Association of high-density lipoprotein cholesterol and wound healing in patients with diabetic foot ulcers

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To the Editor: Diabetic foot ulcers (DFUs) are an important cause of morbidity in patients with diabetes mellitus (DM). The prevalence of foot ulcers in patients with diabetes is 4% to 10%, with the lifetime incidence estimated to be between 19% and 34%.[1] DFUs have become a considerable burden on patients and the healthcare service system. However, the mechanism is not fully understood, and DFUs are still difficult to heal.

High-density lipoproteins (HDL) are circulating particles composed of phospholipids, cholesterol, and proteins. HDL attracted lots of attention mainly because of its protective effect against the development of atherosclerosis. However, it has been shown that decreased HDL levels are correlated with an increased risk of DM and its complications. The association of HDL with DFUs has also received much attention. Lower levels of HDL cholesterol were associated with increased risk for foot ulceration in patients with diabetes (odds ratio 0.427, 95% confidence interval [CI] 0.228–0.799, $P = 0.008$).[2] HDL cholesterol levels were also revealed to be an independent risk factor of lower-extremity amputation and wound-related death in patients with DFUs (hazard ratio [HR] 0.30, 95% CI 0.14–0.63, $P = 0.002$). Therefore, there might be a potential correlation between HDL and wound healing. The objective of this study was to evaluate the association between HDL levels and wound healing.

This was an observational study in the Department of Diabetic Foot Care Center of West China Hospital. Adult patients with a diagnosis of DFUs were eligible for participation. All ulcers corresponded to Wagner grade between 2 and 4. Exclusion criteria included: (1) non-diabetic ulcers, such as malignant ulcers, ulcerated tophaceous gout, and ulcers associated with cryoglobulinemia, (2) active medical diseases, such as diabetic ketoacidosis, hyperosmolar hyperglycemic state, uncontrolled severe systemic infection, advanced cirrhosis, advanced kidney disease, and refractory psychiatric disease, (3) patients being treated with corticosteroids, immunosuppressive drugs, or chemotherapy. The Biomedical Research Ethics Committee of West China Hospital of Sichuan University approved the study (No. IRB 2018-542). Written informed consent was waived.

We enrolled 167 patients between July 2013 and June 2019. All patients received metabolic control, treatment of comorbidities, and associated risk factors including smoking, hypertension, and dyslipidemia. With regard to wound management, interventions included treatment of infection when necessary, local wound care (such as offloading, debridement, negative pressure wound therapy, and autologous platelet-rich gel), and surgery (such as amputation and endovascular intervention), adhering to standardized guidelines at the discretion of the attending clinician. All patients were followed for 12 weeks. The primary outcome was time to healing.

Statistical analysis was performed with Stata version 13 (StataCorp LP, College Station, TX, USA). A P value < 0.05 was considered statistically significant. We summarized data as either the number of patients (%), mean (standard deviation [SD]), or median (interquartile range [IQR]). Between-group comparisons were conducted using Student's t test, Mann-Whitney test, and Chi-square test. The association of HDL cholesterol levels with wound healing within 12 weeks was assessed. Kaplan-Meier curves for wound healing were examined by HDL cholesterol levels (cutoff: 1.03 mmol/L), and the statistical differences between the groups were compared using log-rank test. Unadjusted and adjusted Cox regression models were used to test whether HDL cholesterol levels were associated with wound healing. HDL cholesterol was treated as a categorical variable and continuous variable (per SD, per 0.13 mmol/L, and per quartile) to evaluate the robustness of the association.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001544

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Chinese Medical Journal 2022;135(1)

Received: 22-12-2020; **Online:** 04-05-2021 **Edited by:** Lishao Guo

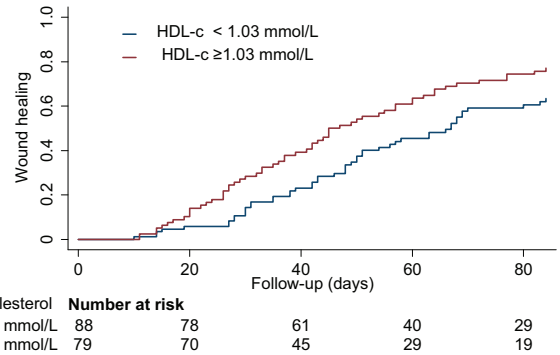

Figure 1: Kaplan-Meier survival estimates of wound healing by HDL-c levels (cutoff: 1.03 mmol/L). HDL-c: High-density lipoprotein cholesterol.

Among the 167 patients, the mean age was 64 ± 11 years and 30% were women. The mean duration of diabetes was 12.8 ± 7.8 years. The median wound duration was 2 (IQR 1–5) months. The mean hemoglobin A1c level was 8.4% ± 2.0%. More than half of the patients with DFUs had decreased HDL cholesterol levels (53%). There was a significant difference in Wagner grade and albumin level between high and low HDL cholesterol levels [Supplementary Table 1, http://links.lww.com/CM9/A581]. A total of 106 DFUs healed within 12 weeks. The overall healing rate was 63.4%. The median follow-up time was 50 (IQR 30–84) days.

