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Original Article

Alterations in the lipid profile associate with a dysregulated inflammatory, prothrombotic, anti-fibrinolytic state and development of severe acute kidney injury in coronavirus disease 2019 (COVID-19): A study from Cincinnati, USA

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Abstract

Background and aims: Reduction of atherogenic lipoproteins is often the ultimate goal of nutritional interventions, however this is complicated given that hypolipidemia is frequently observed in coronavirus disease 2019 (COVID-19) patients. We aimed to explore the association of hypolipidemia with patient outcomes in terms of immunothrombosis and multiorgan injury, focusing on specialized apolipoproteins apo A1 and apo B.

Methods: Lipid profiles of 50 COVID-19 patients and 30 sick controls presenting to the Emergency Department (ED) were measured in this prospective observational study. The primary outcome was development of severe acute kidney injury (AKI). Need for hospitalization and ICU admission were secondary outcomes. Lipoproteins were analyzed for independent association with serum creatinine (SCr) increase ratio and correlated with a wide panel of biomarkers.

Results: COVID-19 cohort had significantly lower apo A1 (p = 0.006), and higher apo B/apo A1 ratio (p = 0.041). Patients developing severe AKI had significantly lower LDL-C (p = 0.021). Apo B/apo A1 was associated with 2.25-fold decrease in serum SCr increase ratio, while LDL-C with a 1.5% decrease. Hypolipidemia correlated with low plasminogen, ADAMTS13 activity/VWF:Ag, and high inflammatory biomarkers (CRP, IL-6, IL-8, IL-10), plasminogen activator inhibitor-1 (PAI-1), ED creatinine, and SCr increase ratio.

Conclusion: Although favored in dietetics, findings of a low LDL-C in COVID-19 patients should be alarming in light of our observations. Low apo B/apo A1 ratio and LDL-C are predictive of renal deterioration in COVID-19 patients, and low LDL-C in particular may potentially serve to indicate COVID-19 related AKI driven by disrupted fibrinolysis and a secondary thrombotic microangiopathy-like process.

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1. Introduction

Several studies have explored the alterations in lipid profile in the setting of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, reporting a state of hypolipidemia during active infection [1–3], with normalization after recovery [4]. These
changes have been attributed to inflammation, liver dysfunction, increased vascular permeability [3] and, interestingly, the interplay between cholesterol and viral replication [5]. However, the role of lipoproteins in the development of SARS-CoV-2-induced immunothrombosis and multi-organ injury has yet to be explored.

Numerous reports of thrombotic events in patients with Coronavirus Disease 2019 (COVID-19) [6–8], now called COVID-19 associated coagulopathy (CAC), have been attributed to endothelial dysfunction, dysregulated immune response, deranged hemostasis, and suppressed fibrinolysis [9]. Lipoproteins play an integral role in hemostasis and thrombosis, and low levels of atherogenic subtypes are sought after to reduce cardiovascular risk. Despite its proatherogenic role in arterial circulation [10], apolipoprotein B (apo B), a lipid largely bound to low density lipoprotein (LDL), possesses an antithrombogenic function in the venous system [11]. On the other hand, apolipoprotein A1 (apo A1), a component of high density lipoprotein (HDL), is ubiquitously antithrombogenic [10]. Morelli et al. observed significantly increased odds for venous thrombosis with lower apo A1 and apo B levels in a large case-control study [11]. In-vitro studies confirmed the role of apo B at inhibiting tissue factor mediated coagulation [12]. Likewise, apo A1 has been shown to prevent venous thrombosis in mice by upregulating nitric oxide availability and reducing inflammation, and in turn maintaining endothelial integrity [13], while in vitro studies demonstrated its potential at fostering the anticoagulant protein C pathway [14]. Thus, we hypothesize that the hypolipidemic state in COVID-19 patients may contribute to CAC, and in turn more severe outcomes via loss of antithrombotic effect provided by these specialized lipoproteins.

We aimed to analyze the lipid profile of COVID-19 patients at Emergency Department (ED) presentation with respect to outcomes over the course of illness, focusing on the role of more specialized apolipoproteins apo A1 and apo B and their relationship to biomarkers of inflammation and hemostasis. As we have previously observed that COVID-19 is associated with signs of a secondary thrombotic microangiopathy (TMA) involving the kidneys [15], we choose the development of severe acute kidney injury (AKI) as primary outcome, whilst need for hospitalization and ICU admission were set as secondary outcomes.

