International Journal of Medical Science and Health Research

Vol. 5, No. 04; 2021

ISSN: 2581-3366

Level of High-density Lipoprotein (HDL) and Triglycerides (TG) Predict Covid-19 Severity: The Systematic Review

Daniel Setiawan Nathan, Hoo Yumilia
Division of Endocrine Metabolic Diabetes Departement of Internal Medicine
Faculty of Medicine Maranatha Christian University/Immanuel Hospital

doi: 10.51505/ijmshr.2021.5408 URL: http://dx.doi.org/10.51505/ijmshr.2021.5408

Abstract

Background: Lipids have many functions that are indispensable in lung biology and the pathophysiology of viral infections. Methods: Systematic review with data sources derived from internet literature in the form of research results, both on Cochrane, Pub Med, Google scholar, and other journal databases. Researchers searched for the keywords "High-Density Lipoprotein (HDL)" or "High-Density Lipoprotein (HDL)"; "Triglycerides (TG)" or "Triglycerides (TG)"; "Predict Covid-19 Severity" or "COVID-19 Severity". The research included in this article is a study that focuses on the severity of Covid-19 based on HDL and TG levels. Results: Searching the Pub med journal database, we found only one journal that discussed the relationship between HDL and TG on the severity of Covid-19. A Google scholar search shows four studies that are relevant to this study. Conclusion: Low HDL levels and high triglyceride levels may be associated with longer hospital stays, increased inflammatory markers, need for ICU and mechanical ventilation, and poorer prognosis.

Keywords: COVID-19, High density lipoprotein, Triglyceride

BACKGROUND

Corona Virus Disease 2019 (Covid-19) (formerly also known as Wuhan Novel Coronavirus) is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is closely related to the SARS virus.[1] Viruses access host cells via angiotensin converting enzyme-2 (ACE2). Angiotensin converting enzyme-2 is found in various organs of the body, but is most abundant in type II alveolar cells of the lung. This explains why the lungs are the most affected organs.[2]

The density of ACE2 in each person is a determinant of the severity of the disease. Along the development of alveolar disease, SARS develops which can lead to respiratory failure and death. Angiotensin converting enzyme-2 can be a pathway for viruses to invade the heart causing acute cardiac injury. People with cardiovascular conditions have the worst prognosis.[2]

The infection can spread from one person infected with Covid-19 to another through respiratory droplets produced by the airways which are often expelled with coughing. The time from exposure to the onset of symptoms is generally between 2-14 days, with an average of 5 days.[3]

Vol. 5, No. 04; 2021

ISSN: 2581-3366

Covid-19 has emerged with various clinical manifestations, ranging from asymptomatic conditions to severe respiratory disorders, dysfunction of various organs, and death.[4]

Lipids have many functions that are indispensable in lung biology and pathophysiology of viral infections. Pulmonary surfactant contains >90% lipid and 10% protein by weight.[8] Cholesterol is the main neutral lipid of pulmonary surfactant, and is involved in suppressing viral respiratory tract infections.[9] Lipid tracking studies have shown that >80% of pulmonary cholesterol is of plasma origin.[10]

Lipids are also involved in various stages of the viral life cycle; they are important components of membranes and thus indispensable for the formation and function of viral replication complexes. Lipids are also an integral part of the innate and adaptive immune systems in the occurrence of infection. The appearance of the lipid profile undergoes significant changes during acute infection. Lipid changes that are commonly found in acute infection are a decrease in total cholesterol (TC) and an increase in the concentration of TG.[10,11]

The standard clinical approach to assessing alterations in lipid metabolism is based on the measurement of cholesterol in several lipoprotein particles and triglyceride levels. Researchers have not determined how these parameters will improve our understanding of the important role of cellular lipids in viral infections. Infectious diseases are usually associated with low HDL cholesterol (HDL-C) concentrations and sometimes with low LDL cholesterol (LDL-C) concentrations, while triglyceride levels are typically maintained or even increased.[6] Low HDL-C levels have been proposed as a risk biomarker for different infections12. Regarding the SARS-CoV-2 infection, low LDL-C, HDL-C and triglyceride (TG) levels have been described to be associated with an increasing infection severity, and a role for these lipids in immune mechanisms has been suggested.[7] Low lipid levels during the infection have been associated with the severity of COVID-19. Meanwhile, low plasma lipid concentrations are regarded as a consequence of the hypermetabolic state and undernutrition in the infected patient; however, many metabolic pathways associated with the immune response and infection itself participate in these alterations.[25] Cytokines, inflammatory mediators, modified lipids and intermediate lipid classes generated during the infection interfere with several steps of lipid metabolism by reducing cholesterol synthesis and absorption, decreasing triglyceride-rich lipoprotein clearance or reducing apolipoprotein (apo) A1 synthesis.[26]

