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HDL proteome remodeling associates with COVID-19 severity

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KEYWORDS
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Background: Besides the well-accepted role in lipid metabolism, high-density lipoprotein (HDL) also seems to participate in host immune response against infectious diseases.
Objective: We used a quantitative proteomic approach to test the hypothesis that alterations in HDL proteome associate with severity of Coronavirus disease 2019 (COVID-19).
Methods: Based on clinical criteria, subjects (n=41) diagnosed with COVID-19 were divided into two groups: a group of subjects presenting mild symptoms and a second group displaying severe symptoms and requiring hospitalization. Using a proteomic approach, we quantified the levels of 29 proteins in HDL particles derived from these subjects.
Results: We showed that the levels of serum amyloid A 1 and 2 (SAA1 and SAA2, respectively), pulmonary surfactant-associated protein B (SFTPB), apolipoprotein F (APOF), and inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) were increased by more than 50% in hospitalized patients, independently of sex, HDL-C or triglycerides when comparing with subjects presenting only mild symptoms. Altered HDL proteins were able to classify COVID-19 subjects according to the severity of the disease (error rate 4.9%). Moreover, apolipoprotein M (APOM) in HDL was inversely associated with odds of death due to COVID-19 complications (odds ratio [OR] per 1-SD increase in APOM was 0.27, with 95% confidence interval [CI] of 0.07 to 0.72, P=0.007).
Conclusion: Our results point to a profound inflammatory remodeling of HDL proteome tracking with severity of COVID-19 infection. They also raise the possibility that HDL particles could play an important role in infectious diseases.
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Introduction

Subjects suffering from Coronavirus disease 2019 (COVID-19) experience a wide range of symptoms, from changes of taste and dry cough to fever, to shortness of breath, and thrombotic complications.[1] They may also present several clinical changes, including hyperinflammation[2] and endothelial dysfunction.[3] Alterations in lipid profile, i.e. HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and triglyceride (TG) levels have also been linked to disease severity.[4-8] Three different studies found an inverse correlation between HDL-C levels and COVID-19 severity.[5-7] Moreover, patients with severe COVID-19 evolution had lower HDL-C and higher triglyceride levels before the infection.[8]

Several studies support the concept that HDL particles may play a role combating infectious diseases.[9, 10] Low HDL-C levels are a poor prognostic for sepsis[11, 12], and low (and high) HDL-C levels associated with risk of infections in two large population studies.[13] Recently, low HDL-C levels were causally linked to infectious hospitalization. Importantly, these studies found an association of the cholesterol content of HDL and infection, but measurement of HDL-C may not capture all of HDL's proposed actions. HDL proteome is composed of about 90 different proteins[14], and it is altered in response to several chronic inflammatory diseases (i.e. type 2 diabetes[15], kidney disease[16], psoriasis[17], rheumatoid arthritis[18]). Loss of HDL functionality in an inflammatory scenario seems to be associated with the replacement of its most abundant protein, apolipoprotein A-I (APOA1), for inflammatory proteins, such as serum amyloid A 1 and 2 (SAA1 and SAA2, respectively).[19] However, it is unknown whether changes in HDL during infection are only reflecting the severity of disease or they play a role modulating the host response.

Contrasting with evidences showing HDL remodeling during bacterial infections, information about HDL and viral infectious is limited. A small study used semi-quantitative proteomics to compare HDL proteins of critically ill COVID-19 patients and healthy controls.[20] They found HDL derived from COVID-19 patients have increased levels of SAA family proteins, and was unable to inhibit apoptosis caused by TNF-α in endothelial cells. We recently standardized targeted mass spectrometric methods to quantify HDL's proteins cargo.[21-23] Unlike the semi-quantitative approach, targeted proteomics has high sensitivity, accuracy, and reproducibility, making it a reliable tool for quantification in a clinical setting.[24]

In the present work, we use robust quantitative proteomics to test the hypothesis HDL proteome composition associates with COVID-19 severity. We showed HDL of critically ill subjects is enriched in proteins related to inflammation and immune response. The results raise the possibility HDL particles are markers, and perhaps players in viral infectious diseases.

