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The impact of dialysis modality on skin hyperpigmentation in haemodialysis patients

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Abstract

Background. Skin hyperpigmentation in end-stage renal disease (ESRD) patients has been attributed to the accumulation of middle-molecular-weight (MMW) substances. Although an MMW mechanism suggests that hyperpigmentation may be improved by high-flux haemodialysis (HF-HD) and haemodiafiltration (HDF), this possibility has not been explored. In the present study, we investigated the impact of different dialysis modalities on skin colour in HD patients.

Methods. Eighty-two ESRD patients on HD were divided into low-flux HD (LF-HD), HF-HD and HDF groups. The melanin index (MI) and erythema index (EI) of the abdomen and the flexor side of the forearm (non-sun-exposed areas) and the forehead (sun-exposed area) were determined by using a narrow-band reflectance spectrophotometer at baseline and after 12 months.

Results. Even though absolute values of baseline and follow-up MI and EI of the three sites were comparable among the three groups, forehead MI and EI were significantly decreased after 12 months in the HDF group ($P < 0.05$). In addition, the change in forehead MI was significantly greater in the HDF than in the LF-HD group ($-1.0 \pm 2.4\%$ versus $0.3 \pm 1.6\%$, $P < 0.05$). Moreover, β_2-microglobulin reduction rates were negatively correlated with both changes in forehead MI ($P < 0.01$) and EI ($P < 0.05$).

Conclusions. Skin colour of sun-exposed areas was significantly decreased in ESRD patients receiving HDF therapy, suggesting that enhanced removal of MMW substances by convection may prevent or reduce hyperpigmentation in HD patients.

Keywords: β_2-microglobulin; haemodiafiltration; hyperpigmentation; low-flux haemodialysis; spectrophotometer

Introduction

Skin hyperpigmentation is a common finding in patients with end-stage renal disease (ESRD) [1–5]. Even though the precise pathophysiologic mechanisms of skin hyperpigmentation in ESRD patients have not been fully explored, the accumulation of middle-molecular-weight molecules, such as urochrome pigments, carotenoids and α- and β-melanocyte-stimulating hormone, is thought to play a role [6–11]. Because the clearance of middle-molecular-weight molecules is higher during high-flux haemodialysis (HF-HD) and haemodiafiltration (HDF) [12,13], it is likely that hyperpigmentation may be improved by these procedures; however, this possibility has not yet been investigated.

Although most previous studies examining skin pigmentation during dialysis were performed in haemodialysis patients treated with low-flux dialyzers [8–10,14,15], some recent studies have examined skin colour in ESRD patients receiving HF-HD or HDF. Lin *et al*. [16] demonstrated an improvement in skin pigmentation in ESRD patients after the frequency of on-line HDF had been increased; however, skin colour was not measured using objective methods. Although a study by Lai *et al*. [17] included patients receiving HF-HD and HDF, they performed only a cross-sectional measurement of skin colour. Even though peritoneal dialysis (PD) is known to more effectively clear middle-molecular-weight uraemic toxins, they failed to find any difference in skin colour between HD and PD patients.

Since visual evaluation of skin colour is highly subjective and is influenced by ambient light, an objective measurement is necessary to accurately determine changes in skin colour [18]. In this prospective study, we compared changes in skin colour, determined by a narrow-band reflectance spectrophotometer, among patients receiving different modalities of haemodialysis.

Methods

Subjects

We recruited stable ESRD patients on maintenance HD at Yonsei University Health System, Seoul, Korea. Inclusion criteria were patients between 18 and 80 years of age who had been on three times weekly HD for at least 6 months. We excluded patients with any of the following: signs of acute illness; pre-existing skin disorders; history of taking potentially depigmenting or hyperpigmenting drugs [19]; history of cosmetic procedures; average haematocrit levels <27%; jaundice; or average ferritin levels >800 ng/mL.

