U-Shaped Relationship Between Proteinuria and High-Density Lipoprotein Cholesterol: Results of Cross-Sectional and Six Years Cohort Studies (KITCHEN-10)

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Abstract

Background: Although a very high level of high-density lipoprotein cholesterol (HDL-C) may be a potential cardiovascular disease risk factor, the detail and underlying mechanism remain unclear. Therefore, we examined the associations of serum HDL-C with the incidence of proteinuria, a predictor for cardiovascular disease, in a community-based study.

Methods: We investigated clinical parameters, including serum HDL-C and proteinuria, among 1,191,409 people aged 40 - 74 years who underwent a health checkup in a cross-sectional study. In the cohort study, the incidence of proteinuria after 6 years was investigated in 451,987 participants without proteinuria at baseline, who were simultaneously enrolled in the cross-sectional study.

Results: The prevalence of proteinuria showed a U-shaped relationship with 10 HDL-C categories, with a minimum of 60 - 89 mg/dL in the cross-sectional study. Logistic regression analysis showed similar U-shaped relationships between odds ratios for proteinuria and HDL-C categories, with a minimum of 70 - 79 mg/dL. The associations between very high HDL-C (≥ 90 mg/dL) and proteinuria were strengthened after adjustment for body mass index (BMI). In the cohort study, a crude L-shaped relationship was observed between the incidence of proteinuria and baseline HDL-C, which turned into U-shaped relationship after adjustment for baseline BMI and HDL-C after 6 years.

Conclusions: Low and very high levels of HDL-C may be associated with the incidence of proteinuria, and BMI may be a potent contributing factor to the underlying mechanism.

Keywords: High-density lipoprotein cholesterol; Proteinuria; Low-density lipoprotein cholesterol; Extremely high HDL-C; Body mass index; Big data

Introduction

In addition to kidney disease, proteinuria is considered a potent predictor for cardiovascular disease [1-3]. In the past two decades, the causes of proteinuria have been attributed to diabetes and hypertension [1, 4], which have been increasing worldwide. However, the association between proteinuria and dyslipidemia, especially in relation to high-density lipoprotein (HDL), which is a potential protector against atherosclerotic disease [5, 6], has been scarcely reported, although a low serum HDL cholesterol (HDL-C) level has been proposed as a risk factor for the incidence of proteinuria and kidney disease [7-9]. Reducing low-density lipoprotein cholesterol (LDL-C) levels with pharmacotherapy, a primary management for dyslipidemia, decreases cardiovascular disease risk, whereas a substantial residual risk remains after such treatment in most patients [10]. In line of this, low level of HDL-C is considered as a therapeutic target for the residual risk management [11].

On the other hand, a very high level of HDL-C may be also a potential cardiovascular disease and increased mortality risk factor [12-16]. Although the association between low HDL-C levels and proteinuria is reasonable, the association between very or extremely high levels of HDL-C and proteinuria has not been explored.

In recent years, we conducted large community-based studies [17, 18] showing that very or extremely high HDL-C levels, such as levels over 100 mg/dL or below 50 mg/dL, may be associated with diabetes and hypertension. These two diseases can impair kidney function over the time and eventually elicit proteinuria, mostly involving albuminuria [1, 4]. Therefore, we hypothesized that people with very high HDL-C may be at increased risk for the incident of proteinuria. In this study, to confirm this hypothesis and to elucidate the underlying mechanism, we investigated the association between levels of serum HDL-C and the prevalence of pro-
proteinuria in a community-based cross-sectional study as well as the association between the incidence of proteinuria after 6 years and baseline HDL-C levels in a cohort study (sub-analysis).

Materials and Methods

Study design and participants

We conducted a composite multidisciplinary study involving secondary health check data in Japan (Kanagawa Investigation of the Total Checkup Data from the National Database; KICHEM) to elucidate the factors primarily associated with cardiometabolic diseases. The overall study concept and design are described elsewhere [19]. The present study included all individuals who underwent a health check, which has been mandatory for Japanese people aged 40 - 74 years old, and were living in Kanagawa Prefecture, the second most populated prefecture in Japan after Tokyo. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Kanagawa University of Human Services (10-43) and the Ministry of Health, Labor, and Welfare of Japan (No. 121).