Methods

Study design

This study was carried out at the Heart and Central Institutes, University of São Paulo Medical School, Brazil, between March 2020 and July 2020 (CAAE 30299620.7.0000.0068). Plasma was collected from subjects (n=41) who tested positive for SARS-CoV-2. All subjects gave informed consent. Initially, three groups were established. Subjects who did not require hospitalization were classified as low-risk (n=11). After diagnosis, they were quarantined at home. Subjects who required hospitalization were classified as high-risk, being divided into two subgroups: severe and non-severe. Those who required the use of Venturi masks, non-invasive or invasive mechanical ventilation, dialysis and/or were admitted to the intensive care unit (ICU) composed the severe group (n=16). The remaining hospitalized patients who did not require mechanical ventilation and ICU were classified in the non-severe group (n=14). Because non-severe and severe groups were homogeneous regarding baseline parameters measured (**Supplemental Table I**), they were combined in a single hospitalized group of patients. In this way, two groups were considered for HDL proteomic analyses: hospitalized patients (n=30), composed of subjects from non-severe and severe subgroups, and non-hospitalized patients (n=11) composed of subjects from low-risk group. Baseline characteristics of these groups are displayed in **Table 1**.

HDL isolation and proteolytic digestion

HDL was isolated and digested as previously described.[21, 23] Details can be found in supporting information. Briefly, HDL was isolated from plasma by sequential density ultracentrifugation and its protein concentration was determined by the Bradford assay (Bio-Rad, Hercules, CA, USA). Ten micrograms of HDL protein were digested with trypsin (Promega, Madison, WI, USA), desalted, dried and stored at -80°C until MS analyses.

Targeted proteomic analyses

Digested HDL proteins (100 ng) were quantified by data-independent acquisition (DIA), as previously described.[21] Details can be found in supplemental methods. Briefly, data acquisition was performed using an Easy-nLC 1200 UHPLC coupled to an Orbitrap Fusion Lumos mass spectrometer (Thermo Scientific, Bremen, Germany). Twenty-nine proteins consistently detected in previous studies were selected

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[1] These authors contributed equally to the work.

Table 1   Baseline Characteristics from hospitalized and non-hospitalized subjects.

Characteristics	Non-Hospitalized (n=11)	Hospitalized (n=30)	P-value
Age, mean (SD)	49 (9)	54 (15)	0.339*
Sex, male, n (%)	2 (18)	23 (77)	0.001[†]
Reported previous comorbidities, yes, n (%)	6 (55)	22 (73)	0.280[†]
Clinical outcome			
Time of hospitalization (days)[‡], median [IQR]	-	6 [8 - 12]	-
Death, n (%)	0	6 (20)	-
Lipid panel			
Total cholesterol (mg/dL), mean (SD)	167 (40)	162 (54)	0.794*
HDL-C (mg/dL), mean (SD)	48 (9)	42 (10)	0.077*
LDL-C (mg/dL), mean (SD)	99 (34)	95 (45)	0.800*
non HDL-C (mg/dL), mean (SD)	119 (36)	121 (52)	0.935*
Triglycerides (mg/dL), mean (SD)	109 (44)	150 (69)	0.072*

Values are means and standard deviations (*two sample t-test), percentage ([†]Fisher's exact test) or [‡]median and interquartile range.

for targeted quantification by DIA.[21-23, 25] To monitor the reliability of the results, quality controls were employed in all steps of the analyses.