Cholesterol *low*- and high-*density lipoprotein cholesterol* (LDL-C and HDL-C), levels of apolipoprotein-A1, and apolipoprotein-B decreased. These lipid changes may have a prognostic and diagnostic role in certain infections. Little is known about the effects of acute viral infection on lipid metabolism, and detailed information on lipid profile changes during COVID-19 infection is lacking.[10,11] This article aims to see the relationship between HDL and LDL levels on the severity of Covid-19.

Vol. 5, No. 04; 2021

ISSN: 2581-3366

METHOD

This research is a systematic review. The source of this research data comes from literature obtained through the internet in the form of research results published on the internet, both in Cochrane, PubMed, Google scholar, and other journal databases. Researchers searched for the keywords "High-Density Lipoprotein (HDL)" or "High-Density Lipoprotein (HDL)"; "Triglycerides (TG)" or "Triglycerides (TG)"; "Predict Covid-19 Severity" or "COVID-19 Severity". The research included in this article is a study that focuses on the severity of Covid-19 based on HDL and TG levels.

The inclusion criteria of the research that will be included are studies that examine the severity of Covid-19 based on lipid profiles, research subjects are adults (not animal studies), and use primary data. The purpose of this study was to examine the relationship between levels of High-Density Lipoprotein (HDL) and Triglycerides (TG) in predicting the severity of Covid-19.

RESULT

There is little to known regarding the research of Covid-19, mainly because Covid-19 is a newly discovered disease. The search results in the Pubmed journal database, we only found one journal that discussed the relationship between HDL and TG on the severity of Covid-19. A Google scholar search shows four studies that are relevant to this study. All information about the studies involved in this systematic review can be seen in Table 1.

Vol. 5, No. 04; 2021

ISSN: 2581-3366

Table 1. Search result

Author	Country	Method	Sample Size	Population	Period	Lipid Level	Outcame Results
Qin, 2020[10]	China	Retrospective study	248 patients	Patients >18 years old admitted to Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, and Yichang Third People's Hospital	February 14 and April 5, 2020	The mean levels of TG and HDL in all patients upon admission to the hospital were 1.11 and 0.89 mmol/L, respectively.	TC < 3.75 mmol/L at admission was an independent predictor of longer LOS. The 29-day LOS group had lower mean concentrations of TC, HDL-C and TG at admission than the >29-day LOS group.
Masana, 2021[12]	Spain	Observational cross-sectional study	1.411 patients	COVID-19 patients present in the STACOV data (cohort registration code NCT04407273-STACOV) with available lipid profiles	Until May 31, 2020	The mean of HDL and TG of the study patients before hospital admission were 1.3 and 1.37 mmol/L, respectively, while after hospital admission were 3.65 and 1.76, respectively.	Patients with advanced disease showed higher TG levels (1.3 for mild vs. 1.44 for severe) and lower HDL (1.32 for mild vs. 1.25 for severe).
Zhang, 2020[13]	China	Retrospective study	98 patients	COVID-19 patients being treated at a tertiary teaching hospital in Wuhan	February 6 to February 28, 2020	The mean of TG and HDL of patients admitted to non-ICU rooms were 1.3 and 1.0, while those admitted to the ICU were 1.5 and 0.8, respectively.	Those who died had mean higher TG levels and lower HDL than survivors (1.6 vs 1.3 for TG and (0.7 vs 0.9 for HDL)
Alonso, 2020[14]	Mexico	Cohort study	43 patients	Adult patient with a diagnosis of COVID-19	May to October 2020	The median and range of TG and HDL of patients admitted to the hospital were 147 (72-513) and 29.5 (9.6-63.5, respectively).	Critically ill patients have higher triglyceride levels and lower HDL.
Peng, 2020[15]	China	Retrospective study	262 patients	Adult patient with a diagnosis of COVID-19	Until March 26, 2020	The mean of TC/HDL ratio of survivors was lower than that of non-survivors (4.5 vs 5.0)	TG/HDL ratio is associated with mortality of COVID-19 patients (p value 0.009)

