spectrophotometric method with fuchsin), CRP (turbidity), calcium (colorimetric method with o-kresoltalen complexone.), phosphate (colorimetric method with ammonium molybdate), total cholesterol (enzymatic colorimetric method), LDL cholesterol, HDL cholesterol (homogenous enzymatic colorimetric test), and triglycerides (enzymatic colorimetric test) were analyzed with the automatic analyzer Modular (Roche/Hitachi, Laval, QC, Canada) using reagents from Roche Diagnostics GmbH (Mannheim, Germany).

### Data analysis

Microcirculation changes were evaluated using software provided by the manufacturer. Statistical evaluation was performed using SigmaStat 3.1 (SPSS, Inc., San Jose, CA, USA). Data were tested for normality using the Kolmogorov-Smirnov test with Lilliefors correction. If the distribution was normal, mean blood flow magnitudes of each AI before and during hemodialysis were compared using a two-sample t test. If the distribution was not normal, a non-parametric test was used. P values < 0.05 were considered statistically significant.

### Results

The baseline clinical characteristics of our patients are summarized in **Table 1**, and the macrocirculatory hemodynamic parameters are summarized in **Table 2**. We found a significant and constant decrease of skin blood flow during the HD procedure (P < 0.001). An overview of the skin blood flow decrease on the toes/instep of the feet during one session of hemodialysis is demonstrated in **Figure 1**. Skin blood flow was significantly correlated with serum albumin level both before and during HD (r = 0.36, P = 0.05 and r = 0.47, P = 0.007, respectively). The correlations between skin microcirculation before and during hemodialysis with S-albumin are shown in **Figure 2**. The number of patients with at least one area of interest with critical perfusion (using biological zero (instep 54 ± 6; toes 32 ± 8) as a cutoff for critical values of skin blood flow) is summarized in **Table 3** according to the later incidence of skin defects, cardiovascular events, and death, respectively. A significantly larger portion of patients with normal perfusion remained defect-free in comparison to patients with critical perfusion (93% versus 38%, P = 0.002, Kaplan-Meier analysis). Comparison of absolute values of blood flow before and during HD according to later occurrence of death, cardiovascular events, and skin defects is shown in **Table 4**. It is apparent from this table that non-survivors had significantly lower skin blood flow in their toes before dialysis. Blood flow was also lower during HD; however, this difference was not statistically significant. No significant difference was apparent between skin blood flow and cardiovascular events. Skin defects developed in 11 patients during the 18-mo follow-up period. Skin blood flow was significantly lower in these subjects compared to patients with no defects. Skin blood flow before and during HD was significantly related to the development of wounds or skin defects in the subsequent 18-mo period (**Table 5** and **Fig. 3**).

### Discussion

The development of ischemic wounds and skin defects is a significant problem in HD patients. These wounds are frequently very difficult to heal and increase chronic inflammation in this group of patients. Given that inflammation is important for the development of atherosclerosis, the careful prevention of wound development and immediate wound treatment is lifesaving. To our knowledge, we have shown for the first time that blood flow in skin microcirculation decreases during hemodialysis by measuring skin blood flow in a large surface area of skin [16]. We have demonstrated that this blood flow might also correlate with serum albumin as a parameter of malnutrition and inflammation. In addition, we found that the decrease in skin microcirculation may predict the future development of skin defects and death. Thus, even a hemodynamically stable and therefore “safe” HD procedure can have silent long-term consequences.
An increasing body of evidence suggests that subclinical ischemia of different organs develops during hemodialysis. Weiss et al. published their results regarding a transcutaneous oxygen tension (tcpO_2) decrease during hemodialysis [20]. Pre-dialysis values were not different from controls; however, during dialysis, a drop in the tcpO_2 was observed in the majority of patients. Recently, their observation was confirmed by Game’s group (authors of the aforementioned observation of the temporal association between foot ulcers and amputations with the start of dialysis). This group found a decrease of tcpO_2 tension during the course of dialysis and for more than 4 h after the end of HD [21].

Hypoxemia during dialysis may be associated with microcirculatory abnormalities, as suggested by both of these authors [20, 21]. Both endothelium-dependent and endothelium-independent microcirculatory dysfunction have been documented during the interdialytic period using these methods [22–24]. Selby et al. demonstrated that subclinical myocardial ischemia occurring during hemodialysis may be a potential causative factor in the development of cardiac dysfunction in this patient group [25].