2. Methods

2.1. Study design and measurements

The lipid profile of 50 reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed COVID-19 patients, as well as that of 30 matched sick controls (respiratory symptoms with a non-COVID-19 discharge diagnosis and confirmed RT-PCR negative), presenting to the ED of the University of Cincinnati Medical Center (UCMC) was assessed using samples prospectively collected with routine blood draws. HDL-cholesterol, LDL-cholesterol, triglycerides (TG), and total cholesterol (TC) were quantified on a Dimension RxL Max System using proprietary materials (Siemens, Siemens, Munich, Germany), whilst the more specialized apo A1 and apo B were assayed with immunonephelometric assays on a Dimension RxL Max System using proprietary materials (Siemens, Munich, Germany), with a threshold of significance being p < 0.05. The Bonferroni method was used to correct for multiple comparisons when appropriate.

2.4. Ethics

This study was approved by the Institutional Review Board (IRB) of the University of Cincinnati and received a waiver of informed consent due to no greater than minimal risk to participants. This study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local and national legislation.

3. Results

3.1. COVID-19 cohort vs sick controls

A total of 80 patients were enrolled. The COVID-19 cohort was comprised of 50 patients, 30 (60%) males, with median age of 50.5 years (IQR: 40.5–66.0) years. The control group consisted of 30 subjects, 20 (66.7%) males, and with median age of 55.5 years (IQR: 33.2–63.7) years. No significant difference was found with respect to age (p = 0.591) or sex (p = 0.721). COVID-19 patients had significantly lower apo A1 levels (0.98 vs 1.23 g/L, p = 0.006) and
correspondingly higher apo B/apo A1 ratio (0.63 vs 0.55, p = 0.041) compared to sick respiratory controls, whilst no differences were observed for other lipoprotein values (Table 1).

3.2. Outcomes and lipid profile

In the COVID-19 cohort, 12 (24%) patients met the primary outcome of severe AKI, 31 (62%) met the secondary outcome of need for hospitalization, and 15 (30%) required ICU admission. Full demographics of COVID-19 patients are presented in Supplement 1. Lipid profiles stratified based on outcome are presented in Table 2. LDL-C was significantly lower in patients who developed severe AKI (55 vs 103 mg/dL, p = 0.007). Apo A1 levels were significantly lower in patients needing ICU admission (0.86 vs 1.01 g/L, p = 0.048). After correction for multiple comparisons, only LDL-C remained significantly different with respect to AKI severity (p = 0.021). Finally, the lowest apo A1, apo B and LDL-C levels were observed in the 3 non-survivors in our cohort.

Significant hypolipidemia (LDL-C <50 mg/dL and TC < 120 mg/dL) was observed in 9 (18%) patients, 5 of whom (55.5%) developed severe AKI. Hypolipidemia was significantly associated with progression to severe AKI (p = 0.0267), as was a low LDL-C (<50 mg/dL) value in isolation (p = 0.0059).

3.3. Multivariate analysis

Results of multivariate linear regression, adjusted for age, sex, comorbidities and statin use, and including apo A1 and apo B, are summarized in Table 3. Each unit increase in apo B/apo A1 was associated with an average decrease of 2.25-fold in SCr increase ratio (p = 0.02), while each unit increase in TG was associated with an average increase of 2.2% in SCr increase ratio (p = 0.003). The results of regression after excluding apolipoproteins are presented in Table 3, where both TG and LDL-C had significant estimated effects on SCr increase ratio. Each unit of TG increase was associated with an average increase of 1.3% in SCr increase ratio (p = 0.01), while each unit of LDL-C decrease was associated with an average decrease of 1.5% in SCr increase ratio (p = 0.04).

3.4. Correlations

Spearman’s correlation coefficients between lipid profile and inflammatory, liver function and kidney function biomarkers are presented in Supplemental Table 2, while correlations with markers of hemostasis are summarized in Supplemental Table 3. Apo A1 correlated inversely with CRP (r = −0.305, p = 0.037), IL-6 (r = −0.467, p = 0.001), IL-8 (r = −0.529, p < 0.001), IL-10 (r = −0.348, p = 0.018), LDH (r = −0.4, p = 0.005), PAI-1 (r = −0.495, p = 0.001), and ADAMTS13 activity/VWF:Ag (r = 0.381, p = 0.008). Apo B, LDL-C and TC all correlated inversely with IL-8 (r = −0.314, p = 0.034; r = −0.345, p = 0.019; and r = −0.369, p = 0.012; respectively) and positively with plasminogen (r = 0.396, p = 0.006; r = 0.301, p = 0.039; and r = 0.304, p = 0.038; respectively). LDL-C and TC all positively correlated with ADAMTS13 activity/VWF:Ag (r = 0.381, p = 0.008; and r = 0.338, p = 0.02; respectively). Apo A1, HDL-C and LDL-C were all correlated with initial ED creatinine (r = −0.41, p = 0.005; r = −0.335, p = 0.023; and r = −0.302, p = 0.041; respectively), but only LDL-C was associated with creatinine increase ratio (r = −0.388, p = 0.037). Apo B/apo A1 correlated with plasminogen (r = 0.331, p = 0.023) and PAI-1 (r = 0.38, p = 0.009) only. TG was not significantly correlated with any biomarker. Moreover, there were no significant correlations with fibrinogen, AST, ALT, D-dimer, platelet count, or PT.