The three groups of patients included those on low-flux haemodialysis (LF-HD), HF-HD and on-line HDF. Patients receiving HF-HD and HDF were switched from LF-HD within 3 months before inclusion. LF-HD patients received dialysis with a Fresenius 5008 dialysis system (Fresenius Medical Care, Bad Homburg, Germany) using a dialyser containing a polyamide blend membrane (Polyflux 17L®, Gambro, Hechingen, Germany). HF-HD and HDF were performed three times a week with the same machine using a polyamide blend or a polysulfone membrane dialyzer (Polyflux 17S®, Gambro; FX50®, FX60®, FX80®, or HF80S®, Fresenius Medical Care). Standard bicarbonate-based dialysates with ultrapure water were used for all patients, and treatment times were individualized for each patient and left unchanged throughout the study.

Biochemical and haematologic tests were performed monthly at midweek before the dialysis session, and the mean values during the 12-month study period were calculated for each patient. The serum concentrations of high-sensitivity CRP (hsCRP) were determined by the latex-enhanced immunonephelometric method every 3 months, and the mean values during the 12-month study period were used for analysis. Hepatitis B virus surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV) were checked every 6 months. At the end of the study, serum β_2-microglobulin (β_2-MG) concentrations were determined by an automated immunochemical analyser (PAMIA-40i, Sysmex Corp., Kobe, Japan) both before and after the midweek dialysis session. Post-dialysis β_2-MG levels were expressed after correcting for haemoconcentration as previously described [20]. β_2-MG reduction rates (β_2-MG RR), based on pre- and post-dialysis β_2-MG concentrations, were calculated as follows:

$$\beta_2\text{-MG RR}(\%) = [(\text{Pre-dialysis } \beta_2\text{-MG} - \text{Post-dialysis } \beta_2\text{-MG})/\text{Pre-dialysis } \beta_2\text{-MG}] \times 100.$$

Skin colour measurements

Skin colour was assessed using a narrow-band reflectance spectrophotometer (Mexameter MX16, Courage-Khazaka Electronic, Köln, Germany) that emits light at three defined wavelengths [568 nm (green), 660 nm (red) and 880 nm (infrared)] and measures absorbed and reflected light at wavelengths for haemoglobin (green and red) and melanin (red and near-infrared) [21]. The melanin index was automatically computed from the intensities of absorbed and reflected light at 660 and 880 nm, respectively, while the erythema index was computed from the intensities of absorbed and reflected light at 568 and 660 nm, respectively. Mexameter readings ranged from 1 to 1000, with higher melanin and erythema indices representing darker and more erythematous skin, respectively.

Skin colour measurements were performed according to manufacturer instructions by the same physician just before the midweek dialysis session at the start of the study (October 2006) and after 12 months (October 2007). These measurements were taken at three skin sites: the abdomen, the flexor side of the forearm (non-sun-exposed) and the forehead (sun-exposed). For each site, five measurements were carried out and the mean value was used for analysis.

This study was approved by the Institutional Review Board for Human Research at Yonsei University College of Medicine, and informed consent was obtained from all patients.

Statistical analysis

All values are expressed as means ± standard deviations (SD) or percentages. Statistical analysis was performed using SPSS for Windows Version 13.0 (SPSS, Inc., Chicago, IL, USA). Results were analysed using appropriate ANOVA, paired *t*-tests or chi-square tests. Significant differences found by ANOVA were further confirmed by Student's *t*-test with the Bonferroni correction. Correlations between changes in the melanin and erythema indices and β_2-MG RR were determined by Pearson's correlation analysis, and independent factors associated with the changes in the melanin index were determined by multiple linear regression analysis and multivariate logistic regression analysis. *P*-values <0.05 were considered to be statistically significant.

