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Circulating high density lipoprotein distinguishes alcoholic hepatitis from heavy drinkers and predicts 90-day outcome

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Abstract

Background: Alcohol-associated liver disease (ALD) and alcoholic hepatitis (AH) significantly impact the liver, an organ central to the lipid and lipoprotein metabolism.

Objective: To define changes in the lipid and lipoprotein profiles in subjects with alcoholic hepatitis (AH) versus heavy drinkers with normal liver function and to determine the association of the AH-mediated lipoprotein phenotype with AH severity and outcomes.

Methods: AH cases (n=196) and a heavy drinker control group (n=169) were identified in a multicenter, prospective cohort. The relationships between lipid panels and lipoprotein profiles among AH and heavy drinkers were interrogated using three common measurements: the conventional lipid panel, extended lipid panel by NMR, and NMR-based direct lipoprotein profiling. Predictive values for AH severity and mortality were determined using Harrell's C-Index.

Results: Lipid and lipoprotein profiles were significantly different in AH compared to heavy drinkers. Among them, high density lipoprotein (HDL) particle concentration exhibited the most

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Authors' contribution

KM, EVG, HH, MAC, ZGJ were involved in data analysis. NC, MAC, ZGJ were involved in the conception of the study, KM and ZGJ prepared the initial draft, and all coauthors were involved in revising the manuscript.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript and take responsibility for the integrity of the work as a whole.

Conflict of interest statement

MAC is an employee of LabCorp that developed the NMR method to measure LP-Z concentration. The authors declare no additional competing interests pertinent to this study.

significant reduction in AH compared to heavy drinkers (5.3 ± 3.4 vs 22.3 ± 5.4 μmol/L, $p < 0.001$). Within AH patients, HDL particle concentration was inversely associated with Maddrey's Discriminant Function (DF) ($p < 0.001$), and independently associated with mortality at both 90 and 365 days even after adjustment for DF ($p = 0.02$, $p = 0.05$ respectively). HDL particle concentration less than 3.5 μmol/L and total cholesterol ≤ 96 mg/dL identified AH patients with higher 90-day mortality.

Conclusion: Lipid and lipoprotein profiles are profoundly altered in AH and can help in prognosticating disease severity and mortality.

Keywords

Alcoholic hepatitis (AH); lipoproteins; high density lipoprotein (HDL); total cholesterol (TC); Nuclear magnetic resonance spectroscopy (NMR)

Introduction

Lipoproteins are complex macromolecules that act as carriers of water-insoluble lipids, facilitating their transport within the circulatory system. The liver plays a central role in the production of lipoprotein particles as well as the enzymes required for lipoprotein metabolism in the circulation[1]. Therefore, the circulatory lipoprotein profile reflects the host's metabolic state as well as hepatic function[2].

Alcohol consumption in moderation impacts lipoprotein metabolism and is associated with an increase in high density lipoprotein cholesterol (HDL-C) as observed in multiple epidemiological and Mendelian randomization studies[3–5]. The cause has been attributed to the ability of alcohol to increase the production of hepatic apolipoprotein A-I (apoA-I), the main protein constituent of HDL particles[6]. However, heavy alcohol consumption may have a multi-pronged effect, as it can cause direct hepatocellular damage resulting in impaired lipoprotein metabolism[7]. Alcoholic Hepatitis (AH) represents a state of subacute liver failure, which is associated with significant morbidity and mortality[8]. Profound changes in lipoprotein metabolism are expected in patients with AH. Zieve syndrome, characterized by a triad of hypertriglyceridemia, jaundice, and hemolysis, is an example of a clinical presentation of abnormalities associated with prolonged alcohol use and liver injury[9]. The changes in lipoprotein metabolism between moderate to heavy drinkers with alcohol-associated liver disease (ALD), and AH patients have been poorly defined.

The conventional lipid panel is the most commonly used test that assesses circulating lipoproteins. The lipid panel measures the concentration of three lipid species: triglyceride (TG), total cholesterol (TC), and HDL-C and estimates the level of low density lipoprotein cholesterol (LDL-C) using the Friedewald equation[10]. The panel provides no information on the distribution of lipoprotein subclasses or sizes, nor does it account for the potential presence of abnormal lipoproteins[11, 12]. Direct lipoprotein profiling is available through the use of nuclear magnetic resonance spectroscopy (NMR)[13]. A recently developed NMR algorithm calculates the concentration of lipoprotein subclasses, including very low-density lipoprotein (VLDL), LDL, HDL, as well as abnormal lipoproteins that are usually absent in healthy individuals[12]. Herein, the current study reports the lipoprotein profiles for subjects

in an observational cohort comprised of cases of AH and controls of heavy drinkers with no evidence of underlying liver dysfunction from the Translational Research and Evolving Alcoholic Hepatitis Treatment (TREAT) consortium.