Using HDL cholesterol levels as a categorical variable, unadjusted survival analysis showed that there was a significant difference in wound healing between high and low HDL cholesterol levels (log-rank $P = 0.016$). Lower HDL cholesterol levels were associated with lower wound healing [Figure 1 and Supplementary Table 1, http://links.lww.com/CM9/A581]. Supplementary Table 1, http://links.lww.com/CM9/A581 shows the association between different HDL cholesterol levels and wound healing using three models with progressive adjustments. Adjusting for age and sex revealed an association between wound healing and HDL cholesterol level in model 2 (HR 1.55, 95% CI 1.06–2.28, $P = 0.025$). In the fully adjusted model (model 3), after adjusting sex, age, Wagner grade, and wound duration before the consultation, there was no significant association between HDL cholesterol levels and wound healing (HR 1.22, 95% CI 0.83–1.81, $P = 0.303$).

Using HDL cholesterol levels as a continuous variable, there was a significant association between HDL cholesterol levels (per SD and per 0.13 mmol/L) and wound healing in the unadjusted and fully adjusted models (per SD: HR 1.30, 95% CI 1.07–1.60, $P = 0.010$; per 0.13 mmol/L: HR 1.10, 95% CI 1.02–1.19, $P = 0.019$). Higher HDL cholesterol levels were associated with higher wound healing. The upper quartile of HDL (Q4, ≥1.30 mmol/L) was significantly associated with higher wound healing before and after adjusting sex, age, Wagner grade, and wound duration (HR 1.89, 95% CI 1.03–3.46, $P = 0.040$). However, no significant difference was revealed between Q2 (<1, ≥0.87 mmol/L) and Q1 (<0.87 mmol/L).

In this study of patients with DFUs, more than half of the patients had decreased HDL cholesterol levels. Lower HDL cholesterol levels were significantly associated with lower wound healing. The association was consistent by treating HDL cholesterol levels as both continuous and categorical variables. To our knowledge, this is the first report to show that lower HDL cholesterol levels might be an independent predictor for delayed wound healing in patients with DFUs.

In patients with diabetes, decreased HDL cholesterol level is a common feature. Insulin resistance and metabolic alterations in type 2 diabetes might lead to glycation of apolipoproteins and other HDL-associated proteins, oxidative modification of HDL lipids and apolipoproteins, and eventually lead to compositional modification of HDL, thereby reducing the intrinsical stability of HDL particles.[3] This would result in rapid clearance of HDL from the circulation. It has been proposed that HDL could facilitate wound healing by accelerating resolution of inflammation, by enhancing granulation tissue formation involving increased endothelial progenitor cells (EPCs) incorporation and increased paracrine effects of EPCs,[4] and by accelerating reepithelialization. Therefore, the decreased levels of HDL in patients with DFUs might contribute to the delayed wound healing of patients with DFUs. A previous study also demonstrated that management of lipid metabolism disorders with fenofibrate was associated with lower-extremity amputations in patients with type 2 diabetes.[5]

In this study, while treating HDL cholesterol as a categorical variable, the association between HDL cholesterol and wound healing significantly decreased after adjusting Wagner grade and wound duration before the consultation. Meanwhile, Wagner grade classification differed significantly between high and low HDL cholesterol levels, which indicated that there might be an association between Wagner grade and HDL levels. This might be the reason why the difference disappeared after adjusting Wagner grade. However, we did not know whether it is a coincidence in our study or whether there was a causal relationship between HDL cholesterol and Wagner grade. Further research is warranted to clarify the association.

This study has several limitations. First, the sample size was small. Second, we only evaluate the HDL cholesterol level and did not assess the other components of HDL, such as apolipoproteins and paraoxonase, which might play a more important role in wound healing for the dysfunction of HDL. Finally, this study was carried out in a tertiary diabetic foot care center, which may not be generalized to the entire population with diabetes.

In brief, this study revealed that decreased HDL levels might be adversely associated with wound healing in patients with DFUs. Further research should be done to investigate the mechanism of how the dysfunction of HDL would impair wound healing, and whether HDL targeted therapy could benefit patients with DFUs.

Funding

This study was supported by grants from the National Science and Technology Major Project (No. 2017ZX09304023), the

Science and Technology Bureau of Chengdu city (No. 2017-CY02-00028-GX), the Health Medical Big Data Application and Innovation Project in Sichuan (No. 2018gfgw001), the 1.3.5 Project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYGD18025), and the National Key R&D Program of China (No. 2017YFC1309605).

Conflicts of interest

None.

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How to cite this article: Chen L, Ma W, Chen D, Wang C, Gao Y, Ran X. Association of high-density lipoprotein cholesterol and wound healing in patients with diabetic foot ulcers. Chin Med J 2022;135:110–112. doi: 10.1097/CM9.0000000000001544