Results

Demographic characteristics and laboratory findings

We analysed data from 82 ESRD patients (Figure 1). The mean age of the patients was 56.0 ± 12.6 years and the sex ratio (M:F) was 0.8:1. The mean dialysis duration was 65.9 ± 48.3 months. The LF-HD group included 26 patients, the HF-HD group had 29 patients and the HDF group had 27 patients. Dialysis duration in the HDF group (73.4 ± 52.4 months) tended to be longer than in the LF-HD (59.7 ± 34.2 months) and HF-HD (65.0 ± 59.4 months) groups, but this difference was not significant. There were no differences in the mean age, sex ratio, underlying disease of ESRD or the proportion of patients with positive HBsAg or anti-HCV among the three groups. The mean haemoglobin levels, serum calcium and phosphorus concentrations,

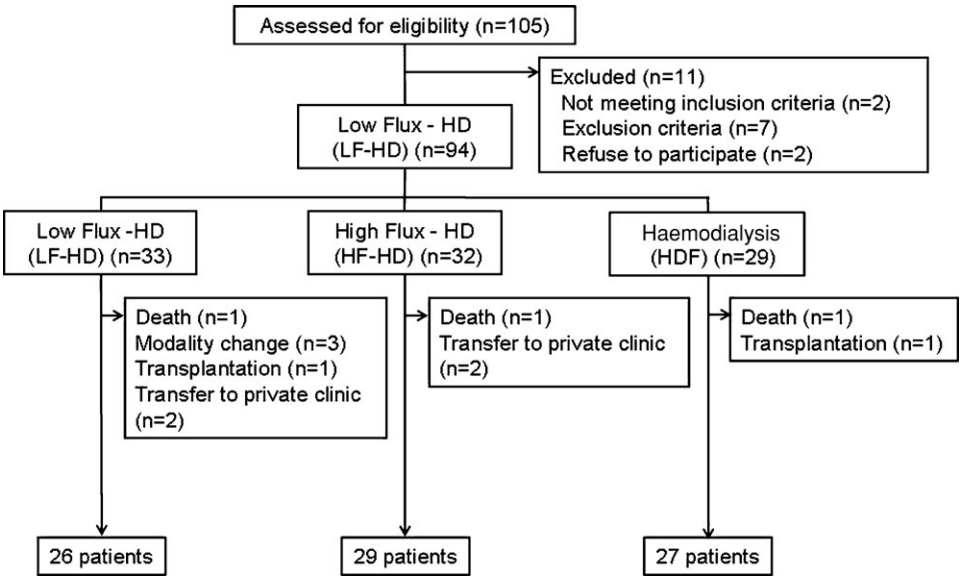

Fig. 1. Participant flow chart.

Table 1. Clinical characteristics and laboratory findings of the patients

	LF-HD ($n = 26$)	HF-HD ($n = 29$)	HDF ($n = 27$)
Age (years)	59.4 ± 13.5	56.1 ± 15.0	57.6 ± 7.3
Sex (M:F)	12:14	12:17	13:14
Haemodialysis duration (months)	59.7 ± 24.2	65.0 ± 59.4	73.4 ± 52.4
Hepatitis (B or C virus)	4 (15.4%)	3 (10.3%)	5 (18.5%)
Cause of ESRD			
Diabetic nephropathy	15 (57.7%)	15 (51.7%)	13(48.1%)
Chronic glomerulonephritis	4 (15.4%)	4 (13.8%)	4 (14.8%)
Hypertensive nephrosclerosis	1 (3.8%)	2 (6.9%)	3 (11.1%)
Polycystic kidney disease	0 (0.0%)	2 (6.9%)	2 (7.4%)
Others/causes unknown	6 (23.1%)	6 (20.7%)	5 (18.5%)
Kt/V urea	1.6 ± 0.2	1.6 ± 0.3	1.7 ± 0.3
Haemoglobin (g/dL)	10.4 ± 1.1	10.5 ± 1.1	10.7 ± 1.3
Calcium (mg/dL)	8.9 ± 0.9	9.0 ± 0.7	8.8 ± 0.8
Phosphorus (mg/dL)	5.2 ± 1.1	4.6 ± 1.3	5.1 ± 1.2
Albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.4	4.2 ± 0.4
Total bilirubin (mg/dL)	0.4 ± 0.3	0.3 ± 0.1	0.4 ± 0.1
Ferritin (ng/mL)	248.8 ± 137.4	195.4 ± 142.5	237.9 ± 135.1
hsCRP (mg/L)	4.71 ± 2.71	5.20 ± 2.65	4.45 ± 2.09