Data from our other set of skin blood flow measurements during HD (Fig. 1) show a constant decrease in blood flow throughout the procedure. If we use the measurements of biological zero (mean skin blood flow measured after inflating the cuff above systolic blood pressure in 15 patients) as the cutoff for critical values, we see that this is, on average, reached between the third and fourth hour. However, the median time of the second measurement in our study was 65 min. About 50% of the patients in this study reached these critical values before this

![Graphs](image)

Fig. 2. Correlation of skin blood flow on toes/instep of feet before/during hemodialysis with S-albumin.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>P</th>
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<tr>
<td>Defect</td>
<td>100%</td>
<td>63%</td>
<td>0.005</td>
</tr>
<tr>
<td>CVS event</td>
<td>90%</td>
<td>66%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>100%</td>
<td>68%</td>
<td>0.006</td>
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</table>

NS, not significant

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Survivals (n = 25)</th>
<th>Non-survivals (n = 6)</th>
<th>P value</th>
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<tr>
<td>Blood flow before HD</td>
<td>Toes</td>
<td>96 (65; 131)</td>
<td>69 (68; 73)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Instep</td>
<td>102 (90; 117)</td>
<td>84 (69; 91)</td>
<td>0.08</td>
</tr>
<tr>
<td>Blood flow during HD</td>
<td>Toes</td>
<td>91 (38; 156)</td>
<td>62 (43; 88)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Instep</td>
<td>65 (40; 84)</td>
<td>46 (25; 50)</td>
<td>0.12</td>
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</table>
time point. If we analyze how many patients from the comparative groups (Table 3, defect no/yes) had at least one area of interest with critical blood flow, we see that this occurred in all patients who had later developed a defect. The frequency among these patients was significantly different from those who did not develop a defect and those who survived the study period.

We next performed a survival analysis using the Kaplan-Meier log rank method using a critical value obtained from the instep of the foot during HD (65 a.u.) as a cutoff to divide patients into two groups. We observed a significantly better defect-free survival for patients in the group above the cutoff value. The same analysis for mortality showed a similar trend; however, we later repeated the measurements with relatively good reproducibility of the absolute values of skin blood flow on a larger patient group and lack of changes.

Table 5
Comparison of absolute values of skin blood flow before and during hemodialysis according to later occurrence of foot skin defect

<table>
<thead>
<tr>
<th>Foot skin defect</th>
<th>No skin defect (n = 20)</th>
<th>Skin defect (n = 11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow before HD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toes</td>
<td>103 (66; 134)</td>
<td>73 (68; 80)</td>
<td>0.001</td>
</tr>
<tr>
<td>Instep</td>
<td>106 (90; 118)</td>
<td>90 (65; 96)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood flow during HD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toes</td>
<td>95 (44; 158)</td>
<td>57 (38; 95)</td>
<td>0.006</td>
</tr>
<tr>
<td>Instep</td>
<td>68 (48; 90)</td>
<td>42 (38; 49)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Fig. 3. Kaplan-Meier graph, which demonstrates the development of skin defects in HD patients. Subsequent development of skin defect was significantly associated with low skin microperfusion.

Blood flow before HD decreases deep underneath the red line chosen for the critical limits before hemodialysis in patients with PAOD, it decreases deep underneath the red line chosen for the critical level during the procedure. This is already apparent at the first hour of the HD procedure and might continue up to 4 h after the end [21]. If added together, this decrease in blood flow lasts for at least 7 h, which occurs three times a week. Based on these calculations, it is not surprising that the incidence of skin defects and amputation rises steeply after the start of hemodialysis [14]. Moreover, the decrease in blood flow can be also accompanied by a higher mortality from comorbidities connected to this phenomenon. However, both peripheral organs (e.g., skin and residual renal function) and vital organs such as the cardiac muscle [25] may be negatively affected during HD.

It should be noted that thermal balance might greatly influence vascular tone. However, this was not the case in our study, as the body temperature of the patients was kept stable throughout the hemodialysis procedure. This control method should eliminate the potential effect of body temperature changes.

The correlation of serum albumin level with skin blood flow increases the importance of nutrition in the prevention of skin defects. To the best of our knowledge, we are the first to describe this phenomenon. In a recent study, albumin was found to be the best predictor for 10-y mortality [15]. Albumin is a late-reacting negative acute phase protein and a marker of nutrition in the absence of inflammation. The albumin level affects skin defect development and healing in several different ways, as follows:

- Low nutritional status directly influences wound healing [26].
- Oncotic pressure (mainly induced by albumin) serves as the main driving pressure (together with hydration status) for vascular refill, which counteracts the ultrafiltration observed with decreases in skin perfusion.
- Malnutrition and inflammation are associated with macrovascular disease in ESRD patients [27].

Our study has some potential limitations. The number of patients was relatively small, and the measurements were taken during only one dialysis session. However, we later repeated the measurements with relatively good reproducibility of the absolute values of skin blood flow on a larger patient group and during more hemodialysis sessions with the same technical parameters (data not published). Further, we only had history data concerning coronary heart disease, PAOD, and cerebrovascular disease; thus, we cannot determine to what extent the degree of large-arteries disease might underlie our results. However, we do not deny the impact of atherosclerosis. We point out that the large-artery disease present to a large extent in ESRD patients can be further aggravated by the HD procedure itself. We propose that short-term tolerability of HD (hemodynamic stability) is not a sufficient approach for the prevention of the long-term consequences of dialysis therapy.

Conclusions

Skin blood flow during hemodialysis can decrease under the level of critical perfusion. We found a correlation between skin blood flow and the level of serum albumin as a marker of malnutrition and inflammation. We further found a relationship...
between low skin blood flow and the later development of skin defects and mortality.

Acknowledgments

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References