Methods:

Patient populations

TREAT was a multicenter, prospective, observational, case-controlled study sponsored by the National Institute of Alcohol Abuse and Addiction (NIAAA). The study protocol and amendments were approved by the Institutional Review Boards (IRB) of participating institutions: Indiana University and affiliated hospitals (Indianapolis, Indiana), Virginia Commonwealth University (Richmond, Virginia), and Mayo Clinic (Rochester, Minnesota).

Recruitment of subjects took place at all three medical centers. Subjects were screened based on predefined eligibility criteria of AH and heavy drinker controls[14]. All AH cases had an average daily ethanol consumption of more than 40 grams for females and more than 60 grams for males with a duration of 6 months or more and last use within 6 weeks of enrollment. Eligible AH subjects also had serum bilirubin level of more than 3 milligrams per deciliter (mg/dl) and aspartate aminotransferase (AST) level more than 50 units per liter (U/L). Subjects with Hepatitis B, Hepatitis C, or HIV were eligible for inclusion. Patients with autoimmune and drug-induced liver conditions, hemochromatosis, Wilson's disease, history of intravenous drug abuse, and significant concomitant medical conditions, including uncontrolled congestive heart failure, chronic obstructive pulmonary disease, and multiple organ failure were excluded. The study selected heavy alcohol drinkers as controls. The average daily consumption and duration of intake of ethanol for controls were the same as AH cases. Lab criteria for controls were bilirubin levels within the normal range and alanine aminotransferase (ALT) and AST levels less than 50 U/L. Cases with underlying, previously diagnosed liver disease, stigmata of chronic liver disease, and hepatosplenomegaly on physical exam were excluded. The rest of the exclusion criteria were the same as those of the cases.

The first 10 cases recruited at each of the 3 sites were evaluated for distribution of age, gender, and race. Controls were recruited based on frequency matching with the same distribution of age, gender, and race. At the baseline visit, data on demographics, medication use, and anthropometric measurements including body mass index (BMI) were collected. Alcohol screening questionnaire (AUDIT) scores were collected to quantify alcohol use. Blood draws were performed to measure the conventional lipid panel by chemistry-based assays, comprehensive metabolic panel, and coagulation profile as clinically indicated. The Model for End-Stage Liver Disease (MELD) and Maddrey discriminant function (DF) scores were calculated based on lab results. Bio-samples were stored at −80°C freezers in the Clinical and Translation Science Institute (CTSI) Specimen Storage Facility at Indiana University. Both groups had follow-up visits at 6 months and 12 months; the latter visit was deemed to be the end of the observational study.

NMR Measurements

Stored serum samples from fasting and non-fasting participants drawn at baseline were used to measure the lipoprotein profile by NMR. NMR spectra were acquired on a Vantera® Clinical Analyzer[13, 15]. Lipoprotein analysis was performed using the newly developed LP4 algorithm[12]. Lipoproteins were classified into three main categories: 1. triglyceride-rich lipoprotein (TRL), including chylomicrons, VLDL, and VLDL remnants, 2. LDL, and 3. HDL. TRL was subdivided into very large, large, medium, small, and very small particles, with sizes of 90–240 nanometer (nm), 50–89 nm, 37–49 nm, 30–36 nm, and 24–29 nm, respectively. Fasting samples will be deficient in very large TRL. LDL was subdivided into large, medium, and small particles with size of 21.5–23 nm, 20.5–21.4 nm, and 19–20.4 nm, respectively. HDL was also subdivided as large (10.3–12 nm), medium (8.7–9.5 nm), and small particles (7.4–7.8 nm). Mean sizes of TRL, LDL, and HDL were calculated based on the weighted average diameters. Derived apolipoproteins (apo) B and A-I concentrations were also calculated using the same method. A Partial Least Squares Regression (PLS) method was used to measure concentrations of TG, TC and HDL-C, as reported in the Extended Lipid Panel and LDL-C was calculated using the Friedewald equation[12]. GlycA, an NMR-specific marker of systemic inflammation, was measured as previously described[16].

Statistical analysis

All continuous variables were tested for normality using the Shapiro–Wilk test. Most lipoprotein measurements were skewed; thus all of them were natural logarithm-transformed in analyses. The independent 2-tailed Student's t and Mann-Whitney U tests were used to compare normally and non-normally distributed data, respectively. Non-transformed values are displayed in tables for easier interpretation. The χ^2 test was used to compare categorical variables. The Cochran-Armitage trend test was used to assess for the presence of an association between a variable with two categories or an ordinal variable with three or more categories. We tested correlations between log-transformed lipoproteins and ALT, AST, MELD or DF by means of bivariate or partial Pearson correlations. Partial correlations were adjusted for age, gender, and BMI.

We then studied the association of lipoprotein measurements and the occurrence of death at 90 or 365 days. Time to death was computed as the number of days from enrollment to the date of death. Subjects lost to follow-up or withdrawn consent were censored at the last date they were known to be alive. Associations between overall mortality and lipoprotein concentration, NMR derived extended lipid or conventional lipid panel were calculated using Cox proportional hazards models. Univariate analysis was initially performed before employing progressively refined models by adjusting for age, sex, and BMI (model 1), plus DF (model 2), or MELD score (model 3). Covariates were selected according to their biological plausibility to act as confounders or established predictors of mortality in cases of DF or MELD score. A graphical assessment of proportional assumptions was performed using log–log survival curves. In addition, deviations from the assumption of proportionality were tested for each covariate and globally using Schoenfeld residuals. The assumptions of proportionality were met both globally (the overall models) and individually for each predictor variable.