Statistical rationale and analyses

For baseline characteristics (**Table 1** and **Supplemental Table I**), categorical variables are presented as percentages, and continuous variables as means and standard deviations or medians and interquartile ranges for variables with non-normal distribution. Protein data were log2 transformed and statistical analyses between hospitalized and non-hospitalized COVID-19 patients were performed by linear regression, followed by Benjamini-Hochberg correction of the P-values (**Supplemental Table II**). Only proteins with corrected P-values < 0.05 were considered as statistically different. For HDL proteins significantly altered in hospitalized patients when compared with non-hospitalized group, a multiple linear regression controlling for sex, HDL-C and triglycerides (TG) was performed. Adjusted and non-adjusted beta coefficients and P-values are reported in **Table 2**. Principal Component Analysis (PCA) was employed to reduce data dimensionality and assess the variability among samples. A linear discriminant analysis (LDA) was applied to estimate the capabilities of selected proteins in discriminating between hospitalized and non-hospitalized patients (details in Supplemental Methods). For proteins with significant altered values comparing hospitalized and non-hospitalized groups (without controlling for multiple comparisons, **Supplemental Table II**), an exact logistic regression was used to estimate the association between deaths and HDL protein levels. Odds ratio are reported for a 1-SD increase in HDL protein level. Statistical analyses and plots were performed using R Studio software version 3.6.1 (RStudio, Inc.) or STATA software version 13.1. String version 11.0 was employed for functional enrichment analysis.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Study design and baseline characteristics

Our study was designed to investigate if alterations in HDL proteome associate with COVID-19 severity. Subjects who tested positive for SARS-CoV-2 (n=41, Fig. 1) were first classified in three distinct groups according to clinical criteria (details in Methods). The low-risk group (n=11) was composed of subjects who did not require hospitalization. Subjects requiring hospitalization were classified as high-risk, and further divided into non-severe (required hospitalization without respiratory interventions nor admission to the ICU, n=14) and severe (required respiratory interventions and/or were admitted to the ICU, n=16) groups. High-risk patients were homogeneous regarding all baseline parameters (**Supplemental Table I**), and were therefore combined into a single hospitalized group for HDL proteomics (n=30). HDL from non-hospitalized and hospitalized subjects was isolated by ultracentrifugation, its proteins digested with trypsin, and analyzed by quantitative mass spectrometry. Data from previous studies were employed to select 29 HDL proteins for relative quantification.[21-23, 25] Strict statistical analysis was used to control for multiple comparisons (see **Fig. 1** for workflow). Importantly, quality controls (QCs) were included in each step of the analysis (HDL isolation, digestion and mass spectrometry runs). Median CVs for all QCs are shown in **Fig. 1**.

Non-hospitalized and hospitalized subjects had similar age, similar number of previous comorbidities, and

Table 2   Beta coefficients for the association between protein abundance and hospitalization.

Protein	Non-Adjusted Model		Adjusted Model[†]	
	β* (95% CI)	P-value	β* (95% CI)	P-value
APOA2	-1.41 (-1.97 to -0.85)	<0.0001	-1.47 (-2.13 to -0.82)	<0.0001
APOA4	-0.95 (-1.60 to -0.29)	0.0056	-0.69 (-1.48 to 0.11)	0.087
APOF	1.41 (0.85 to 1.97)	<0.0001	1.52 (0.92 to 2.12)	<0.0001
APOL1	-0.91 (-1.57 to -0.25)	0.0079	-0.88 (-1.69 to -0.07)	0.034
C4A/B	0.85 (0.18 to 1.51)	0.015	0.83 (-0.02 to 1.67)	0.054
CLU	-0.83 (-1.50 to -0.16)	0.016	-0.20 (-0.95 to 0.55)	0.593
ITIH4	0.92 (0.27 to 1.58)	0.0071	1.26 (0.48 to 2.04)	0.0023
PLTP	-1.18 (-1.79 to -0.57)	<0.001	-1.12 (-1.89 to -0.36)	0.0051
SAA1	1.75 (1.30 to 2.20)	<0.0001	1.69 (1.17 to 2.27)	<0.0001
SAA2	1.57 (1.06 to 2.08)	<0.0001	1.49 (0.83 to 2.14)	<0.0001
SAA4	0.88 (0.21 to 1.54)	0.011	0.83 (-0.02 to 1.68)	0.055
SFTPB	1.51 (0.98 to 2.04)	<0.0001	1.27 (0.61 to 1.93)	<0.001

*Beta coefficient per 1-SD increase in protein abundance
[†]Linear model adjusted for Sex, HDL-C and Triglycerides.