4. Discussion

In this prospective study, we report measurements of lipid profiles in patients with COVID-19, and describe their relationship to developing severe AKI. Severe AKI in patients with COVID-19 has been found to be associated with poor outcomes, including significantly increased mortality and prolonged ICU stays [17,18].

Although apo A1, apo B, HDL-C and LDL-C displayed a trend toward lower levels in more severe outcomes, only apo A1 and LDL-C were significantly different between groups. Apo A1 was higher in sick controls, while LDL-C was higher in patients without severe AKI, which is consistent with linear regression for LDL-C that displayed an inverse relationship with SCr. A significant inverse effect of apo B/apo A1 on SCr is also consistent with findings for LDL-C, since apo B is the main protein moiety of LDL. Thus, lower LDL-C and apo B/apo A1 ratio seem to reflect deteriorating kidney function. While increased SCr predicted by increasing TG aligns with a large body of research demonstrating its role in progression of renal disease [19], a lack of differences between any outcome group, nor correlation with any biomarker, suggest that TG may be an independent predictor of renal deterioration, though not directly associated with the COVID-19 disease process. Elevations of TG in COVID-19 patients and sick controls, may be attributed to increased fatty acid re-esterification and inhibition of lipoprotein lipase, as observed in many other infectious and inflammatory processes [20].

Overall, our observations align with previous reports, wherein low HDL and LDL levels have been associated with disease severity and progression [1,2] as well as with increased length of hospitalization [4].

In correlation with other biomarkers, we observed that a hypolipidemic state in COVID-19 would potentially be associated with an “anti-fibrinolytic state”, as apo A1 negatively correlated with PAI-1, while apo B, apo B/apo A1, LDL-C, and TC were positively associated with plasminogen. Thus, the low LDL-C that we observed to be independently associated with elevated SCr, would likely be accompanied by low plasminogen state, resulting in reduced fibrinolytic capacity. Moreover, as most of the lipoprotein parameters were inversely correlated with inflammatory biomarkers (i.e., CRP, IL-6, IL-8, and IL-10), it follows that a state of dysregulated immune response would likely accompany low apo A1, apo B, LDL-C and TC, and concomitantly be associated with a temporary “fibrinolysis shutdown”, giving some ground to the findings suggestive of hypolipidemia in severe AKI.

We also observed that apo A1 and LDL-C positively correlated with ADAMTS13 activity/VWF:Ag ratio, an indicator of the balance
between the levels of pro-aggregant VWF and the protease (ADAMTS13) which cleaves it to prevent excessive and inappropriate thrombosis [15]. Low ADAMTS13 activity/VWF:Ag ratio reflects a heightened state of hypercoagulability and is characteristic of TMA, a phenomenon which we previously reported as potential contributor of AKI in COVID-19 patients [15]. In keeping with our findings, it follows that the low LDL-C values seen in patients with high SCr would be accompanied by low ADAMTS13 activity/VWF:Ag ratio, a pattern strongly suggestive of TMA.

Given that apo B is conventionally characterized as being pro-atherogenic, and apo A1 anti-atherogenic [10], such that a high apo B/apo A1 ratio reflects an elevated risk of cardiovascular disease, a low apo B/apo A1 ratio and low LDL-C predicting depressed kidney function suggest that hypolipidemia may be a more important factor in COVID-19 prognosis than any thrombomodulating effect that lipoproteins may have. However, the low ratio predicting depressed renal function may not be explained in terms of loss of anticoagulant properties of apo A1 and apo B in the venous system in COVID-19 associated hypolipidemia either, as previously hypothesized [11]. We failed to observe any significant correlations with fibrinogen nor with PT, a marker of extrinsic pathway which should be concomitantly prolonged via apo B-mediated inhibition of tissue factor [12]. Instead, our observations seem to point at a picture of thrombosis and organ failure in the setting of hypolipidemia precipitated by "fibrinolysis shutdown" and TMA.