To further assess the effect of baseline lipoprotein values on outcomes, risk groups were determined based on tertiles: upper and middle tertiles were defined to be low-risk and lower tertile high-risk groups. The cumulative probability for the study outcome (overall mortality) was analyzed by the standard Kaplan–Meier method and differences among groups were compared using the log-rank test.

Harrell's C-index was used to assess the ability of each lipid or lipoprotein measurement to predict death at 90 and 180 days. Perfect discrimination is indicated by a value of 1, while a value of less than 0.5 is expected by chance.

All the statistical analyses were performed using statistical packages Stata, release 16 (StataCorp, College Station, TX) and SPSS, version 26 (Chicago, IL, USA). All P values were two-sided, with a level of 0.05 considered statistically significant.

Results

Study Population

A total of 365 subjects were enrolled in the TREAT study, including 196 cases of AH and 169 heavy-drinker controls without evidence of liver disease. Study participants in both groups had a high Caucasian and male predominance, with mean ages at enrollment (45.5 years in cases *vs.* 44.4 years in controls, $p = 0.4$) (Table 1). There was no difference in BMI between the two groups ($p = 0.4$). As expected, MELD and DF scores were significantly higher in the AH case group ($p < 0.001$). Out of the 196 AH cases, 47 died, and 36 withdrew the informed consent or were lost to follow-up with a median follow-up duration of 259 days (IQR: 161–270). Among the mortalities, 36 were directly or indirectly related to AH, including five sepsis, two renal failure and three multiorgan failure, four deaths were by accidents, and seven had unknown causes. In the control group, two participants died, 74 were lost to follow-up, and eight withdrew the consent.

Significant changes in lipoprotein profiles in AH compared to heavy drinkers

Significant differences in both lipid and lipoprotein profiles were noted between the AH patients and heavy drinkers. In the lipid panel, the mean levels of TG, TC, LDL-C, and HDL-C were significantly lower in AH than in controls (Table 2). Among these lipid measurements, the mean HDL-C level in AH was 14.8 ± 14.9 mg/dL, one-quarter of heavy drinkers. Lipoprotein profiles by NMR provided further insights into the lipoprotein subclass distributions that underscored the differences in the lipid panel. The mean concentration of total HDL particles in AH was approximately one-quarter of those in the heavy drinkers (Figure 1A). Small HDL particles were the most dominant HDL subclass, accounting for an average of 50.6% and 81.5% of total HDL particles in heavy drinkers and AH, respectively. All classes of HDL particles were lower in AH compared to controls ($p < 0.001$) (Figure 1B–D). However, medium-sized HDL had the most significant difference, representing a greater than 15-fold reduction (0.6 ± 1.6 vs. 8.9 ± 3.2 μmol/L) in AH (Figure 1C). This was in keeping with a decrease in mean HDL particle size from 9.1 nm in controls to 8.8 nm in AH. In contrast, the mean total LDL particle concentration was higher in AH compared to controls (2436 ± 1250 vs. 1456 ± 458 nmol/L, $p < 0.001$) (Table 2). In comparison, large,

medium, and small LDL particles were lower in AH than heavy drinkers. In contrast to the much lower TG in AH compared to controls, total TRL particles were only slightly lower in AH (142.2 ± 144.0 vs. 159.4 ± 78.4 nmol/L, $p < 0.001$) (Table 2). However, the differences in very large and large TRL were far more striking, with more than a 10-fold reduction in AH compared to heavy drinkers, leading to a decrease in the mean TRL size (Table S1, Table 2).

Lipoprotein changes associated with AH disease severity

The striking differences in lipid and lipoprotein profiles between AH and heavy drinkers raised the possibility that these changes also reflect AH disease severity. Higher DF scores were associated with lower levels of lipoproteins or lipids except for total LDL particles (Table 3). Similar inverse associations were observed with MELD score (Table S2). Among serum lipids, LDL-C and HDL-C showed similar inverse correlations with AH severity. All three subclasses of HDL held up the inverse correlation (Table S3). Total TRL ($p = 0.02$), very large TRL ($p = 0.003$) and large TRL ($p < 0.001$) also had inverse correlations with AH severity (Tables 3 and S3). The differential associations between subclasses of TRL and HDL particles and DF scores led to smaller TRL and HDL particles among patients with higher DF scores (Table S3). A sensitivity analysis was performed by excluding individuals with hepatitis B, C, or HIV, and resulted in similar findings. We found some lipid and lipoprotein levels were strongly associated with liver enzymes (Table S4). TG and LDL particle concentrations were positively associated with both ALT and AST. While HDL particle concentration was positively associated with ALT, HDL size was negatively associated with AST.