lipid levels (**Table 1**). The median time of hospitalization was 6 days, and 6 (20%) deaths occurred in the hospitalized group. No deaths occured in the non-hospitalized group of subjects. Among the 30 hospitalized patients, 23 (77%) were men. Indeed, males are more susceptible to progress to more severe clinical outcome.[26]

HDL proteome is remodeled to an inflammatory profile in hospitalized patients

We first applied principal component analysis (PCA) to identify cluster of subjects based upon similarities in their HDL proteome, regardless their prespecified group (**Fig. 2**). Importantly, the first two dimensions on PCA were able to separate hospitalized and non-hospitalized subjects. With a combined variance of 41.7%, the two first dimensions (Dim1 and Dim2), explained 24.0% and 17.7% of the HDL proteome variance, respectively. The homogeneity of the hospitalized and non-hospitalized groups was also confirmed when we analyzed the PCA based upon the three initial groups: low-risk, non-severe and severe (**Supplemental Figure I**).

Next, we tested if the levels of HDL proteins would be altered depending on COVID-19 severity. After controlling for multiple comparisons, levels of 12 of 29 HDL proteins differed significantly in hospitalized patients when comparing with non-hospitalized subjects (**Fig. 3A**). HDL of hospitalized subjects was enriched with proteins of the serum amyloid A family (SAA1, SAA2, and SAA4). SAA1 and SAA2 were increased respectively by 19 and 31 times (P<0.0001), while constitutive SAA4 was increased by 33% (P=0.031) in hospitalized patients when compared with non-hospitalized subjects. In addition, increases of approximately 5 times in the mean levels of pulmonary surfactant-associated protein B (SFTBP, P<0.0001), 69% in the levels of apolipoprotein F (APOF, P<0.0001), 57% for inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4, P=0.025), and 34% for complement C4-A/B levels (C4A/B, P=0.038) were also seen. Interestingly, APOF and SFTPB negatively correlate with HDL-C (ρ=-0.46, P=0.003; ρ=-0.33, P=0.03, respectively).

A functional enrichment analysis showed acute-phase response, positive chemotaxis, cell chemotaxis, and inflammatory response are the most enriched biological processes in HDL of hospitalized subjects (**Supplemental Table III**).

In contrast, APOA2 (P<0.0001), phospholipid transfer protein (PLTP, P=0.002), apolipoprotein A-IV (APOA4, P=0.023), apolipoprotein L1 (APOL1, P=0.025), and clusterin (CLU, P=0.039) had their levels reduced by at least 30% in hospitalized subjects. All the reported P-values were adjusted for multiple comparisons. Distribution of the data for the 4 most significantly elevated proteins in hospitalized
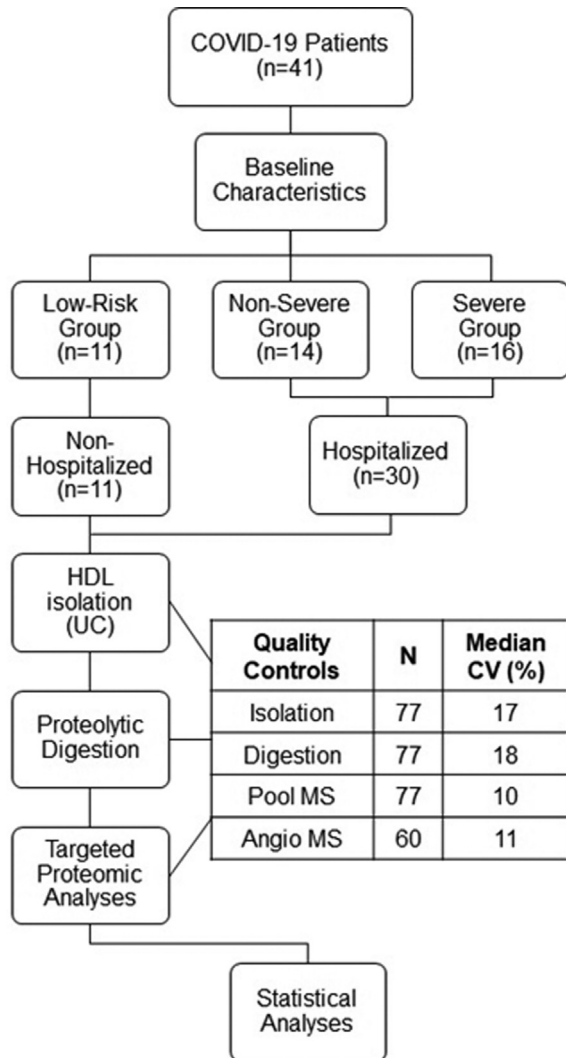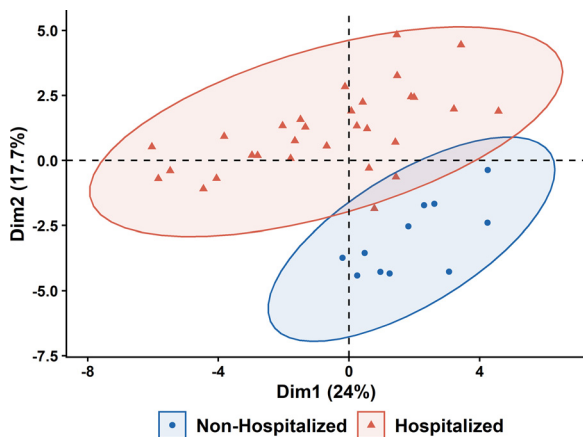
Fig. 1   Workflow.

