Letter to the Editor

Oxidized HDL status in hemodialysis patients with peripheral arterial disease: a pilot study

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Kidney failure, an end-stage kidney disease, is commonly treated with hemodialysis (HD) [1]. This condition presents a high risk for developing atherosclerotic disease; for instance, over 20% of HD patients have peripheral arterial disease (PAD), which is characterized by chronic peripheral ischemia, and it can increase atherosclerosis-related mortality [2]. Understanding the pathophysiology and treatment of PAD is therefore required for HD. The exploration of the markers related to PAD is a strategy that is currently under investigation.

Blood markers of lipids and lipoproteins are candidates for risk assessment in HD patients with PAD. High-density lipoprotein (HDL) is known to have anti-atherosclerotic properties [3]. In a previous report [2], a low level of HDL cholesterol (HDL-C) was suggested to be a useful marker for PAD in HD patients. In addition, oxidative stress is reportedly involved in PAD [4, 5]. Recently, the dysfunction of HDL due to oxidative modification has received special attention in the development of atherosclerosis [3]. The relationship between oxidatively modified HDL and PAD is still unclear. As a result, a pilot study was conducted to investigate this relationship in HD patients.

A total of 52 patients (mean age = 64 [standard deviation (SD) = 11] years; male, n = 37) on maintenance HD (approximately three HD sessions per week) were enrolled in a clinic for HD. In serum samples before the HD session, the lipids were enzymatically measured, and oxidized HDL (oxHDL) was measured using an enzyme-linked immunosorbent assay (Hoken-Kagaku West, Co. Ltd., Kyoto, Japan) [3]. In the present study, the ratio of oxHDL to HDL-C, expressed as oxHDL/HDL-C, was applied because this ratio is proposed to emphasize the qualitative relevance of HDL, as HDL-C is a quantitative marker [3]. PAD was diagnosed in cases with an ankle-brachial index of < 0.9 using an oscillometric measurement device to compare blood pressure in the ankles to the arms (Fukuda Colin Co. Ltd., Tokyo, Japan) [2]. Information on smoking and diabetes mellitus history was obtained from medical charts. The Ethics Committee approved the study, and informed consent was obtained from all patients.

A t-test and χ^2 or Fisher's exact test were performed to compare the data between the patient groups with and without PAD. A general lin-

Table I. Clinical profiles of study patients

Variables	All (n = 52)	Non-PAD (n = 41)	PAD (n = 11)	P-value
Age [years]	64 ±11	64 ±12	63 ±11	0.78
Men/women [n]	37/15	31 10	6 5	0.85
Smoking history [%]	27 (52%)	21 (51%)	6 (55%)	0.99
Diabetes mellitus [%]	30 (58%)	22 (54%)	8 (73%)	0.32
Total cholesterol [mg/dl]	171 ±35	165 ±32	191 ±39	0.03
Triglycerides [mg/dl]	111 (81–192)	106 (80–163)	163 (107–214)	0.13
HDL-C [mg/dl]	46 ±14	47 ±14	43 ±11	0.19
OxHDL [U/ml]	818 (649–1073)	793 (650–1049)	943 (642–1362)	0.08
OxHDL/HDL-C ratio	18 (14–24)	17 (14–22)	22 (16–37)	0.02

PAD – peripheral arterial disease, HDL – high-density lipoprotein, OxHDL – oxidized HDL. Data are shown as the mean ± standard deviation, median (interquartile range), or subject number (%). The values of triglycerides, oxHDL, and oxHDL/HDL-C were analyzed after log-transformation because of their skewed distribution. Significance (non-PAD vs. PAD): P < 0.05.

ear analysis of oxHDL/HDL-C, after adjusting for variables, was also performed. Skewed variables were log-transformed. $P < 0.05$ was considered significant.

The clinical profiles of patients are shown in Table I. The present study included 11 patients with PAD and 41 without PAD, which were not significantly different in terms of age and sex distribution. Patients with PAD exhibited higher levels of total cholesterol than those without PAD. Patients with PAD exhibited non-significantly lower levels of HDL-C and non-significantly higher levels of oxHDL compared to those without PAD. Patients with PAD exhibited significantly higher oxHDL/HDL-C than those without PAD.

The difference in oxHDL/HDL-C between the patients with and without PAD remained significant after adjusting for age and sex ($p = 0.02$), age and sex plus smoking and diabetes mellitus history ($p = 0.02$), as well as age and sex plus levels of total cholesterol and triglycerides ($p = 0.02$).

In the present study, the levels of oxHDL/HDL-C were higher in HD patients with PAD than in those without PAD. This suggests that oxidative modification of HDL, as an aspect of HDL dysfunction, could contribute to PAD in HD. Oxidative modification of HDL might thus be a target of study for pathophysiological and therapeutic strategies in this population.

Vascular impairment of hemodynamics in PAD includes a lack of nitric oxide synthesis for vasodilation and damage of antioxidant defense systems in the bloodstream and arteries, which is associated with the production of reactive oxygen and nitrogen species [4, 5]. Such species lead to the oxidation of lipid and protein biomolecules [4, 5]. In addition, a low level of HDL-C was previously reported to be observed in PAD in HD patients (as was also observed in the present study, although it was not significant), while it is unclear whether the phenomenon is a cause or effect (e.g., less HDL-C is produced or more is consumed in PAD) [2]. Thus, previous knowledge of the presence of oxidative stress and the low level of HDL-C [2, 4, 5] may partially explain the high oxHDL/HDL-C observed in the present study in HD patients with PAD.

The present study has some limitations. The sample size was relatively small. The study was based on a cross-sectional design, in which causality was not completely determined. A comparison of results may be required using other markers related to oxidative stress, such as malondialdehyde and isoprostanes [5]. This was a pilot study, and these limitations will be addressed in the next step of our investigation.

In conclusion, there was a high level of oxHDL/HDL-C in HD patients with PAD. This suggests the possible contribution of oxidative modification of HDL to the development of PAD in HD. The clinical implications of these findings should be confirmed in the future.

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Ethical approval

Approval number: No. 23-R15.

Conflict of interest

The authors declare no conflict of interest.

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