Lipoprotein profiles predict mortality in AH

Out of 196 AH patients, 30 (15%) patients died within 90 days, and 47 (24%) died by one year at the end of follow-up. There was no statistically significant difference in age between deceased and survivors (Table S5). Both groups were also similar in gender, race, BMI, and mean AUDIT score at the time of enrollment in the study. Expectedly, deceased patients had higher DF scores (54.9 ± 25.3 vs 39.2 ± 26.0, $p < 0.001$) and MELD scores (25.8 ± 6.1 vs 21.6 ± 6.6, $p < 0.001$) than survivors at baseline.

Consistent with the trend noted with AH disease severity, patients deceased in one year had consistently lower levels of total TG, TC, LDL-C, HDL-C, and all major classes of lipoproteins at enrollment than survivors at one year (Table 4). The differences in HDL and TRL levels between deceased and survivors were largely driven by small HDL and very small TRL (Table S6). Furthermore, total LDL, along with large, medium, and small LDL particle concentrations were also lower in deceased patients. There were no differences in the mean size of baseline TRL, LDL, and HDL between the deceased and survivors.

Lipid and lipoprotein measurements were assessed for the ability to predict mortality in AH. TC, LDL-C, and HDL-C were inversely associated with mortality at 90 days and one year, whereas TG was only significant at one year (Table 5). This observation was confirmed using a chemistry-measured conventional lipid panel in a subpopulation of 129 AH patients where such measurements were available, and the association remained significant. Among

lipoproteins, HDL particle concentration was inversely associated with mortality at 90 days and one year with adjusted HR of 0.18 (95% CI 0.04–0.75, p = 0.02) and 0.38 (95% CI 0.14 – 0.99, p = 0.05) respectively (Table 5, S7).

The relationship between NMR-derived TC and HDL particle concentrations was further analyzed by tertiles and 90-day mortality. To do so, the upper and middle tertiles of HDL particles were grouped into the low-risk subgroup and the lower tertile into the high-risk subgroup. On Kaplan-Meier analysis, both lower tertiles subgroups of TC (<96 mg/dL) and HDL particle concentration (<3.5 μmol/L) were associated with increased risks of death as compared with the low-risk subgroups (Figures 2A and 2B).

Discussion

Heavy alcohol use and AH are expected to influence lipoprotein metabolism in profound ways. However, these relationships have never been well defined. This study aims to address this knowledge gap. The current study revealed that lipoprotein profiles in AH are characterized by reductions in large VLDL (also reported as TRLP) and HDL particles and accumulation of abnormal LDL particles[12]. Meanwhile, the severity and mortality of AH are associated with reductions in circulating cholesterol in all of the lipoproteins. This observation is best exemplified by profound decreases in HDL particles (Figure 3).

Natural history between alcohol and lipoproteins

ALD has become increasingly prevalent in the US over the past two decades[17]. Moderate drinking is associated with favorable changes in serum lipids, especially a rise in HDL-C[18]. This contrasts the metabolic associated fatty liver disease (MAFLD), where HDL-C is often reduced due to metabolic syndrome. The current study indicates that significant changes in the lipid and lipoprotein profiles occur when AH develops (Figure 3). With regard to the lipid panel, this change is characterized by a substantial reduction in HDL-C and persistent decline in TG, while the changes in LDL-C are small. NMR-based lipoprotein profiling indicated that this change is driven by a reduction in very large and large TRL and HDL particles of all sizes. The decline in large and very large TRL particles suggests reduced lipidation of Apolipoprotein B (apoB) during VLDL assembly in hepatocytes. AH patients usually have hepatic steatosis. Typically, hepatic steatosis augments VLDL lipidation, leading to larger VLDL particle size[19]. Observations here suggest impaired lipoprotein assembly in AH, which may exacerbate hepatic steatosis. The decrease in HDL particles is likely caused by impaired apoA-I production[20]. There is also a shift toward decreased HDL size in AH, driven by a disproportionate reduction in large and medium-sized HDL particles. The liver produces lipid-poor apoA-I and premature HDL particles, while HDL lipidation and maturation occur in circulation. The formation of large HDL particles requires lecithin cholesterol acyltransferase (LCAT), an enzyme that converts free cholesterol to cholesteryl esters and internalizes cholesterol to the lipid core. A reduction in mean HDL particle sizes suggests impaired HDL lipidation or LCAT-mediated HDL maturation.