Fig. 2   **Principal Component Analysis (PCA).** PCA plot representing 29 HDL proteins quantified by proteomics. Hospitalized subjects are represented as red triangles and non-hospitalized subjects are represented by blue circles.

patient (SAA1, SAA2, SFTPB and APOF), as well as for the 2 proteins with most significantly reduced levels (APOA2, PLTP) are shown in **Fig. 3**B.

For proteins significantly increased or reduced in hospitalized patients, we adjusted the linear regression model to control for sex, HDL-C and TG as covariates, because those variables either differed between the hospitalized and non-hospitalized groups (sex, **Table 1**) or because they are considered predictors for the severity of COVID-19 (HDL-C and TG).[8] The associations of COVID-19 severity and HDL protein levels do not depend on sex, HDL-C and TG for the majority of the proteins tested (APOA2, APOF, APOL1, ITIH4, PLTP, SAA1, SAA2 and SFTPB, **Table 2**). However, the adjusted model showed that APOA4, C4A/B, CLU and SAA4 do not remain statistically significant when controlling for sex, HDL-C and TG, as seen by the P-values and confidence intervals (CI) for the beta coefficients in **Table 2.** To facilitate interpretation, all beta coefficients were expressed as 1-SD increase in protein abundance.

HDL proteome is capable of classifying patients according to the disease severity

Next, we used linear discriminant analysis (LDA) to investigate if HDL proteome could discriminate whether or not a patient would be hospitalized. The final LDA model consisted of five proteins (APOA2, APOF, APOL1, SAA2 and SFTPB) which were chosen after a classification analysis using random forest algorithm (**Supplemental Figure II**). Applying a leave-one-out cross validation, our model was capable of classifying correctly 95.1% of the patients (classification error rate of 4.9%). The difference between scores for each group provided by LDA can be accessed in **Fig. 4**.

Apolipoprotein M is inversely associated with chances of deaths by COVID-19 complications

