Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(3)

Lipid Profile in Confirmed Covid-19 Patients with Type 2 Diabetes Mellitus At Haji Adam Malik General Hospital Medan from March 2020 to December 2021

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ARTICLE INFO

Article history:
Received
14 March 2023

Accepted
30 March 2023

Manuscript ID:
JSOCMED-230314-23-2

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Introduction: Diabetes can cause secondary hyperlipidemia. In COVID-19, dyslipidemia is thought to be the result of biological and pathological processes triggered by SARS-CoV-2. Altered lipid profiles have been reported since the beginning of the COVID-19 pandemic, where the alteration of lipid profile and the severity of SARS-CoV-2 infection were positively correlated. This study aims to analyze the lipid profile in confirmed COVID-19 patients with T2DM at H. Adam Malik General Hospital Medan.

Method: This was a descriptive study with a cross-sectional design using a total sampling technique by collecting secondary data on inpatients with confirmed COVID-19 with T2DM at H. Adam Malik General Hospital from 2020 to 2021 which was then analyzed using the SPSS version 25 application.

Results: Of the 372 subjects, the most common sex was male (57.3%), 193 people had a BMI of 18.5 - 24.9kg/m2 (51.9%), the mean overall age was 57.5 ± 10.4 years, and the median length of stay was 8 days. The most common comorbid was hypertension (n=189, 50.8%), 176 people had severe COVID-19 (47.3%), and 225 patients were discharged (60.5%). Based on laboratory data, 327 people had dyslipidemia (87.9%), 31 people had mild acute liver impairments (8.3%), the average of HbA1c was 9.0±2.5%, the average fasting blood glucose was 221.7±122.2 mg/L, the average 2 hours post-prandial blood glucose was 261.7±125.8 mg/L, an average of total cholesterol was 151.2±52.2 mg/L, an average of triglycerides was 147.5±99.1 mg/L, an average of HDL was 33.1±14.6 mg/L, an average of LDL was 97.4±44.5 mg/L, the median of ALT was 25 µ/L, and an average of AST was 30.45±27.42 µ/L.

Conclusion: Total cholesterol, triglyceride, and LDL were lower in T2DM patients with a critical illness of COVID-19 and patients who died.

Keywords

T2DM, COVID-19, Dyslipidemia, Lipid profile

How to cite: Sitepu AN, Lindarto D, Nasution MS. Lipid Profile in Confirmed Covid-19 Patients with Type 2 Diabetes Mellitus At Haji Adam Malik General Hospital Medan from March 2020 to December 2021. Journal of Society Medicine. 2023;2(3): 66-75. DOI : https://doi.org/ 10.47353/jsocmed.v2i3.37

INTRODUCTION

Coronavirus disease 2019 (COVID-2019) is a disease caused by a new coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1,2] Several comorbidities have emerged as risk factors for the development of severe COVID-19, including Type 2 Diabetes Mellitus (DMT2), obesity, hypertension, and dyslipidemia.[1–4]

COVID-19 is associated with poorer outcomes in patients with T2DM. In particular, the infection rate of SARS-CoV-2 and other markers of disease severity is increased in patients with diabetes.[1–3,5] Diabetes is one of the causes of secondary hyperlipidemia and is associated with hyperglycemia, insulin resistance, and insulin deficiency which contribute to the characteristics of dyslipidemia.[6]

Metabolic abnormalities such as dyslipidemia, hyperinsulinemia or insulin resistance, and obesity have a key role in the induction and development of T2DM. Immunometabolism implies a two-way relationship between the immune system and metabolism, in which inflammation has an important role in promoting metabolic abnormalities (eg, obesity and T2DM), and metabolic factors, in contrast, regulate immune cell function. Hyperglycemia and inflammation are the main causes of micro- and macroangiopathy in the circulatory system. A compromised immune system along with an imbalance in metabolism increases the susceptibility of patients to several pathogenic agents such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4]

SARS-CoV-2 is an enveloped RNA virus surrounded by a lipid bilayer, with a genome of approximately 30,000 nucleotides, encoding four structural proteins: spike protein (S), an envelope protein (E), membrane protein (M), and protein nucleocapsid protein (N). Lipids are an important cellular component of SARS-CoV-2, in particular, involved in the fusion of viral membranes to host cells, viral replication, and endocytosis and exocytosis.[7–10]

Dyslipidemia in COVID-19 is thought to be the result of complex biological and pathological processes triggered by SARS-CoV-2. COVID-19 results in several pathological characteristics that can lead to dyslipidemia.[11,12] Changes in lipid profiles have been reported since the early stages of the COVID-19 pandemic; especially reduced cholesterol levels.[13,14] Qin et al found reduced total cholesterol (TC) and LDL-C levels in a retrospective study of the lipid profiles of 248 COVID-19 patients. The results of this measurement are negatively correlated with the patient's length of stay in the hospital.[13,15,16]