Clinical implications of lipid and lipoprotein changes in AH

The present study demonstrates that serum lipid and lipoprotein profiles change in predictable patterns in AH. Hence, lipid and lipoprotein measurements may prognosticate outcomes in AH. The severity and mortality of AH are associated with a decrease in all forms of lipoproteins that are best captured by HDL particle concentration. TC is also associated with mortality and demonstrated even better performance than HDL. However, the utility of TC in AH may require further study. In general, a low TC is associated with good health, while low HDL is not. The mean levels of TC among AH patients, even those who die in one year, do not deviate significantly from a normal range. This U-shaped association of TC with disease states will require clinicians to interpret its significance in the proper clinical setting. Furthermore, the accuracy and reproducibility of the conventional lipid panel in severe disease with high bilirubin has not been well-established, although NMR lipid panel can overcome this technical challenge. The decrease in circulating lipoproteins reflects the severity of liver synthetic dysfunction. Previous studies have reported the associations of liver cirrhosis and low lipoprotein levels[21, 22]. Trieb et al. described that low HDL-C and apoA-I levels served as independent predictors of 90-day mortality in patients of cirrhosis independent of MELD score[23]. Changes in HDL or TC may not be specific to AH, but nonetheless reflect liver dysfunction in general. It is notable that the association of TC or HDL particle concentration and 90-day or one-year mortality remained significant after adjustment for Maddrey's Discriminant Function or MELD. This suggests that the lipoprotein phenotype represents essential pathophysiology of liver failure that is not captured by Maddrey's or MELD scores.

Limitations and contextual factors

This study has several limitations. Albeit reflective of AH epidemiology in the US, TREAT has enrolled fewer African Americans and females, limiting the generalizability to these populations. Alcohol consumption was self-reported by research participants and not biochemically validated. The use of quantitative measurements of alcohol consumption such as carbohydrate-deficient transferrin (CDT) or phosphatidylethanol (PEth) could further minimize misclassification bias. It will also be interesting to define the impact of alcohol consumption on lipoprotein profiles in healthy subjects using age- and gender-match controls that do not drink excessive alcohol. Loss of follow-up was noted in both cases and controls, in keeping with a well-known challenge of ALD studies. Future studies should also validate the reliability of conventional lipid panels in the presence of high bilirubin in AH, which may provide equally effective prognosticative capacity.

In conclusion, lipoprotein changes in AH are characterized by a significant decrease in the levels of HDL and large VLDL particles in the circulation compared to heavy drinkers without liver dysfunction. AH patients with low HDL particle levels (< 3.5 μmol/L) or total cholesterol (<96 mg/dL) are associated with significantly higher mortality. Conventional lipid panel, lipid and lipoprotein measurements by NMR can provide valuable prognostication value of AH outcomes that are not captured by existing biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Highlights:

- Alcoholic hepatitis is associated with a significantly altered lipoprotein profile.
- NMR lipoprotein profiling captures lipoprotein changes in alcoholic hepatitis.
- HDL level is significantly reduced in alcoholic hepatitis.
- HDL and total cholesterol levels are predictive of AH severity and mortality.