Values are means ± SD or numbers (percent).
LF-HD, low-flux haemodialysis; HF-HD, high-flux haemodialysis; HDF, haemodiafiltration; hsCRP, high sensitivity C-reactive protein.

serum albumin, total bilirubin, ferritin and hsCRP levels were also comparable (Table 1). In addition, there were no differences in these values at the start and at the end of the study among the three groups (data not shown).

Skin colour measurements

As seen in Table 2, there were no differences in baseline melanin and erythema indices of the abdomen, forearm or forehead among the three groups, and the absolute values of these indices after 12 months were also comparable. However, in the HDF group, melanin and erythema indices of the forehead were significantly decreased after 12 months compared with baseline values ($P < 0.05$). In addition, changes

Table 2. Baseline and follow-up melanin and erythema indices of the patients

	LF-HD	HF-HD	HDF
Baseline melanin index			
Forehead	498.5 ± 18.4	500.6 ± 23.8	500.2 ± 27.2
Forearm	489.8 ± 15.7	487.3 ± 16.9	493.3 ± 22.6
Abdomen	469.3 ± 20.0	474.3 ± 18.2	474.1 ± 23.7
Melanin index after 12 months			
Forehead	500.1 ± 18.7	497.4 ± 17.3	495.1 ± 21.9*
Forearm	487.5 ± 16.5	487.7 ± 16.7	490.0 ± 17.3
Abdomen	471.2 ± 22.1	474.0 ± 16.9	475.1 ± 22.4
Changes in the melanin index (%)			
Forehead	0.3 ± 1.6	−0.6 ± 2.6	−1.0 ± 2.4#
Forearm	−0.4 ± 2.5	−0.1 ± 2.0	−0.6 ± 1.8
Abdomen	0.4 ± 2.7	−0.1 ± 2.0	0.5 ± 2.4
Baseline erythema index			
Forehead	610.1 ± 24.9	613.8 ± 22.8	614.7 ± 26.4
Forearm	587.0 ± 17.6	586.2 ± 23.5	589.5 ± 23.6
Abdomen	571.7 ± 14.4	575.8 ± 20.9	572.2 ± 32.2
Erythema index after 12 months			
Forehead	609.0 ± 23.3	608.8 ± 18.4	604.7 ± 23.4*
Forearm	584.6 ± 12.7	587.6 ± 17.7	586.6 ± 19.5
Abdomen	569.5 ± 15.3	573.1 ± 17.3	573.6 ± 16.1
Changes in the erythema index (%)			
Forehead	−0.1 ± 2.5	−0.8 ± 2.4	−1.6 ± 2.5#
Forearm	−0.4 ± 1.9	0.0 ± 2.6	−0.4 ± 3.2
Abdomen	−0.4 ± 1.8	−0.4 ± 2.5	0.4 ± 5.5

Values are means ± SD.
LF-HD, low-flux haemodialysis; HF-HD, high-flux haemodialysis; HDF, haemodiafiltration.
*$P < 0.05$ versus baseline; #$P < 0.05$ versus LF-HD.