In the cross-sectional study, we retrospectively reviewed electronic record data for clinical parameters, including HDL-C and proteinuria assessed using dipstick urinalysis, in 1,209,118 people aged 40 - 74 years who underwent a health checkup between April 2008 and March 2009. In the 6-year cohort study (sub-analysis), the incidence of proteinuria between April 2014 and March 2015 was investigated among participants who did not have proteinuria at baseline (April 2008 and March 2009) and who underwent the same health checkup after 6 years. All participants in the cohort study were simultaneously enrolled in the cross-sectional study.

After excluding individuals with incomplete available clinical and lifestyle data, the data for 1,191,409 and 451,987 individuals were included in the cross-sectional and cohort studies. Individuals at moderate to severe conditions were unlikely to be enrolled in our studies because healthcare staff in checkup institutions advised such people to go a medical in-patient, but it was not conducted according to sex because the number of participants was lower than the number in the cross-sectional study.

As in the cross-sectional study, confounding factors were chosen based on biological plausibility, but we did not follow a stepwise procedure to automatically select confounding factors. In the cohort study, the analysis was conducted for the whole study population, but it was not conducted according to sex because the number of participants was lower than the number in the cross-sectional study.

To consider the changes in the levels HDL-C during 6 years, which can be influenced by the regression towards the mean [28], the HDL-C after 6 years was finally included as a confounding factor in the multivariate logistic regression analysis. Statistical analyses were performed using SAS-Enterprise Guide (SAS-EG 7.1) in the SAS system, version 9.4 (SAS Institute, Cary, NC, USA). A two-tailed P < 0.05 was considered significant.
Results

Cross-sectional study

Mean HDL-C levels were 59.0 mg/dL in men and 70.6 mg/dL in women, and 37,640 (3.2%) participants had HDL-C ≥ 100 mg/dL. Overall, 45,959 (3.9%) participants had proteinuria, which was higher in men (4.7%) than women (2.8%; P < 0.0001). In the total participants, the incidence of proteinuria showed a U-shaped relationship with 10 HDL-C categories, with a minimum of 60 - 89 mg/dL (Fig. 2). Paradoxically, the relationship between ORs for proteinuria and HDL-C was more clearly visible in men than in women.

Table 1 shows the clinical characteristics of participants according to serum HDL-C levels. Most parameters, including BMI, systolic blood pressure, and LDL-C, as well as the prevalence of current smokers and pharmacotherapy for hypertension, diabetes, or dyslipidemia, decreased with increasing HDL-C level whereas age increased (ANOVA and Cochran-Armitage test, all P < 0.0001). However, female sex, daily alcohol consumption, and the amount of alcohol consumed per session increased with increasing HDL-C level (Cochran-Armitage and \( \chi^2 \) test, all P < 0.001). In the total participants, the incidence of proteinuria showed a U-shaped relationship with 10 HDL-C categories, with a minimum of 80 - 89 mg/dL (2.7%).

Figure 1 shows the percentages of proteinuria in 10 HDL-C categories according to sex. A U-shaped relationship was more clearly visible in men than in women.

Multivariate logistic regression analysis showed a similar U-shaped relationship between ORs for proteinuria and HDL-C categories, with a minimum of 60 - 89 mg/dL (Fig. 2). Particularly in men, the associations between very high HDL-C (≥ 90 mg/dL) and proteinuria were strengthened after adjustment for confounding factors including serum triglyceride level and BMI, whereas the association between low HDL-C and proteinuria was attenuated.

When we restricted subjects to those who drank < 23 g alcohol per session or who rarely drank alcohol, the percentages of proteinuria were decreased across the increasing HDL-C in both men and women (Table 2) (Cochran-Armitage test, both P < 0.0001). As Figure 3 shows the results of logistic regression analysis, the association between very high HDL-C (≥ 100 mg/dL) and proteinuria remained statistically significant, regardless of whether participants consumed less alcohol or infrequently drank alcohol. Overall, U-shaped associations were observed between proteinuria and HDL-C categories. Further sub-analysis after classification according to sex was not conducted because of the small sample size in the two highest HDL-C categories (n = 372 and 273).