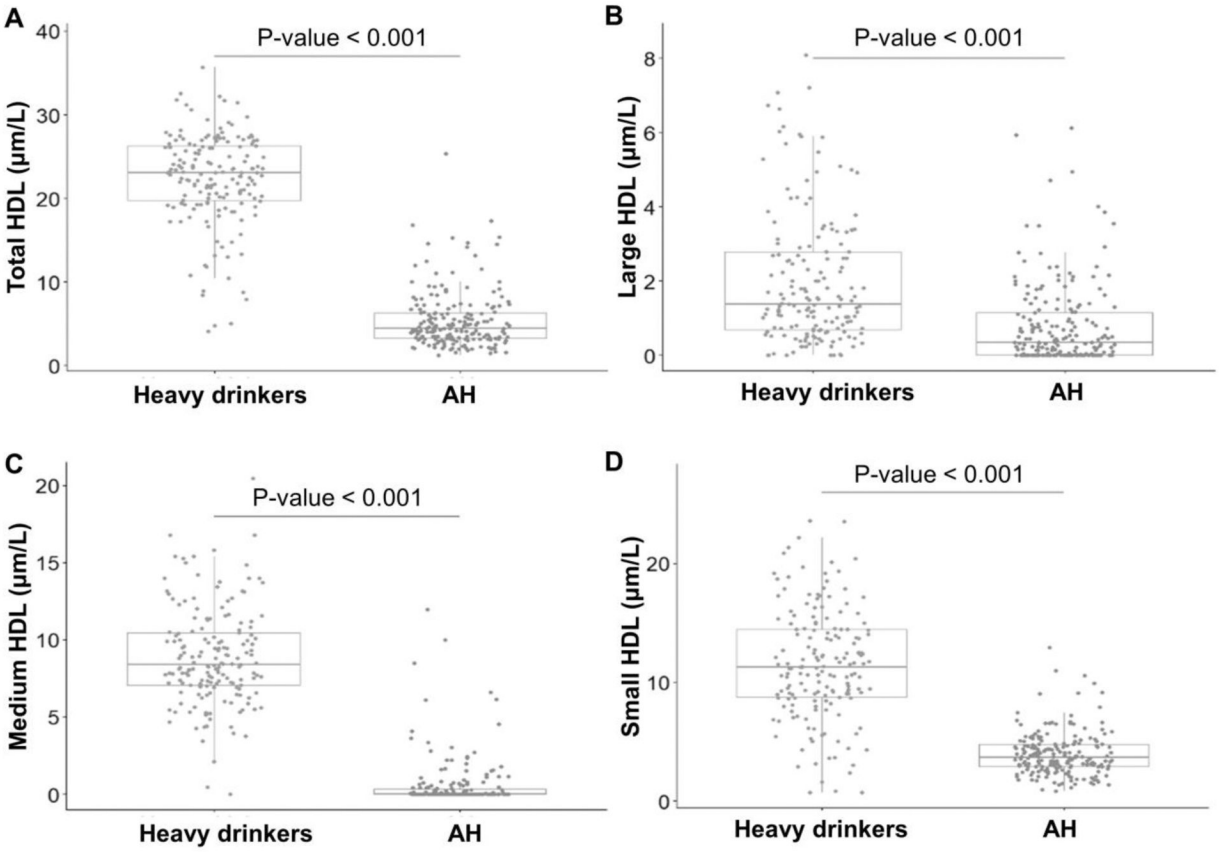

Figure 1. Comparisons of HDL levels between heavy drinkers and AH patients.

Box and Whisker plots of total HDL (A) and its subclasses: large (B), medium (C), and small (D) particle concentrations in heavy drinkers and AH patients. P-values calculated by Student's t-test.

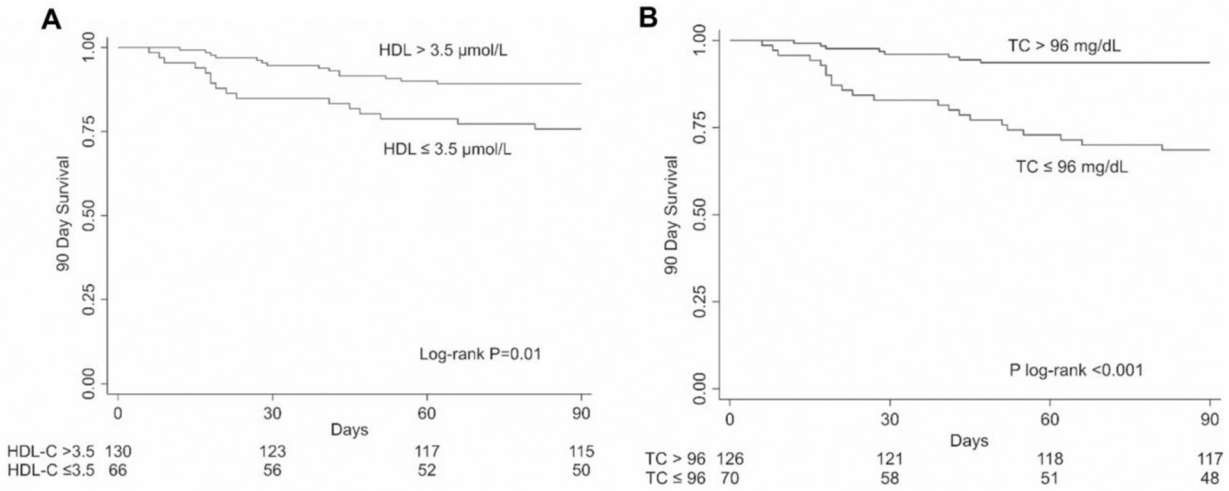

Figure 2. Kaplan-Meyer analysis of HDL and TC levels predicting 90-day survival.

Kaplan-Meyer survival curves at 90 days are compared between AH patients with HDL particle molar concentration ≤ 3.5 μmol/L vs. HDL > 3.5 μmol/L (A), and total cholesterol (TC) ≤ 96 mg/dL vs. TC > 96 mg/dL (B). P-values calculated by log-rank test. The number-at-risk tables are shown under each plot.