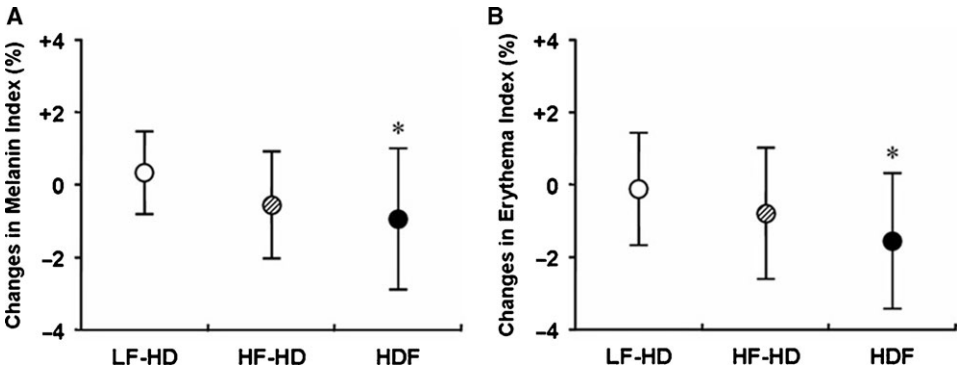

Fig. 2. Changes in melanin (**A**) and erythema indices (**B**) of the forehead in the LF-HD, HF-HD and HDF groups. Compared to the LF-HD group, changes in melanin and erythema indices were significantly lower in HDF patients. Changes in the forehead melanin and erythema indices in the HF-HD group were intermediate. $^{*}P < 0.05$ versus the LF-HD group.

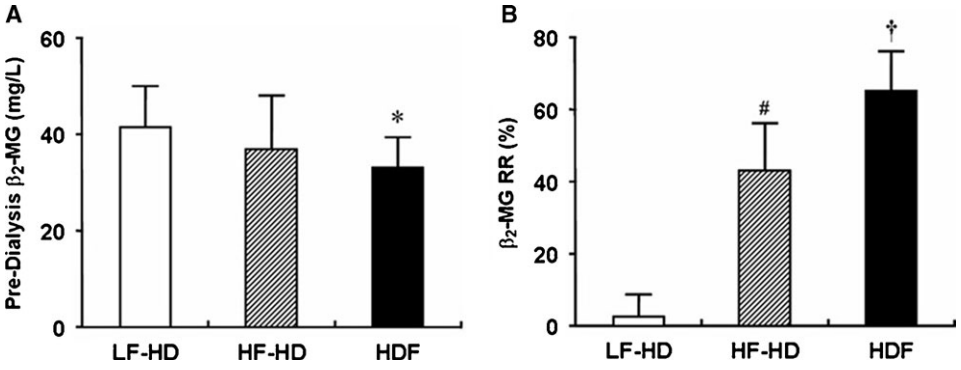

Fig. 3. Pre-dialysis β_2-microglobulin (MG) concentrations (**A**) and β_2-MG reduction rates (RR) (**B**) in the LF-HD, HF-HD and HDF groups. Pre-dialysis β_2-MG concentrations were significantly lower in the HDF group relative to the LF-HD group. In contrast, β2-MG RR was significantly higher in the HDF group than in the HF-HD and LF-HD groups. $^{*}P < 0.01$ versus the LF-HD group; $^{\#}P < 0.005$ versus other groups; $^{\dagger}P < 0.0001$ versus the LF-HD group.

in the forehead melanin index were significantly greater in HDF than in LF-HD patients ($-1.0 \pm 2.4\%$ versus $0.3 \pm 1.6\%$, $P < 0.05$). After 12 months, the erythema index of the forehead showed a decrease from baseline in all three groups, and this decrease was significantly greater in the HDF group ($-1.6 \pm 2.5\%$) than in the LF-HD group ($-0.1 \pm 2.5\%$) ($P < 0.05$). Changes in the melanin and erythema indices of the forehead in the HF-HD group were intermediate (Figure 2).

We found no differences in melanin and erythema indices of abdomen and forearm among the three groups.

Pre-dialysis β_2-MG concentrations and β_2-MG RR

Pre-dialysis β_2-MG concentrations were significantly higher in the LF-HD group (41.5 ± 8.5 mg/L) than in the HDF group (33.2 ± 6.3 mg/L) ($P < 0.01$). In contrast, β_2-MG RR was higher in the HDF ($65.1 \pm 11.2\%$) group than in the HF-HD ($42.9 \pm 13.1\%$) ($P < 0.005$) and LF-HD groups ($2.5 \pm 5.1\%$) ($P < 0.0001$) (Figure 3).