The degree of lipid change and the severity of the infection are positively correlated, and many research projects have found an association between COVID-19 and lipid biomarkers.[13,16] A cross-sectional analysis of 1411 hospitalized patients with confirmed COVID-19 in Spain showed that low HDL, TC, and high TG before infection and on admission are strong predictors of disease severity and correlate with higher levels of D-dimer and ferritin.[13,17] Another large study in China showed that the development of hypolipidemia started in patients with mild symptoms, and progressively got worse in relation to disease severity.[13,18] A study of lipid profile parameters in COVID-19 patients admitted to the ICU showed that all patients had low LDL-C and HDL-C levels; although this problem was not a predictor of death, lower cholesterol levels in early ventilator-associated pneumonia were associated with increased mortality.[13,19]

Based on the background described above, researchers wanted to know about the lipid profile in confirmed COVID-19 patients with Type 2 Diabetes Mellitus at H. Adam Malik General Hospital Medan from March 2020 to December 2021.

METHOD

Study Sample

The population of this study was all T2DM patients with confirmed COVID-19 through the swab examination of the SARS-CoV-2 RT-PCR from March 2020 to December 2021. The study sample was all populations that met the inclusion and exclusion criteria. Inclusion criteria: all hospitalized patients with T2DM confirmed COVID-19 through a SARS-CoV-2 RT-PCR swab examination and aged ≥ 18 years. The exclusion criteria were patients whose medical record data was incomplete.

Study Design

This study was a descriptive study with a cross-sectional design. The sampling technique used was total sampling, where all the samples were included in the study. This study used secondary data. We obtained the age, gender, weight and height, comorbid (HT, CVD, obesity), COVID-19 severity, length of stay, outcome (discharged, transfer to the non-isolation unit, or died), and laboratory data of the sample from the medical records of Haji Adam Malik General Hospital Medan.

Statistical Analysis

Univariate analysis was performed to obtain an overview of each variable studied. The data obtained were then processed using SPSS version 25. The data will be tabulated and analyzed statistically. The resulting data will be presented in the form of statistical software results tables.

RESULTS

The baseline characteristics of patients on admission are presented in Table 1.

Table 1. Clinical characteristics of the study

Parameter	n	%
Gender		
- Male	213	57.3
- Female	159	42.7
BMI		
- ≥40 (Very Obese)	0	0
- 30.0 - 39.9 (Obese)	22	5.9
- 25.0 - 29.9 (Overweight)	148	39.8
- 18.5 - 24.9 (Normoweight)	193	51.9
- <18.5 (Underweight)	9	2.4
Type of Comorbid		
- Hypertension	189	50.8
- CVD	92	24.7
- Obesity	22	5.9
Dyslipidemia		
- Yes	327	87.9
- No	45	12.1
COVID-19 Severity		
- Moderate illness	134	36.0
- Severe illness	176	47.3
- Critical illness	62	16.7
Acute Liver Impairment		
- None	317	85.2
- Mild	31	8.3
- Moderate	24	6.5
- Severe	0	0
Outcome		
- Discharged	225	60.5
- Transfer to the non-isolation ICU unit	13	3.5
- Transfer to the non-isolation unit	10	2.7
- Died	124	33.3
Variables	**Average**	
- Age, years	57.5±10.4[a]	
- Length of stay, days	8 (1 - 45)[b]	
- HbA1c, %	9.0±2.5 [a]	
- GDp, mg/L	221.7±122.2 [a]	
- GD2pp, mg/L	261.7±125.8 [a]	
- Total Cholesterol, mg/L	151.2±52.2 [a]	
- Triglycerides, mg/L	147.5±99.1[a]	
- HDL, mg/L	33.1±14.6 [a]	
- LDL, mg/L	97.4±44.5 [a]	
- AST, µ/L	25 (3 - 725) [b]	
- ALT, µ/L	30.45±27.42 [a]	

[a] normal distribution, mean±SD

[b] abnormal distribution, median (min-max)

The lipid profile of the sample based on the severity of COVID-19 is presented in the following table 2.

Table 2. The lipid profile based on the severity of COVID-19

Variables	Moderate Illness	Severe Illness	Critical Illness
	n=134 36%	n=176 47,3%	n=62 16,7%
Mean of variables	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**
- Total Cholesterol, mg/L	153.61±52.3	153.77±51.2	138.58±53.9
- Triglycerides, mg/L	143.05±95.8	153.30±100.1	140.53±103.8
- HDL, mg/L	33.48±12.7	32.34±15.0	34.39±16.9
- LDL, mg/L	99.51±42.5	100.10±44.1	85.31±48.3

The lipid profile based on patient outcomes is presented in the following table 3.