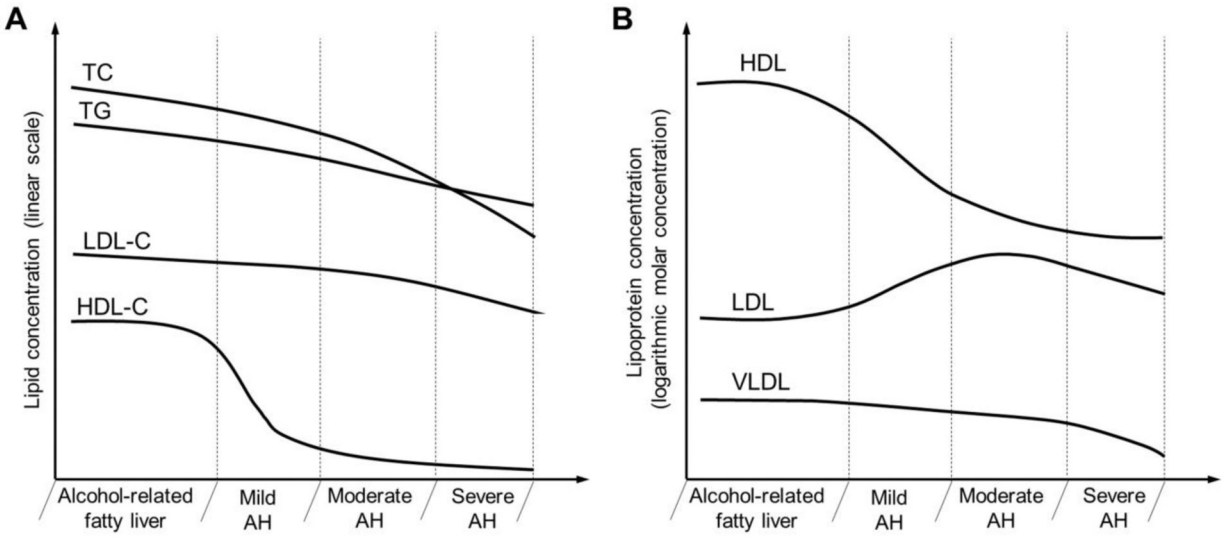

Figure 3. Diagrams of lipid and lipoprotein changes in ALD and AH

Conceptual diagrams of serum lipids (A) and lipoproteins (B) across alcohol-related fatty liver to mild, moderate, and severe alcoholic hepatitis.

Table 1.

Characteristics of study population at baseline.

	Heavy Drinker N=169	AH N=196	P-value
Age, years	44.4 ± 12.4	45.5 ± 10.9	0.4
Gender (male), n (%)	110 (65)	117 (60)	0.3
Race, n (%)			0.4
White	138 (81.7)	172 (87.8)	
Black	23 (13.6)	15 (7.7)	
American Indian or Alaska native	1 (0.6)	2 (1)	
More than 1 race	5 (3%)	5 (2.6)	
Unknown	2 (1.2)	2 (1)	
BMI (kg/m ^{2})	28.5 ± 6.7	29.1 ± 7.3	0.4
Comorbidities			
Hypertension, n (%)	33 (20)	24 (12)	0.06
Type 2 diabetes, n (%)	1 (1)	3 (2)	0.4
Hyperlipidemia, n (%)	2 (1)	2 (1)	0.9
Laboratory values			
Albumin (g/dL)	4.0 ± 0.6	2.8 ± 0.6	<0.001
Total bilirubin (mg/dL)	0.6 ± 0.6	14.2 ± 11.0	<0.001
INR	1.1 ± 0.3	1.8 ± 0.5	<0.001
ALT (U/L)	26.5 ± 12.4	62.2 ± 63.8	<0.001
AST (U/L)	28.5 ± 10.7	136.8 ± 83.5	<0.001
ALP (U/L)	76.5 ± 31.1	188.0 ± 137.1	<0.001
Creatinine (mg/dL)	0.9 ± 0.3	1.0 ± 0.9	0.170
AUDIT Score (Mean, SD)	27.2 ± 7.5	24.0 ± 8.7	<0.001
AUDIT Categories, n (%)			<0.001
0–10	8 (4.7)	15 (7.7)	
11–20	23 (13.6)	51 (26.3)	
21–30	72 (42.6)	83 (42.3)	
31–40	66 (39.1)	47 (24.7)	
Maddrey score (Mean, SD)	2.8 ± 9.6	42.97 ± 26.66	<0.001
MELD score (Mean, SD)	7.3 ± 2.4	22.55 ± 6.75	<0.001

Abbreviations: AH: Alcoholic hepatitis, BMI: Body mass index, INR: International normalized ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, AUDIT: Alcohol screening questionnaire, kg/m^2: kilogram per square meter, g/dL: gram per deciliter, mg/dL: milligram per deciliter, U/L: units per liter

Table 2.

Comparison of lipid and lipoprotein profiles between AH and heavy drinkers

	Heavy Drinker N=169	AH N=196	P-value
Lipid panel			
TG (mg/dL)	175.4 ± 121.9	127. 4 ± 78.0	<0.001
TC (mg/dL)	184.5 ± 38.0	137.4 ± 80.8	<0.001
LDL-C (mg/dL)	91.5 ± 26.9	82.7 ± 41.5	0.001
HDL-C (mg/dL)	59.0 ± 18.8	14.8 ± 14.9	<0.001
Lipoprotein Profiles			
Major lipoprotein classes			
Total TRL (nmol/L)	159.4 ± 78.4	142.2 ± 144.0	<0.001
Total LDL (nmol/L)	1456.1 ± 457.9	2435.8 ± 1250.0	<0.001
Total HDL (μmol/L)	22.3 ± 5.5	5.6 ± 3.4	<0.001
Mean lipoprotein sizes			
TRL (nm)	46.7 ± 10.5	38.6 ± 7.3	<0.001
LDL (nm)	20.8 ± 0.6	20.4 ± 1.2	0.002
HDL (nm)	9.1 ± 0.5	8.8 ± 1.2	<0.001

Abbreviations: AH: Alcoholic hepatitis, TG: Triglycerides, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, mg/dL: milligram per deciliter, TRL: triglyceride-rich lipoprotein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, nmol/L: nanomoles per liter, μmol/L: micromoles per liter, nm: nanometer,

Table 3.