For HDL proteins with significant differences between low and high-risk patients (before adjusting for multiple comparisons, **Supplemental Table II**), we investigated if their levels would be associated with increased risk of death due to COVID-19 complications. In an exact logistic regression analysis, apolipoprotein M (APOM) levels in HDL were inversely associated with the risk of dying by COVID-19 complications (odds ratio [OR] per 1-SD increase in APOM was 0.27, with 95% CI of 0.07 to 0.72, P=0.007, **Supplemental Table IV**). Indeed, linear regression analysis showed subjects who died due to COVID-19 complications had lower levels of APOM in their HDL at entry into the hospital comparing with those who survived (P=0.004). SAA1 and SAA2 levels in HDL were positively associated with the odds of death by COVID-19, however with low precision. Thus, for each 1-SD increase in SAA1 levels in HDL, the odds ratio of death due to COVID-19 complications was 4.57 (95% CI 1.01 to 47.07, P=0.048). Likewise, for each 1-SD increase in SAA2 levels in HDL, the odds ratio of death by COVID-19 complications was 3.34 (95% CI 1.06 to 13.82, P= 0.037).
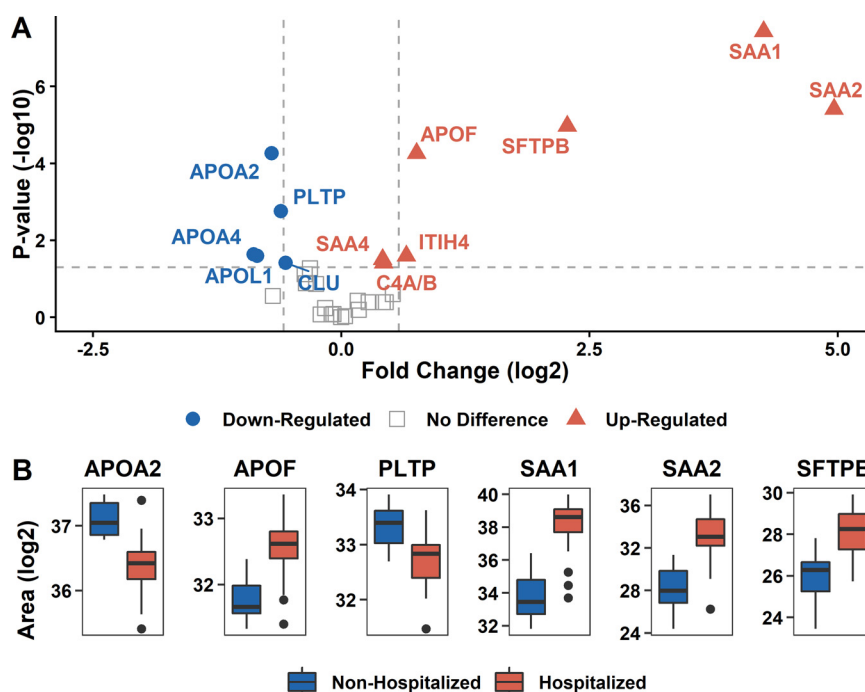
Fig. 3 HDL proteome associates with COVID-19 severity. (A) Differentially expressed HDL proteins obtained comparing hospitalized and non-hospitalized subjects. For each protein, the –log 10 of the adjusted P-value from linear regression is plotted against the log2 fold change between hospitalized (n=30) and non-hospitalized (n=11) groups. Proteins more abundant in HDL of hospitalized subjects are displayed to the right of the value 0 on the x-axis, while proteins less abundant are to the left. (B) Distribution of the most significantly altered proteins in hospitalized patients. The line in the center of each rectangular box is the median of the data, the upper and lower values of the rectangular box indicate the 75th and 25th percentiles, respectively, and the spikes are the range of the data.
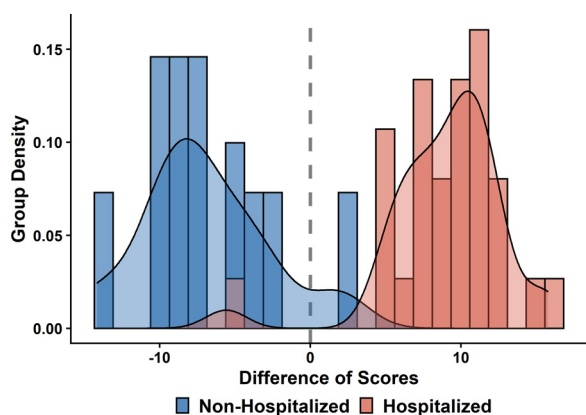

Fig. 4 HDL proteome is capable of classifying COVID-19 patients according to disease severity. Difference of scores provided by the linear discriminant analysis model. The bars and density plots represent the distribution of the data in the original group. Difference of scores lower than zero in the x-axis represent subjects classified as non-hospitalized according to LDA, while subjects classified as hospitalized are to the right (values greater than zero).