Correlations between changes in melanin and erythema indices and β_2-MG RR

Pearson's correlation analysis revealed that there were significant negative correlations between the changes in the melanin and erythema indices of the forehead and β_2-MG RR (melanin index, $R = -0.348$, $P < 0.01$; erythema index, $R = -0.265$, $P < 0.05$) (Figure 4). In contrast, changes in melanin and erythema indices of the abdomen and forearm did not correlate with β_2-MG RR (data not shown). There were no correlations between changes in skin colour and patient age, dialysis duration, serum albumin, or hsCRP levels.

Independent factors associated with changes in the forehead melanin index

Multiple linear regression and multivariate logistic regression analyses were performed to identify the independent factors associated with the change in the forehead melanin index. During initial analysis, multiple linear regression analysis revealed that both HF-HD ($P < 0.05$) and HDF ($P < 0.005$) were independently associated with changes in the forehead melanin index, while the presence of hepatitis B or C, sex, age, dialysis duration, serum albumin and hsCRP levels had no effect on the changes in the forehead melanin index (Table 3). Patients were then divided into two groups for multivariate logistic regression analysis: Group 1 consisted of patients with an increased melanin index after 12 months and Group 2 included patients with a decreased melanin index after 12 months. This

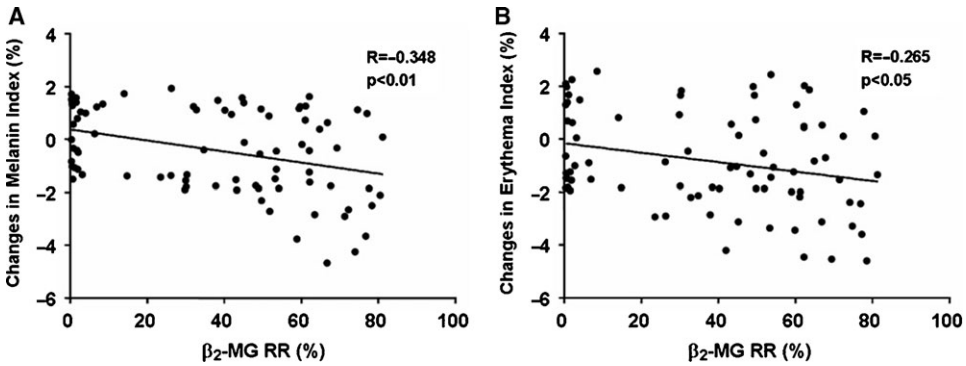

Fig. 4. Correlations between changes in the forehead melanin (**A**) and erythema (**B**) indices and β2-microglobulin reduction rates (β2-MG RR). Pearson's correlation analysis revealed significant negative correlations between the changes in the melanin and erythema indices and the β2-MG RR.

Table 3. Multiple linear regression of independent factors associated with changes in the forehead melanin index

	β	*P*-value	R^2
Dialysis modality			
HF-HD (versus LF-HD)	−1.077	<0.05	
HDF (versus LF-HD)	−1.603	<0.005	
Presence of hepatitis B or C	−0.228	0.648	
Sex (versus male)	−0.606	0.092	0.193
Age (per year)	−0.024	0.104	
Dialysis duration (per month)	0.001	0.775	
Albumin (per g/dL)	−0.065	0.897	
hsCRP (per mg/L)	0.022	0.282	

LF-HD, low-flux haemodialysis; HF-HD, high-flux haemodialysis; HDF, haemodiafiltration; hsCRP, high sensitivity C-reactive protein.