Cohort study

The incidence of proteinuria after 6 years was determined in 11,497 (2.5%) participants. An L-shaped relationship was observed between the incidence of proteinuria and the 10 baseline HDL-C categories (Table 3).

As shown in Figure 4, HDL-C increased over 6 years in men with baseline HDL-C < 60 mg/dL and in women with HDL-C < 70 mg/dL; HDL-C decreased in men with baseline HDL-C ≥ 70 mg/dL and in women with HDL-C ≥ 80 mg/dL. Actual levels of HDL-C after 6 years are shown according to baseline HDL-C categories here (Supplementary Material 1, www.jocmr.org). In the group of very high HDL-C (HDL-C ≥ 100 mg/dL) at baseline, 48.7% of male subjects and 55.1% of female subjects remained in the same HDL-C group.

The RRs for incidence of proteinuria showed a similar L-shaped relationship with HDL-C categories (Fig. 5), which did not change after adjustment for confounding factors including serum triglyceride level. However, after further adjustment for BMI, the relationship changed to a blunt U-shaped relationship with HDL-C categories. Final model including HDL-C after 6 years as a confounding factor showed a small J-shaped relationship.

Discussion

It has been reported that microalbuminuria is observed in patients with diabetes who have low HDL-C levels [1, 7]. Additionally, higher levels of serum HDL-C have been shown to be associated with decreased rates of microalbuminuria in patients with type 2 diabetes [8]. However, the average HDL-C in the highest quartile group in that study was 56 mg/dL; this was not high in our study consisting of a mostly healthy general population with relatively high levels of HDL-C.

Our study is the first to show the relationship between a broad range of circulating HDL-C levels (20 to > 120 mg/dL) and proteinuria assessed using dipstick urinalysis. Our cross-sectional study consisted of 1 million people, which enabled us to classify participants into 10 HDL-C categories, namely, from very low levels to very or extremely high levels of HDL-C > 120 mg/dL, with adequate sample sizes and case (proteinuria) numbers even after further classification by sex.

Our results obtained from the cross-sectional study demonstrated a U-shaped relationship between the prevalence of proteinuria and HDL-C levels, which suggests that low (< 60 mg/dL) but also very high levels of HDL-C (≥ 90 or 100 mg/dL) are associated with proteinuria. These associations were not altered after adjustment for relevant confounding factors. Interestingly, the association between proteinuria and very high HDL-C was strengthened after adjustment for confounders particularly BMI, whereas the association was attenuated in cases of low HDL-C.

In our and other previous studies [29, 30], a J-shaped association was found between the incidence of proteinuria and BMI, suggesting that obesity, but also low body weight, can lead to incident proteinuria. In the current study, obesity accompanied with high serum triglyceride level was more prevalent in the categories of low HDL-C whereas low body weight accompanied with relatively low serum triglyceride level was more prevalent in the categories of very high HDL-C. Thus, the association between proteinuria and low HDL-C may be largely dependent on higher BMI, a potent background factor, whereas the observed association between proteinuria and very high HDL-C may be independent of lower BMI. Taken these together, it is possible that BMI is a potent contributing factor to the underlying mechanism. However, it is unknown whether this hypothesis is applicable to other populations with larger BMI such as Western populations.
### Table 1. Clinical Characteristics of Participants