Vol. 5, No. 04; 2021

ISSN: 2581-3366

DISCUSSION

Coronaviruses are a large family of zoonotic respiratory viruses that can cause seasonal flu symptoms and respiratory failure associated with severe inflammation of the lower respiratory tract. Comorbidities such as cardiovascular disease, diabetes, respiratory disease, hypertension and old age can exacerbate disease manifestations. Moderate and severe cases of COVID-19 infection can cause pneumonia with subtle cloudiness on a chest computer tomography scan, pulmonary edema and accumulation of pleural fluid in the lungs. Severe cases may require invasive oxygen supply.[16]

The lipid profile is associated with pulmonary biology and pathophysiology of viral infection, but several studies have demonstrated altered lipid profile in viral pneumonia. There is no specific information regarding the relationship between lipids and Covid-19.[17.18] There is a large gap between dyslipidemia before infection and the time at which lipid disturbances were detected during hospitalization.[12] Infected patients had lower TC, LDL, HDL and non-HDL levels than before the disease, but significantly higher TG levels.[12]

Qin (2020) also points out that The gradual increase in TC, LDL, and HDL levels in their examination was inconsistent with other reports of studies of acute infectious disease, namely changes in the overall lipid profile, including decreased levels of TC, LDL-C, and HDL-C and increased TG concentrations.[11] Patients with length of stay <29 days had lower concentrations of TC, LDL-C, HDL-C, and TG than those with length of stay >29 days.[10]

Rate The TC in the study was lower than the threshold for hypocholesterolemia, included in the second and third examinations.[10] The increase in TC and LDL-C concentrations in the group with length of stay >29 days remained lower than in the group with length of stay <29 days. This shows that lower cholesterol levels are correlated with length of stay and recovery from Covid-19.[10] Hypocholesterolemia is associated with exacerbation of viral infections.[19]

Research conducted by Alcantara (2021) shows that low plasma HDL levels and an elevated Tg/HDL ratio at the time of diagnosis of Covid-19 are associated with hospitalization requirements and disease severity as critical care patients exhibit the lowest HDL concentrations and the highest Tg/HDL ratio compared to severe and mild/asymptomatic COVID-19 patients.

Persistent increases in TG levels and decreases in HDL levels are associated with clinical and biochemical data on COVID-19 severity, such as elevated levels of LDH, which is an Inflammatory markers previously proposed as predictors of poor prognosis in COVID-19 patients and with the NEWS 2 early warning score published by the Royal College of Physicians performed well in the prediction of severity and mortality in COVID-19 patients.[14]

Low HDL concentrations are also associated with high levels of ferritin, a protein associated with inflammatory process and has previously been reported to be elevated in severe COVID-19 patients, is associated with SARS-CoV-2 viremia has been proposed as a predictor of mortality

Vol. 5, No. 04; 2021

ISSN: 2581-3366

for the disease. Low HDL levels are also associated with high qSOFA which is another early warning score associated with COVID-19 mortality.[14]

We also found a negative correlation between plasma HDL and length of hospitalization within the needeed for invasive mechanical ventilation and the positive correlation with the SaO2/FiO2 index, all variables associated with the severity of COVID-19.[14] Studies conducted by Kaysen (2018) show that lipid levels are inversely related to death from viral infection.[19]

Other studies have shown that mortality of Covid-19 are associated with ARDS requiring invasive ventilation. Based on available statistics, a number of clinical predictors of damage and death from COVID-19, including secondary infection, lymphopenia, comorbidities, increased production of cytokines and serum ferritin. Elevated of serum creatinine, D-dimer, lactate dehydrogenase, CRP, procalcitonin, and elevated white blood cell count may indicate impending respiratory failure and the need for invasive oxygen supply.[16]

The mechanism of reducing lipid profile levels in patients with Covid-19 infection is still not well understood. One acceptable hypothesis said that increased of cholesterol consumption is associated with pulmonary surfactant synthesis and viral replication. Inadequate nutritional intake and inability to synthesize cholesterol in weak and severely ill of Covid-19 patients can also be the reasons.[10]