Table 4. Multivariate logistic regression of factors associated with decreases in the forehead melanin index

	OR	95% CI	*P*-value
Dialysis modality			
HF-HD (versus LF-HD)	3.18	0.84–12.05	0.084
HDF (versus LF-HD)	3.60	1.11–11.64	<0.05
Presence of hepatitis B or C	1.14	0.29–4.36	0.85
Sex (versus male)	0.81	0.31–2.10	0.65
Age (per year)	1.02	0.98–1.06	0.37
Dialysis duration (per month)	1.00	0.99–1.01	0.78
Albumin (per g/dL)	1.19	0.29–4.94	0.81
hsCRP (per mg/L)	1.04	0.59–1.81	0.90

LF-HD, low-flux haemodialysis; HF-HD, high-flux haemodialysis; HDF, haemodiafiltration; hsCRP, high sensitivity C-reactive protein; CI, confidence interval; OR, odds ratio.

analysis showed that decreases in the forehead melanin index were associated with dialysis modality but not with the presence of hepatitis B or C, sex, age, dialysis duration, serum albumin or hsCRP levels (Table 4).

Discussion

Skin hyperpigmentation is a common clinical finding in ESRD patients undergoing dialysis [1–5] and can lead to cosmetic and psychological concerns [22,23]. Retention of middle-molecular-weight molecules, such as urochromic pigments, carotenoids and α- and β-melanocyte-stimulating hormone, has been implicated in the pathogenesis of diffuse pigmentation in ESRD patients [6–11]. However, changes in skin colour have been largely unexplored in patients on HDF, in whom middle-molecular-weight molecular clearance is significantly higher compared to conventional LF-HD [12,13]. In this study, we demonstrated for the first time that hyperpigmentation was significantly improved in patients on HDF, whereas skin colour was not altered in LF-HD patients. These findings indicate that enhanced removal of middle-molecular-weight substances by convective therapy may reduce skin hyperpigmentation in ESRD patients.

Most prior investigations examining skin colour during ESRD were observational studies in patients on LF-HD, and these demonstrated that skin colour was significantly darker in dialysis patients compared to controls [8–10,14,15]. In contrast, skin colour in patients treated with HF-HD, HDF and PD, which are known to be more effective in removing middle-molecular-weight uraemic toxins, has been largely unexplored. Lin *et al*. [16] examined changes in skin colour in 111 ESRD patients and observed less hyperpigmentation during increased frequency of on-line HDF; however, they did not measure skin colour using objective methods. Recently, Lai *et al*. [17] evaluated the skin colour of the abdomen (non-sun-exposed site) and the forearm (sun-exposed site) in 59 healthy controls, in 51 patients on HD (including HF-HD and HDF) and in 73 PD patients by using a reflected-light colorimeter. Skin colour in the non-sun-exposed area was significantly darker in patients with ESRD compared to controls, while skin brightness in sun-exposed sites was not different between ESRD patients and controls. In addition, HD and PD patients had similar skin colour in both non-sun-exposed and sun-exposed skin areas. Even though skin colour was quantified objectively in this cross-sectional observational study, the authors did not examine changes in skin colour according to the modality of dialysis.

The present study is the first to prospectively investigate the impact of dialysis modality on skin colour in HD patients. In May 2006, a new HD centre at Yonsei University Health System was opened with new HD machines, which made the present investigation possible. The

patients in our study, however, could not be randomized due to the 25% higher cost of HF-HD and HDF treatments (compared to LF-HD). In spite of this, we found no significant differences in baseline demographic characteristics or laboratory findings among the three groups and found that the baseline melanin and erythema indices were also comparable. During the study period, we found that the melanin index of the forehead significantly decreased in patients undergoing HDF. In addition, HDF patients had a significantly greater percentage change (decrease) in the forehead melanin index than HDF and LF-HD patients, whereas the indices of the non-sun-exposed sites were comparable between the two groups. Moreover, there was a significant negative correlation between the changes in melanin and erythema indices and the β_2-MG RR, which represents middle-molecular-weight molecular clearance, while the changes in skin colour on the abdomen and forearm did not correlate with the β_2-MG RR. Based on these findings, we suggest that some middle-molecular-weight uraemic substances, which can largely be removed by HDF, may stimulate melanogenesis under sunlight, whereas hyperpigmentation of non-sun exposed areas may be largely attributed to certain large-molecular-weight substances, such as protein-bound 3,4-dihydroxyphenylalanine (PB-DOPA) and PB-5-S-cysteinyldopa (PB-5SCD).