| HDL-C categories (mg/dL) | 30 - 39 | 40 - 49 | 50 - 59 | 60 - 69 | 70 - 79 | 80 - 89 | 90 - 99 | 100 - 109 | 110 - 119 | ≥ 120 |
|-------------------------|---------|---------|---------|---------|---------|---------|---------|-----------|-----------|-------|
| N (% of total)          | 50,786 (4.3) | 193,046 (16.2) | 284,677 (23.9) | 265,804 (22.3) | 192,420 (16.2) | 112,276 (9.4) | 54,760 (4.6) | 23,073 (1.9) | 8,968 (0.8) | 5,599 (0.5) |
| S-age                   | 52.7 ± 10.1 | 52.6 ± 9.9 | 53.1 ± 9.9 | 53.3 ± 9.9 | 53.2 ± 9.8 | 53.2 ± 9.7 | 53.4 ± 9.3 | 53.5 ± 9.1 | 53.8 ± 8.9 | |
| Women, n (%)            | 5,743 (11.3) | 37,022 (19.2) | 90,628 (31.8) | 123,705 (46.5) | 111,787 (58.1) | 73,387 (65.4) | 37,530 (68.5) | 16,032 (69.5) | 6,152 (63.7) | 6,152 (63.7) |
| BMI (kg/m²)             | 25.3 ± 3.4 | 24.7 ± 3.3 | 23.8 ± 3.2 | 22.8 ± 3.1 | 21.9 ± 2.9 | 21.3 ± 2.7 | 20.9 ± 2.6 | 20.6 ± 2.5 | 20.4 ± 2.5 | 20.5 ± 2.6 |
| SBP (mm Hg)             | 127 ± 16.8 | 127 ± 17.0 | 126 ± 17.2 | 125 ± 17.6 | 123 ± 17.8 | 122 ± 17.9 | 123 ± 18.0 | 123 ± 17.9 | 124 ± 18.4 | 126 ± 18.3 |
| TG (mg/dL)              | 191 (134 - 279) | 145 (104 - 205) | 112 (82 - 155) | 90 (67 - 124) | 77 (58 - 104) | 69 (53 - 92) | 65 (50 - 85) | 61 (48 - 81) | 61 (48 - 79) | 60 (47 - 80) |
| LDL-C (mg/dL)a          | 191 (134 - 279) | 145 (104 - 205) | 112 (82 - 155) | 90 (67 - 124) | 77 (58 - 104) | 69 (53 - 92) | 65 (50 - 85) | 61 (48 - 81) | 61 (48 - 79) | 60 (47 - 80) |
| HDL-C (mg/dL)           | 35.9 ± 3.0 | 45.1 ± 2.8 | 54.6 ± 2.8 | 64.3 ± 2.9 | 74.1 ± 2.8 | 84.0 ± 2.8 | 93.8 ± 2.8 | 104 ± 2.8 | 114 ± 2.8 | 131 ± 14.3 |
| HbA1c (%)b              | 5.8 ± 0.9 | 5.7 ± 0.8 | 5.6 ± 0.7 | 5.5 ± 0.6 | 5.5 ± 0.5 | 5.5 ± 0.5 | 5.5 ± 0.5 | 5.4 ± 0.6 | 5.5 ± 0.6 | 5.5 ± 0.6 |
| Proteinuria, n (%)      | 3,553 (7.0) | 10,324 (5.4) | 11,759 (4.1) | 8,742 (3.3) | 5,691 (2.7) | 3,069 (2.9) | 1,583 (2.9) | 702 (3.0) | 291 (3.2) | 245 (4.4) |
| Hypertension, n (%)     | 11,380 (22.4) | 40,148 (20.8) | 53,410 (18.8) | 44,209 (16.6) | 27,191 (14.1) | 13,983 (12.5) | 6,404 (11.7) | 2,575 (11.2) | 1,047 (11.7) | 774 (13.8) |
| Diabetes, n (%)         | 3,262 (6.4) | 9,780 (5.1) | 11,391 (4.0) | 8,153 (3.1) | 4,545 (2.4) | 2,165 (1.9) | 1,077 (2.0) | 452 (2.0) | 169 (1.9) | 157 (2.8) |
| Dyslipidemia, n (%)     | 4,756 (9.4) | 18,331 (9.5) | 28,169 (9.9) | 25,569 (9.6) | 17,198 (8.9) | 9,222 (8.2) | 4,451 (8.1) | 1,930 (8.4) | 733 (8.2) | 496 (8.9) |
| CVD, n (%)              | 2,511 (6.2) | 7,521 (4.9) | 9,750 (4.3) | 8,231 (3.8) | 5,215 (3.3) | 2,772 (3.0) | 1,251 (2.8) | 507 (2.7) | 204 (2.8) | 135 (2.9) |
| Current smokers, n (%)  | 23,766 (46.8) | 71,284 (36.9) | 81,472 (28.6) | 59,418 (22.4) | 35,330 (18.4) | 18,227 (16.2) | 8,562 (15.6) | 3,509 (15.2) | 14,89 (16.6) | 1,128 (20.2) |
| Heavy alcohol drinkers, n (%)c | 1,730 (3.4) | 6,696 (3.5) | 9,293 (3.3) | 8,062 (3.0) | 5,424 (2.8) | 3,071 (2.7) | 1,589 (2.9) | 731 (3.2) | 333 (3.7) | 302 (5.4) |
| Daily alcohol drinkers, n (%) | 8,339 (16.4) | 39,790 (20.6) | 66,990 (23.5) | 65,497 (24.6) | 47,859 (24.9) | 29,100 (25.9) | 15,331 (28.0) | 7,122 (30.9) | 3,155 (35.2) | 2,184 (39.0) |
| Regular exercisers, n (%)d | 10,158 (20.0) | 42,096 (21.8) | 68,417 (24.0) | 68,609 (25.8) | 51,899 (27.0) | 31,969 (28.2) | 16,001 (29.2) | 7,002 (30.4) | 2,811 (31.3) | 1,768 (31.6) |