Hypercatabolic status and malnutrition during acute infection also play a role. Patients with severe evolution show significantly higher TG and lower HDL levels. This condition indicates that the factors associated with the evolution of Covid-19 and affect these lipid parameters. Patients with poorer clinical outcomes are generally older and have more comorbidities that may account for differences in lipid levels.[12]

The combination of low HDL levels and high triglycerides is known as atherogenic dyslipidemia. This condition is associated with qualitative changes in LDL particles that lead to increased levels of small and LDL particles solid. This pattern is driven by insulin resistance and usually associated with diabetes and obesity. Body mass index and prevalence rates of diabetes and obesity were similar between groups with mild or severe COVID-19 changes.[12]

Strong scientific evidence supports the hypothesis that inflammatory states and infectious diseases are associated with marked changes in lipid metabolism.[11] The general pattern is exactly that observed in Masana's (2021) study which showed that HDL-C levels were low and triglycerides were normal or even high for the clinical context. LDL levels can remain or decrease, but are generally associated with an increase in smaller LDL particles.

Viral infections can also cause changes in lipid biomarkers in the host. This can cause the cholesterol transport process to being disrupted. These conditions can help them invade the host's defenses. The acute inflammatory response in COVID-19 called a cytokine storm can also cause dysfunction of HDL and LDL particles. In addition, a spike in pro-inflammatory cytokines can

Vol. 5, No. 04; 2021

ISSN: 2581-3366

lead to consumption of albumin, ApoA1, HDL, TC, TG, LDL-C, along with a decrease in lymphocytes.[20.21]

Insulin resistance plays an important role in lipid disorders and the pathophysiology is more complex. The key enzymes that participate in this change are *lipoprotein lipase* (LPL). Several mediators interfere with glucose and lipid metabolism. Several cytokines and inflammatory mediators that are overexpressed during COVID-19 may interact directly with LPL or the proteins that regulate it, such as apo CII.[22]

Inflammatory cells can release large amounts of cytokines in a pathophysiological process during SARS-CoV-2 infection, thereby causing inflammation.of cytokines that induce the rapid development of multiple organ dysfunction or even death.[23] Several products transferred by activated macrophages, such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-11, and Interferon-γ as well as products of bacterial origin, such as lipopolysaccharide (LPS) are associated with septicemia, whereas lipoproteins are associated with septicemia. Modifications such as oxidized LDL or lysophosphatidylcholine have been shown to inhibit LPL activity.[12]

Lots of evidence demonstrate that impaired function and an exaggerated inflammatory response are associated with death from COVID-19. Peng's (2020) study showed that the TG/HDL ratio was positively related to leukocyte, neutrophil, and CRP levels. An increase in the TG/HDL ratio can lead to an increase in interleukin-6. Two studies also support the link between HDL and TG to increase D-Dimer. All the processes mentioned above are related to the cytokine storm.[14.15]

The causal and bidirectional relationship between the inflammation and thrombosis is well established. COVID-19 causes a highly pro-inflammatory state, as evidenced by several reports showing increased levels of C-reactive protein, lactate dehydrogenase, ferritin, interleukin-6 and D-dimer. The levels of IL-6 and fibrinogen have been shown to be closely related in COVID-19 patients, thus convincing experts that the notion of inflammatory thrombosis is possible.[24]

Zhang (2020) demonstrated that the TG/HDL-C ratio, an indicator of insulin resistance, was independently associated with myocardial infarction, heart failure, disease severity (needing ICU), and fatal seal in patients with COVID-19. Evaluation of the TG/HDL-C ratio is required for clinical management in adult patients with COVID-19. Close monitoring and intensive treatment of patients with an elevated TG/HDL ratio are necessary to avoid adverse events (myocardial infarction, heart failure, etc.). However, Zhang's research conclusions still need to be confirmed by further prospective studies.

CONCLUSION

Low HDL levels and high triglyceride levels may be associated with longer of hospitalization, increased inflammatory markers, need for ICU and mechanical ventilation, as well as worse prognosis.