We did not find associations of HDL-C (95% CI 0.63 to 4.51, P=0.359) or triglycerides (95% CI 0.65 to 3.86, P=0.317) with odds of death due to COVID-19 (**Supplemental Table IV**).

Discussion

Besides its well-defined roles in lipid metabolism, HDL is known to participate in inflammatory and immune responses[27] and to play a role in infectious diseases.[13, 28] In this work, we investigated the association of HDL proteins with COVID-19 severity. Using quantitative mass spectrometry, we compared HDL proteome of hospitalized and non-hospitalized COVID-19 subjects. We identified five proteins highly increased (>50%) in hospitalized COVID-19 patients: SAA1, SAA2, SFTPB, APOF, and ITIH4, regardless of sex, HDL-C or TG levels. Functional analysis showed HDL of hospitalized COVID-19 subjects is enriched in proteins related to inflammation and immune response. In contrast, three proteins were found decreased by more than 30% in those same patients (APOA2, APOL1 and PLTP). Moreover, APOM in HDL was inversely associated with odds of death due to COVID-19 complications.

Acute phase proteins SAA1 and SAA2 have been previously associated with COVID-19 severity and prognosis.[29] In the present work, levels of SAA1 and SAA2 were elevated by more than 15 times comparing COVID-19 patients that required hospitalization with those presenting mild symptoms. These proteins may play an important role in disease severity, by promoting a pro-inflammatory HDL profile.[30-32] SAA-remodeling of HDL's protein cargo also im-

pairs cholesterol efflux capacity in mice and humans[33], and it is at least partially responsible for preventing mice HDL to inhibit palmitate-induced adipocyte inflammation.[34]

Surfactant protein B (SFTPB) is produced by type II pneumocytes and play an important role in the assembly of pulmonary surfactant film at the air-liquid alveolar interface.[35] SFTPB is increased in patients with acute respiratory syndrome, although the mechanism of SFTPB transference from lungs to plasma remains unclear.[36] In this report, HDL-associated SFTPB is increased more than 4 times in hospitalized patients, probably reflecting the respiratory distress seen in COVID-19 patients.

APOF was increased by more than 60% in hospitalized patients. APOF plays a role in inhibiting CETP-mediated exchange of cholesteryl esters and triglycerides between lipoproteins, but other physiological functions remain unknown.[37] A study employing clinical genetics and a humanized mouse model showed CETP inhibition preserved HDL-C levels and improved the outcomes in sepsis.[38] Interestingly, APOF knockout mice had reduced expression of Interferon alpha (IFN-α) responsive genes in liver and spleen.[39] Type I interferons (IFN-α and IFN-β) are secreted by cells in response to viral infection.[40] In a small study, APOF was elevated in serum of human papillomavirus (HPV) subjects comparing with negative controls.[41] These studies may point to a previous unsuspected role of APOF in viral infections, and reinforce a putative role of HDL against infectious diseases.

Studies of inflammatory HDL, i.e. enriched in SAA1 and SAA2, also show HDL is depleted in specific proteins, including several proteins that may be cardioprotective, such as APOA1.[33] APOA2 and PLTP are structural and metabolism-related proteins within HDL particle. APOA2-enriched HDL increases ABCA1-mediated cholesterol efflux, while APOA1-only containing HDL increases processes related to inflammation, immune response and acute phase response.[42] PLTP acts by transferring phospholipids from APOB-containing lipoproteins to HDL or between HDL particles.[43] The reduction in APOA2 and PLTP seen in hospitalized COVID-19 subjects raises the possibility severe COVID-19 infection remodels HDL to an inflammatory profile, with replacement of lipid metabolism-related proteins with proteins linked to inflammation and immunity. It is noteworthy altered HDL proteins (APOA2, APOF, APOL1, SAA2 and SFTPB) were capable of classifying correctly 95% of subjects according to the disease severity.