Data are presented as mean ± standard deviation, median (interquartile range) for triglycerides, or n (%). aAvailable n = 1,179,643. bAvailable n = 938,010. cDrinkers who consume 69 g ethanol or more per session. dRegular exercise defined as ≥ 30 min at least twice a week. All continuous and categorical variables showed significant differences with analysis of variance or χ² test, with P < 0.0001 across the 10 categories of HDL-C concentration. S-age: substituted age; BMI: body mass index; SBP: systolic blood pressure; HDL-C: high-density lipoprotein cholesterol; CVD: cardiovascular disease; TG: triglycerides; LDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin.
In sub-analysis in the 6 year-cohort study, we found that very high and extremely high HDL-C at baseline decreased over 6 years (up to -12 mg/dL in men) whereas HDL-C increased with low HDL-C (up to 6 mg/dL in women) mostly due to the phenomenon of regression towards the mean [28]. Because the effect of alcohol on HDL-C appears to be reversible [25], elevated HDL-C owing to transient high alcohol consumption at baseline may be reduced by an improved life-style, including reduced alcohol consumption. However, this was not confirmed in this study.

Under crude conditions, an L-shaped relationship between proteinuria and HDL-C was observed, which transformed into a blunt U-shaped after adjustment for BMI. This change suggests that BMI may be a pivotal contributor to the underlying relationship.
ing mechanism. The most plausible reason for the L-shaped and blunt U-shaped association in the cohort study, rather than the clear U-shaped association in the cross-sectional study, is that the 6-year study period may have been too short to evaluate the incidence of proteinuria in participants with very high HDL-C. Additionally, the decrease in HDL-C in the categories of very high HDL-C may attenuate the effect of very high HDL-C. Nevertheless, final adjustment for HDL-C after 6 years showed relatively distinct U-shaped relationship, which may attribute to the attenuation of changes in HDL-C during 6 years particularly in the high HDL-C groups.

In recent years, we have demonstrated the association of extremely high HDL-C, mostly defined as > 100 mg/dL, with diabetes [17], high blood pressure [18], and hypertensive retinopathy [31]. All of these are well-known risk factors for the incidence of kidney disease and proteinuria [1, 2, 4]. Considering these previous studies, the current results are not surprising and were somewhat expected. Furthermore, in the past decade, several studies have shown that extremely high HDL-C is associated with elevated mortality [12-16]. Additionally, increased HDL-C owing to the use of cholesteryl ester transfer protein (CETP) inhibitors does not protect against the incidence of cardiovascular disease or mortality [32-35]. Although genetic variation in CETP is a major determination for high HDL-C in Japan [36, 37], such genetic information was not investigated in this study.