In the current study, baseline skin colour was comparable among the three groups even though initial dialysis duration was slightly longer in the HDF group than in the other groups. In addition, dialysis duration did not affect the changes in the forehead melanin index as assessed by multiple linear regression and multivariate logistic regression analyses. These results are in accordance with most previous studies that have shown that there is no significant correlation between dialysis duration and skin hyperpigmentation in ESRD patients [15,17]. In contrast, a recent study demonstrated that serum levels of free 5SCD, one of the markers of pigmentation, were positively correlated with the duration of HD treatment, suggesting that skin colour may become darker in ESRD patients with increasing dialysis duration [24]. However, serum-free 5SCD levels in that study were significantly decreased to one-fourth of baseline values during each 4-h HD session. Furthermore, there were no significant correlations between HD duration and the serum levels of other pigmentation markers, such as pheomelanin, PB-DOPA and PB-5SCD. Therefore, further study will be needed to clarify whether free 5SCD is responsible for skin hyperpigmentation in patients on HD. As an additional mechanism, Takiwaki *et al*. [25] demonstrated that topical anti-inflammatory agents inhibited ultraviolet B-induced erythema and pigmentation, implicating inflammation in the pathogenesis of hyperpigmentation. We therefore determined whether inflammation status had an effect on skin hyperpigmentation in our HD patients. Serum albumin and hsCRP levels were used as markers of inflammation and were included in the analyses. Pearson's correlation analysis revealed that there were no significant correlations between changes in skin colour and serum albumin and hsCRP levels. In addition, albumin and hsCRP were not independently associated with changes in skin colour. Based on these findings, we suggest that systemic inflammation may have little effect on skin hyperpigmentation in uraemic patients.

In conclusion, hyperpigmentation in sun-exposed areas was significantly improved in ESRD patients receiving HDF therapy, suggesting that enhanced removal of middle-molecular-weight substances by convection may prevent or reduce skin hyperpigmentation in dialysis patients.

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Conflict of interest statement. None declared.

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Prescription of antihypertensive agents to haemodialysis patients: time trends and associations with patient characteristics, country and survival in the DOPPS

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Abstract

Background. Haemodialysis patients were studied in 12 countries to identify practice patterns of prescription of antihypertensive agents (AHA) associated with survival.

Methods. The sample included 28 513 patients enrolled in DOPPS I and II. The classes of AHA studied were beta blocker (BB), angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), peripheral blocker, central antagonist, vasodilator, long-acting dihydropyridine calcium channel blocker (CCB), short-acting dihydropyridine CCB and non-dihydropyridine CCB. To reduce bias due to unmeasured confounders, the associations with mortality were assessed by separate Cox models based on patient-level prescription and facility prescription practice.

Results. An increase in prescription of ARBs (9.5%) and BBs (9.1%) was observed from DOPPS I to II. Prescription of AHA classes varied significantly by country, ranging for BBs from 9.7% in Japan to 52.7% in Sweden and for ARBs from 5.5% in Italy to 21.3% in Japan in DOPPS II. Facilities that treated 10% more patients with ARBs had, on average, 7% lower all-cause mortality, independent of patient characteristics and the prescription patterns of other antihypertensive medications ($P = 0.05$). Significant and independent associations with reduction in cardiovascular mortality were observed for ARBs (RR = 0.79; $P = 0.005$) and BBs (RR = 0.87, $P = 0.004$) in analyses of patient-level prescriptions. These associations in the facility-level model followed the same direction.

Conclusions. DOPPS data show large variations across countries in AHA prescription for haemodialysis patients.