Vol. 5, No. 04; 2021

ISSN: 2581-3366

REFERENCE

1. World Health Organization (WHO). Naming the coronavirus disease (COVID-19) and the virus that causes it. Geneva: 2020.
2. Hessen MT. Novel Coronavirus Information Center: Expert guidance and commentary. Else Connect: 2020.
3. Gorbale AE. Severe acutee respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. BioRxiv. 2020;2(7):93–7.
4. Huang C; Wang Y; Li X; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, Cdespicable. Lancet. 2020;395(10334):497–506.
5. ICM Anesthesia COVID-19. Pediatric tracheostomy and tracheostomy long-term ventilated care during the COVID-19 pandemic. Latest Updates. 2020.
6. Trinder, M., Boyd, J. H. & Brunham, L. R. Molecular regulation of plasma lipid levels during systemic inflammation and sepsis. Curr. Opin. Lipidol. 2019;30, 108–16.
7. Harris, H. W., Gosnell, J. E. & Kumwenda, Z. L. The lipemia of sepsis: Triglyceride-rich lipoproteins as agents of innate immunity. J. Endotoxin Res. 2000;6, 421–30.
8. Han S, Mallampalli RK. The role of surfactant in lung disease and host defense against pulmonary infections. Ann Am Thorac Soc. 2015;12:765–74.
9. Fessler MB, Summer RS. Surfactant lipids at the host-environment interfaces. metabolic sensors, suppressors, and effectors of inflammatory lung disease. Am J Respirator Cell Mol Biol. 2016;54:624–35.
10. Qin C, Minghan H, Ziwen Z, et al. Alteration of lipid profile and value of lipids in the prediction of the length of hospital stay in COVID-19 pneumonia patients. Food Science Nutr. 2020;8(11):6144–52.
11. Filippas-Ntekouan S, Liberopoulos E, Elisaf M. Lipid testing in infectious diseases: Possible role in diagnosis and prognosis. infections. 2017;45:575–88.
12. Masana L, Correig E, Ibarretxe D, et al. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep. 2021;7217(11).
13. Zhang B, Dong C, Li S, et al. Triglyceride to High-Density Lipoprotein Cholesterol Ratio is an Important Determinant of Cardiovascular Risk and Poor Prognosis in Coronavirus Disease-19: A Retrospective Case Series Study. dovepress. 2020;3925–36.
14. Alcantara-Alonso E, Molinar-Ramos F, Gonzalez-Lopez JA, et al. High triglyceride to HDL-cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients. Clin Nutr ESPEN. 2021;
15. Peng F, Wu S, Lei S, et al. Triglyceride/High-Density Lipoprotein Cholesterol Ratio is associated with the mortality of COVID-19: An Observational Study. Res Sq. 2020;
16. Gubernatorova EO, GOrshkova EA, Polinova AI, et al. IL-6: Relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 2020;53:13–24.
17. Cao Y, Liu X, Xiong L, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Med Virol. 2020;92(9):1449–59.

Vol. 5, No. 04; 2021

ISSN: 2581-3366

18. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846–8.
19. Kaysen GA, Ye X, Raimann JG, et al. Lipid levels are inversely associated with infectious and all-cause mortality: International MONDO study results. J Lipids Res. 2018;59:1519–28.
20. Malik J, Laique T, Ishaq U, et al. Effect of COVID-19 on Lipid Profile and its Correlation with Acute Phase Reactants. Medrxiv. 2021;
21. Kočar E, Režen T, Rozman D, et al. Cholesterol, lipoproteins, and COVID-19: Basic concepts and clinical applications. Biochem Biophys Acta Mol Cell Biol Lipids. 2021;1866(2):1588–9.
22. Cheung Ng P, Ling Ang I, Kwun C RW, et al. Host-responge biomarkers for the diagnosis of late-onset septicemia and necrotizing enterocolitis in preterm infants. J Clin Invest. 2010;120(8):2989–3000.
23. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607–13.
24. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020;18(5):1020–2.
25. Trinder, M., Boyd, J. H. & Brunham, L. R. Molecular regulation of plasma lipid levels during systemic inflammation and sepsis. Curr. Opin. Lipidol. 2019;30, 108–16.
26. Mead, J. R., Irvine, S. A. & Ramji, D. P. Lipoprotein lipase: Structure, function, regulation, and role in disease. J. Mol. Med. 2002;80, 753–769.