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HDL cholesterol as a predictor for the incidence of lower extremity amputation and wound-related death in patients with diabetic foot ulcers

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ABSTRACT

Objective: We examined whether HDL cholesterol levels are a predictor for an incidence of lower-extremity amputation (LEA) and wound-related death in patients with diabetic foot ulcers (DFUs).
Research design and methods: This was a single-center, observational, longitudinal historical cohort study of 163 Japanese ambulatory patients with DFUs, 45 woman and 118 men, with a mean (standard deviation) age of 62 (14) years. The primary composite endpoint was defined as the worst of the following outcomes for each individual; (1) minor amputation, defined as amputation below the ankle, (2) major amputation, defined as amputation above the ankle, and (3) wound-related death.
Results: During the median follow-up period of 5.1 months, 67 patients (41.1%) reached the endpoint (43 minor amputations, 16 major amputations, and 8 wound-related deaths). In the univariate Cox proportional hazard model analysis, lower HDL cholesterol levels (mmol/L) were significantly associated with the incidence of the primary composite endpoint (hazard ratio 0.16 [95% CI 0.08–0.32], $p < 0.001$). In the multivariate Cox proportional hazard model analysis using a stepwise variable-selecting procedure, HDL cholesterol levels in addition to the presence of ankle brachial index <0.9 or ≥1.4 and serum albumin levels were selected as independent risk factors for the incidence of the endpoint (hazard ratio 0.30 [95% CI 0.14–0.63], $p = 0.002$). Similar results were obtained when HDL cholesterol levels were treated as a categorical variable (≥1.03 mmol/L or less).
Conclusions: HDL cholesterol levels might be a novel clinical predictor for the incidence of LEA and wound-related death in patients with DFUs.

1. Introduction

Lower-extremity amputation (LEA) is one of the most feared diabetic complications because of its impact on health and quality of life. Furthermore, mortality after LEA is extremely high [1,2]. Diabetic foot ulcers (DFUs) precede most of non-traumatic LEA [3], and patients with diabetes have been shown to have a 15–25% chance of developing DFUs during their lifetime [4,5], which implies that foot ulcers are a great risk factor for LEA as well as a common complication in these patients. Currently, optimized vascular supply, appropriate plantar pressure redistribution, and infection control and treatment are needed for the management of DFUs [6]; however, the mechanism and predictors for developing LEA in patients with DFUs are not fully understood, and DFUs are still difficult to treat.

HDL has pleiotropic effects such as anti-oxidant and anti-inflammatory properties in addition to promoting the efflux of cholesterol from cells [7,8]. Previous reports have clearly shown that in patients with diabetes, lower HDL cholesterol levels were associated with the development of chronic complication such as kidney disease and cardiovascular disease [9–11]. In addition, HDL has a pivotal role in the host defenses as the innate immune system [12], and the association of HDL with the pathogenesis of acute-phase response such as infections and sepsis has received much attention [13]. An earlier study of patients with sepsis has shown an association between lower HDL cholesterol levels and their mortality [14]. Furthermore, other clinical studies have shown that lower HDL cholesterol levels were associated with the development of in-hospital infections [15,16]. Here, we aimed to examine

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the hypothesis that HDL cholesterol levels are a predictor for the incidence of LEA and wound-related death in patients with DFUs.

2. Materials and methods

2.1. Study design and participants

This was a hospital-based, single-center, observational, longitudinal cohort study using a historical cohort of adult Japanese ambulatory patients with DFUs. The present study was conducted in adherence to the Declaration of Helsinki and was approved by the ethics committee of Tokyo Women's Medical University Hospital. The present study used data from a clinical information system (electronic medical records). We recruited 177 consecutive patients with the chief complaint of DFU at the foot care unit in the Diabetes Center of Tokyo Women's Medical University Hospital in Tokyo, Japan, between January 2008 and September 2012. All patients were treated at our foot care unit during the study period. Patients with missing values for baseline profiles (n = 14) were excluded. Overall, a total of 163 patients were enrolled.

Blood sample data at baseline included serum lipids, creatinine, and plasma hemoglobin A1C (HbA1c) levels were determined when a patient first visited our foot care unit with the chief complaint of DFU. The severity of foot ulcers was classified according to the Wagner classification [17].

2.2. Measurements

HDL cholesterol levels were determined by polyethylene glycol-pretreated enzymes, triglycerides by enzymatic methods, and LDL cholesterol by enzymatic methods or Friedewald's equation (if triglycerides were <4.52 mmol/L). Serum creatinine was determined by enzymatic methods. HbA1c levels were measured by high-performance liquid chromatography (HPLC). HbA1c values measured using a set of calibrators assigned by the Japan Diabetes Society (JDS, normal range, 4.3–5.8%) were converted to the National Glycohemoglobin Standardization Program (NGSP)-equivalent values using the following equation: HbA1c (%) = 1.02 × HbA1c (JDS) (%) + 0.25% [18]. Glomerular filtration rate (GFR) was estimated using the following modified three-variable equation, as proposed by the Japanese Society for Nephrology: eGFR (mL/min/1.73 m^2) = 194 × age (years)$^{-0.287}$ × serum creatinine level (in mg/dL)$^{-1.094}$ × (0.739 if female) [19].