Observed lipoprotein alterations, including low LDL-C, HDL-C, and apo A1 may be explained by changes characteristic to the acute phase response, as seen in many other inflammatory processes, such as acute coronary syndrome [20]. Despite increased LDL-C synthesis, serum LDL-C decreases due to concurrently greater increase in LDL receptor expression [21], while activation of endothelial lipase and soluble phospholipase A2 results in serum HDL-C depletion [20]. Apo A1 content in HDL-C is reduced by as much as 73% in the acute phase response [22]. Moreover, accumulation of serum amyloid A and ceruloplasmin in HDL-C during the acute phase response results in a more pro-inflammatory molecule [22].

Additionally, Wei et al. attributed this hypolipidemic state to increased extravasation of lipids and synthetic liver dysfunction [3]. However, the lack of correlation with AST and ALT in our cohort alludes to a more complex explanation. Extensive research on SARS-CoV has demonstrated that cholesterol microdomains found on plasma membranes are critical for attachment of coronaviruses [23–25]. With respect to SARS-CoV-2, Roccaforte and colleagues linked the hypolipidemic state to the process of viral internalization into host cells [5], and a recent meta-analysis observed statin use to be associated with improved outcomes, by reducing the amount of cholesterol available for viral attachment, being associated with a lower basal cardiovascular risk (including renal arterial atherosclerosis), or both [26]. Importantly, Wang et al. outlined that severe drops in blood cholesterol may in fact indicate loading of cholesterol onto cell membranes to facilitate viral entry [27]. Given that statins reduce apo B levels [28], concerns have previously arisen as to their potential to reverse the anticoagulant effect of atherogenic lipoproteins [11,12]. Nonetheless, having observed no correlation with the coagulation cascade in our cohort, this effect might be clinically insignificant, at least in COVID-19 patients.

Interestingly, the 3 non-survivors in our cohort had the most drastically depleted apo A1, apo B and LDL-C levels, which corroborates observations of several other reports [1,3,29], although no effect has been previously observed with apo B. Although statin use might have been a confounder to some extent in these patients, such significant depletions may actually represent vigorous viral replication explaining the unfavorable outcome [27]. Whether hypolipidemia is directly involved in poor outcome in COVID-19 is unclear, nonetheless the correlations we found with dysregulated inflammation, TMA-like process and "fibrinolysis shutdown" support the idea that lipid status at minimum may be a "bystander" that mirrors the pathological processes occurring within the body during progression of SARS-CoV-2 infection.

Our study has several methodological limitations. First, with
only 80 patients, the sample size was fairly small, which may have limited the power to identify certain differences in lipoproteins. For instance, Wang et al. observed that HDL was significantly lower among those that developed severe events in a cohort of 228 COVID-19 patients [2]. While in this study, we only observed a statistically insignificant trend of lower HDL in patients with more adverse outcomes. Thus, a study with a larger cohort is merited. However, finding a statistically significant difference with LDL-C in a study with high likelihood of making a false negative error, even after correction for multiple comparisons, increases our confidence that this result is valid and consistent with prior research findings. Moreover, our study is benefited by the large number of correlated biomarkers analyzed, enabling multi-system analysis. Second, this study was exploratory, so we did not control for multiple comparisons. Third, severe AKI may have been too specific a biomarkers analyzed, enabling multi-system analysis. Second, this after correction for multiple comparisons, increases our confidence

In conclusion, we found evidence of alterations in lipoproteins at ED presentation in COVID-19 patients subsequently developing severe AKI. A low apo B/apo A1 ratio and LDL-C are predictive of elevated Scr increase ratio and may potentially serve as indicators of renal deterioration in COVID-19 patients. Despite being desired in dietetics, a significantly low LDL-C may be an alarming finding in COVID-19 patients. Hypolipidemia, in particular low LDL-C, is associated with dysregulated immune response, decreased fibrinolysis, with low plasminogen and high PAI-1, as well as decreased ADAMTS13 activity/VWF:Ag ratio, which seems suggestive of a secondary TMA-like process driving COVID-19 related AKI.

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**Ethical statements**

Ethical Review: This study was approved by the Institutional Review Board (IRB) of the University of Cincinnati.

Informed Consent: This study received a waiver of informed consent due to no greater than minimal risk to participants.

**Data availability**

Data available on reasonable request from the authors.

**Declaration of competing interest**

The authors declare that they do not have any conflict of interest.

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None.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsx.2021.04.011.

**Author contributions**

BMH and GL conceived and designed the study. BMH, SWB, and JLB collected samples and ran experiments. JLB and MHSO performed data acquisition and collection. BMH, IS, and MHSO did data analysis. BMH, IS, MFA, SWB, JLB, and GL interpreted the data. IS prepared the first draft. BMH, MHSO, MFA, SWB, JLB, and GL critically revised the manuscript for important intellectual content. All authors have approved the final article.

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