Correlations between Lipoproteins and Maddrey score among AH patients

Variables	β coefficient[1]	95% CI	P-value	Adj. P-value[2]
Lipid panel				
TG (mg/dL)	−0.17	−0.31 to −0.03	0.02	0.002
TC (mg/dL)	−0.43	−0.54 to −0.31	<0.001	<0.001
LDL-C (mg/dL)	−0.42	−0.53 to −0.30	<0.001	<0.001
HDL-C (mg/dL)	−0.41	−0.52 to −0.28	<0.001	<0.001
Lipoprotein profiles				
Major lipoprotein classes				
Total TRL (nmol/L)	−0.17	−0.30 to −0.03	0.02	0.002
Total LDL (nmol/L)	−0.13	−0.26 to 0.01	0.08	0.01
Total HDL (μmol/L)	−0.49	−0.59 to −0.38	<0.001	<0.001
Mean lipoprotein sizes				
TRL (nm)	−0.19	−0.32 to −0.05	0.01	0.007
LDL (nm)	−0.09	−0.22 to 0.06	0.2	0.2
HDL (nm)	−0.18	−0.31 to −0.04	0.01	0.02

[1] Log transformed lipid and lipoprotein concentrations were used for analyses

[2] P-values adjusted for age, gender, and BMI.

Abbreviations: TG: Triglycerides, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, mg/dL: milligram per deciliter, TRL: triglyceride-rich lipoprotein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, nmol/L: nanomoles per liter, μmol/L: micromoles per liter, nm: nanometer

Table 4.

Baseline lipoproteins among patients with alcoholic hepatitis by outcomes

	Death (360 days)		
Variables	**No N=149**	**Yes N=47**	**P-value**
Lipid panel			
TG (mg/dL)	136.1 ± 80.5	99.4 ± 62.1	0.001
TC (mg/dL)	151.6 ± 84.1	92.03 ± 46.5	<0.001
LDL-C (mg/dL)	89.2 ± 42.8	61.7 ± 28.4	<0.001
HDL-C (mg/dL)	15.9 ± 16.1	11.2 ± 9.8	0.03
Lipoprotein profiles			
Major lipoprotein classes			
Total TRL (nmol/L)	156.1 ± 153.3	98.1 ± 97.7	0.003
Total LDL (nmol/L)	2560.1 ± 1280.4	2041.8 ± 1067.6	0.004
Total HDL (μmol/L)	5.7 ± 3.6	4.1 ± 2.1	0.001
Mean lipoprotein sizes			
TRL (nm)	39.3 ± 7.9	36.0 ± 3.4	0.09
LDL (nm)	20.4 ± 1.1	20.3 ± 1.2	0.2
HDL (nm)	8.8 ± 1.1	8.8 ± 1.2	0.5

Abbreviations: TG: Triglycerides, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, mg/dL: milligram per deciliter, TRL: triglyceride-rich lipoprotein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, nmol/L: nanomoles per liter, μmol/L: micromoles per liter, nm: nanometer

Table 5.

Mortality risk at 90 and 365 days associated with circulating lipids and lipoproteins

	Death at 90 days (n=30)					Death at 365 days (n=47)				
Variables	**Crude HR[1]**	**P-value**	**Adj. HR[2] (95% CI)**	**Adj. P-value**	**C-statistics**	**Crud e HR**	**P-value**	**Adj. HR (95% CI)**	**Adj. P-value**	**C-statistics**
Lipid panel										
TG	0.64	0.09	0.77 (0.45–1.34)	0.4	0.57	0.53	0.003	0.64 (0.42–0.98)	0.04	0.61
TC	0.18	<0.001	0.19 (0.08–0.45)	<0.001	0.75	0.23	<0.001	0.29 (0.15–0.55)	<0.001	0.72
LDL-C	0.22	<0.001	0.27 (0.12–0.58)	0.001	0.71	0.27	<0.001	0.37 (0.20–0.68)	0.001	0.68
HDL-C	0.39	0.003	0.49 (0.25–0.95)	0.04	0.67	0.65	0.05	-	-	-
Lipoproteins										
TRL	0.69	0.01	0.76 (0.54–1.06)	0.1	0.62	0.72	0.003	0.81 (0.62–1.06)	0.1	0.61
LDL	0.62	0.1	0.78 (0.41–1.50)	0.5	0.55	0.50	0.008	0.63 (0.38–1.05)	0.08	0.59
HDL	0.12	0.001	0.18 (0.04–0.75)	0.02	0.69	0.24	0.002	0.38 (0.14–0.99)	0.05	0.65

[1]HR calculated using Cox proportional-hazard model. Log transformed lipid and lipoprotein concentrations used for all analyses.

[2]Adjusted HR calculated when crude HR is significant. HR adjusted for age, gender, BMI, and Maddrey score.

Abbreviations: TG: Triglycerides, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TRL: triglyceride-rich lipoprotein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HR: Hazard ratio