2.3. Study endpoint

The worst of the following outcomes for each individual was defined as the primary composite endpoint; [1] minor amputation (defined as amputation below the ankle), [2] major amputation (defined as amputation above the ankle), or [3] wound-related death. Amputation was defined as a complete loss in the transverse plane of any part of the lower limb. Wound-related death was defined as a death with unhealed ulcers with or without any amputation.

2.4. Statistical analysis

Continuous variables were expressed as arithmetic mean ± standard deviation (SD), or geometric mean with 95% CI, as appropriate according to data distribution. Categorical data were expressed by number (%). In the univariate correlational analysis, Spearman rank-correlation coefficients were calculated. The cumulative incidence of the endpoint was estimated using the Kaplan–Meier method, and the statistical differences between the groups were compared by log-rank test. Hazard ratios were estimated using Cox proportional hazard model analysis. In the multivariate Cox proportional hazard model analysis, a stepwise variable-selecting procedure was performed, specifying the significant levels for entering another explanatory variable into the model as 0.05, and that for removing an explanatory variable from the model as 0.05, respectively. In addition to HDL cholesterol levels, the following variables were incorporated into the multivariate Cox proportional hazard model as independent variables; age, sex, body mass index, smoking status, serum albumin levels, HbA1c, logarithmically transformed triglycerides levels, LDL cholesterol levels, logarithmically transformed C-reactive protein levels, presence of renal dysfunction defined as eGFR <60 (mL/min/1.73 m^2) or dialysis, history of amputation, presence of ankle-brachial index (ABI) < 0.9 or ≥1.4. P values <0.05 were considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline demographic and clinical characteristics

Baseline clinical characteristics and laboratory data for all participants were presented in Table 1. There were 45 women and 118 men, with a mean (SD) age of 62 (14) years. Most patients had type 2 diabetes. 67 (41.1%) patients took drugs influencing HDL cholesterol levels. No patient took probucols. Patients with Wagner grade 4 or 5 had significantly lower HDL cholesterol levels than those with Wagner grade 1–3 ($p < 0.001$). In addition, HDL cholesterol levels had a strong inverse correlation with C-reactive protein levels ($rs = 0.521$, $p < 0.001$) and white blood cell counts ($rs = 0.407$, $p < 0.001$).

Table 1
Baseline demographic and laboratory data of 163 participants.

Age	62 ± 14 (years)
Men	118 (72.4)
Type 2 diabetes	147 (90.2)
Duration of diabetes	20 ± 11 (years)
BMI	24.1 ± 4.7 (kg/m^2)
Systolic blood pressure	134 ± 26 (mmHg)
Diastolic blood pressure	71 ± 17 (mmHg)
Smoking (current or ever)	102 (62.6)
Wagner grade 4 or 5	53 (32.5)
ABI < 0.9 or ≥ 1.4	68 (41.7)
History of lower limb revascularization	54 (33.1)
History of amputation	25 (15.3)
Ischemic heart disease	66 (40.5)
Cerebral vascular disease	34 (20.9)
Dialysis	55 (33.7)
Use of drugs influencing HDL cholesterol levels	
Pioglitazone	7 (4.3)
α-blocker or αβ-blocker	29 (17.8)
Statin, ezetimibe, fibrate or nicotinic acid	41 (25.2)
Laboratory data	
WBC count	11.1 ± 6.4 (× 10^9/L)
HbA1c	8.3 ± 2.4 (%)
Triglycerides	1.2 (1.1–1.2) (mmol/L)
HDL cholesterol	
Women	1.2 ± 0.5 (mmol/L)
Men	1.0 ± 0.4 (mmol/L)
LDL cholesterol	2.3 ± 0.7 (mmol/L)
Albumin	32.1 ± 7.5 (g/L)
Creatinine (non-dialysis patients)	110.0 ± 89.3 (umol/L)
eGFR (non-dialysis patients)	64.3 ± 35.1 (mL/min/1.73 m^2)
C-reactive protein	3.8 (3.0–4.9) (mg/dL)

Data are expressed as number (%), mean ± SD, or geometric mean (95% confidence interval). Abbreviations: BMI: body mass index, ABI: ankle-brachial index, WBC: white blood cell, HbA1c: hemoglobin A1C, eGFR: estimated glomerular filtration rate, SD: standard deviation.