In this dataset, three proteins were also associated with odds of death. SAA1 and SAA2 were directly associated with increased odds of death due to complications caused by COVID-19, while APOM was inversely associated. Thus, subjects that progress to death during hospitalization had lower levels of APOM in their HDL at entry into the study (P=0.004). One possible mechanism linking APOM in HDL with lower odds of death from COVID-19 complications may come from the signaling lipid molecule sphingosine 1-phosphate (S1P). S1P is transported mainly bound to APOM (and thus, to HDL) in plasma and participates in vascular and immune responses.[44] APOM limits endothelial dysfunction by delivering S1P to its receptor in endothelial cells.[45, 46] Interestingly, endothelial dysfunction and dysregulated immune responses have been previously linked to the pathogenesis of severe COVID-19 patients.[47] HDL isolated from severe COVID-19 patients have shown a decrease in endothelial barrier function as measured in cultured endothelial cells challenged with TNF-α.[20] Moreover, HDL-bound S1P negatively associates with endothelial functional damage during sepsis.[48] In women with type I diabetes, APOM/S1P complex shifted from denser HDL to light HDL particles. Of note, APOM/S1P complex in light HDL particles was inefficient in inhibiting TNF-α–induced vascular cellular adhesion molecule-1 expression.[49] Thus, APOM levels may be important in preventing vascular inflammation in COVID-19 patients. In future studies, it may be important to evaluate the composition of HDL subclasses.

Two large prospective studies showed low and high concentrations of HDL-C are associated with risk of infectious disease in the general population.[13] Besides, measured levels of HDL-C were inversely associated with risk of infectious hospitalizations in a large prospective cohort from UK Biobank.[28] Interestingly, subgroup analyses suggested that the HDL-C polygenic score associated with protection against bacterial and viral infection, but not against fungal infection.[28] Also, HDL-related biomarkers robustly predicted survival in patients with chronic liver failure, who commonly suffer from bacterial infection mortality.[50] These studies provide strong evidence that HDL, quantified as HDL-C, is causally linked to host defense mechanisms against infection.[51] These studies do not address, however, potential mechanisms linking HDL and infectious diseases. Our results point to a profound inflammatory remodeling of HDL proteome tracking with severity of COVID-19 infection. They also raise the possibility that HDL proteins may play a role in preventing an uncontrolled inflammatory response.

Strengths of this work are a precise quantitative proteomic approach used to monitor differences in HDL proteins of severe versus mild COVID-19 infection. Furthermore, careful monitoring was performed for each step of the analysis (HDL isolation, digestion and mass spectrometry runs), indicating that the results were analytically robust.[52]

This work has also some limitations. First, we have a relatively small, unbalanced dataset. In this dataset, men were more likely to be hospitalized and die due to complications caused by COVID-19. Therefore, in our regression models, we controlled for sex. In fact, men are more susceptible to develop complications.[26] Moreover, our data on odds ratio is based on few outcomes. Thus, we used exact logistic regression to model the odds of death due to COVID-19 complications, and we are careful to point out the results should be confirmed in future studies.

Conclusion

In conclusion, SARS-CoV-2 infection induces a profound remodeling of HDL proteome, increasing proteins linked to immune response and inflammation, and reducing proteins related to lipid metabolism. The degree of changes in HDL proteome associate with severity of disease, and altered HDL proteins are able to classify COVID-19 subjects according to the severity of the disease. These findings raise the possibility HDL particles play an important role in infectious diseases.

Disclosures

None.

Contribution statement

G.E.R., L. R., and G.P. conceived and designed the study. L.R., F R.G., T.F.D., A.J.B., J.C. N., C.R.F.M., C.W., and R.F.S. acquired clinical data. D.R.S.J., A.R.M.S, L.R.R, G.A., S.D.B., M.R.L., and P.D.M. contributed with MS data acquisition. D.R.S.J., A.R.M.S., and G.E.R. performed data analysis and interpretation. D.R.S.J., A.R.M.S., and G.E.R. drafted the article. All authors reviewed and approved the final version of the article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2021.10.005.

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