In contrast, habitual alcohol consumption, an acquired lifestyle, raises serum HDL-C levels [25, 26]. The amount and frequency of alcohol consumption were higher in groups with higher HDL-C levels in this study. However, the association between proteinuria and very high HDL-C remained statistically significant in participants who drank lower amounts of alcohol or who drank infrequently, although the association of very high level of HDL-C with proteinuria was attenuated. Therefore, the current results suggest that alcohol consumption cannot fully explain the mechanism underlying the association of very high HDL-C levels with proteinuria.

Taken together, our results indicate that the most plausible explanation for the association between very high HDL-C and proteinuria is that the quality of HDL (in other words, a favorable function of HDL for cardiometabolic conditions [38-40]) rather than circulating HDL-C concentration [41] may be impaired in some people with very high levels of HDL-C, although there are no standardized assays to evaluate HDL function. Alternatively, very high HDL-C may be a marker of specific conditions related to cardiovascular diseases, which warrants further study.

**Limitations**

Several limitations should be mentioned in this study. First, proteinuria assessed using dipstick urinalysis may have limited usefulness in clinical settings [42, 43], particularly because the

| HDL-C category (mg/dL) | 20 - 39 | 40 - 49 | 50 - 59 | 60 - 69 | 70 - 79 | 80 - 89 | 90 - 99 | ≥ 100 |
|------------------------|--------|--------|--------|--------|--------|--------|--------|-------|
| Subjects who consume low amount of alcohol (n = 460,837) |        |        |        |        |        |        |        |       |
| Case of proteinuria, n (% in each group) | 1,383 (7.4) | 3,797 (5.5) | 4,299 (4.1) | 3,268 (3.1) | 2,132 (2.7) | 1,170 (2.5) | 532 (2.4) | 372 (2.6) |
| Subjects who hardly or not drink alcohol (n = 402,180) |        |        |        |        |        |        |        |       |
| Case of proteinuria, n (% in each group) | 1,467 (7.6) | 3,606 (5.5) | 3,908 (4.1) | 2,828 (3.1) | 1,775 (2.7) | 978 (2.6) | 443 (2.5) | 276 (2.7) |

a. Low amount of alcohol consumption (less than 23 g of ethanol per session). bLow frequency of alcohol consumption (rarely drinks or cannot drink alcohol). The percentages of proteinuria were decreased across the increasing HDL-C in the both conditions (Cochran-Armitage test, both P < 0.0001).
term proteinuria does not always reflect albuminuria, a major outcome of kidney disease. Additionally, other information concerning urine specimens including urine protein creatinine ratio, hematuria, and urine specific gravity, was unavailable. However, in this study, over half of dipstick urinalysis was performed with automated reading, which can eliminate potential sources of error commonly observed in manual performance [44]. Second, a lack of data for eGFR hampered our speculation about the mechanisms underlying the relationship between HDL-C and proteinuria. Third, factors related to the function of HDL, such as apolipoprotein (apo) A-I, apo A-II, HDL-2, and HDL-3 [41, 45, 46], were also unknown in this study. Therefore, it is unknown whether dysfunctional HDL exists in people with very high HDL-C. Finally, the cause-effective relationship between HDL-C and proteinuria remains unknown in this study, although a retrospective cohort study was also conducted. Particularly very high HDL-C might reflect some unfavorable conditions for the incident of proteinuria regardless of the direct causality. Taken these limitations into consideration, further studies are required to confirm current results.

### Conclusions

Low and very high levels of HDL-C may be associated with a high proportion of proteinuria and the incidence of proteinuria. BMI may be a potent contributing factor to the underlying mechanism.

### Supplementary Material

Suppl 1. HDL-C after 6 years according to baseline HDL-C categories.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Informed consent was not required because of anonymous data from the MHLW of Japan, as part of its nationwide program involving the provision of medical data to third parties. Instead, we have opened the study protocol online (https://www.kuhs.ac.jp/research/nationaldatabase/).

Author Contributions

KN and MI contributed to the overall study design, the interpretation of the initial analysis, and the discussion of the literature. KN prepared the first draft of the manuscript, and both authors read and approved the manuscript. Both authors agreed to the published version of the manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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