Table 3. The lipid profile based on patient outcomes

Variables	Discharged	Transfer to the non-isolation ICU unit	Transfer to the non-isolation unit	Died
	n=225 60,5%	n=13 3,5%	n=10 2,7%	n=124 33,3%
Mean of variables	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**
- Total Cholesterol, mg/L	158.44±50.0	171.00±35.3	149.10±44.3	136.10±55.1
- Triglycerides, mg/L	153.12±101.3	170.69±104.8	162.00±115.4	133.64±92.5
- HDL, mg/L	33.01±13.9	31.00±11.9	28.20±12.5	33.85±15.9
- LDL, mg/L	102.74±41.4	113.08±34.9	88.30±36.9	86.86±49.3

The lipid profile of the sample with an acute liver impairment is presented in the following table 4.

Tabel 4. The lipid profile of the sample with an acute liver impairment

Variables	None	Mild	Moderate
	n=317 85.2%	n = 31 8.3%	n = 24 6.5%
Mean of variables	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**	**($\bar{x}$ ±SD)**
- Total Cholesterol, mg/L	152.42±52.8	146.61±45.5	140.75±52.3
- Triglycerides, mg/L	150.55±103.4	127.68±64.6	132.58±71.5
- HDL, mg/L	32.95±14.8	33.97±10.6	33.83±15.9
- LDL, mg/L	97.47±44.4	93.29±46.3	102.13±43.2

DISCUSSION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to defects in insulin secretion, insulin action, or both.[20,21] In particular, the infection rate of SARS-CoV-2 and the degree of disease severity increase in patients with diabetes.[22–24] Potential mechanisms include: cytokine-mediated increase in insulin resistance and hypercoagulability; increased expression of the SARS-CoV-2 (ACE2) receptor with renin-angiotensin system (RAS) agents; effect of SARS-CoV-2 on pancreatic ACE2 with decreased b-cell insulin reserves; immunosuppression; glycosylation of viral spike proteins and ACE2 with increased viral binding/entry; decreased virus clearance and increased virus replication; and comorbidities.[25]

Based on existing data, hypertension, diabetes mellitus, male sex, and active smoking are risk factors for SARS-CoV-2 infection. The more male sex distribution is thought to be associated with a higher prevalence of active smokers.[2] Epidemiological data from China shows that regardless of age, men are at greater risk for developing severe COVID-19 compared to women.[1,26] The above data is in line with the research conducted, in which the sex of the patient was mostly male (n = 213; 57.3%). Limited evidence also suggests that ACE-2 expression is attenuated in women compared to men, which may justify the higher number of COVID-19 cases in men. This is also what underlies Song, et al. include the male gender as one of the parameters in the COVID-19 Early Warning Score (COVID-19 EWS) in China.[1,27,28]

Based on the research results, 39.8% of the research sample had a BMI of 25.0 - 29.9 (overweight) and 5.9% of people had a BMI of 30.0 - 39.9 (obese). Obesity is a major global problem. According to WHO, more than 1.9 billion people aged >18 years were overweight (39%) or obese (13%) in 2016.[25] Obesity is the strongest risk factor for T2DM and is associated with metabolic abnormalities that result in insulin resistance.[20,29,30] Substances such as glycerol, non-esterified fatty acids, cytokines (interleukin (IL)-6, IL-1, leptin, fibrinogen, tumor necrosis factor-alpha (TNF), PAI-1, MCP-1 resistin, angiotensin), hormone, a proinflammatory marker involved in the development of insulin resistance, is increased in obese patients.[30,31]

The metabolic disturbances associated with obesity and diabetes have many effects on how the body responds to viral infections that can impact the course of the disease. The underlying effect of the increased general predisposition to all infections is a compromised immune system that is the result of metabolic disturbances in obesity and diabetes.[32,33] Many aspects of the innate and adaptive immune systems are impaired in diabetes and obesity including inappropriate T-cell action, impaired natural killer (NK) cell activity, phagocytic cell dysfunction, inhibition of neutrophil chemotaxis, and defects in complement action.[32,34–36]

In some studies,[37–39] patients with COVID-19 and obesity are also more likely to be admitted to the intensive care unit (ICU) and have a higher death rate than those who are not obese. Possible mechanisms for this observation include dysregulation of immunity by a high, sedentary leptin/adiponectin ratio, increased expression of angiotensin-converting enzyme 2 (ACE2) in epicardial adipose tissue, concomitant cardiopulmonary disease, and lipotoxic adiposity. This phenomenon holds not only for Americans who have a greater BMI and are at risk of visceral/ectopic fat but also for Asians who are more prone to visceral/ectopic fat accumulation and dysglycemia at mild increases in BMI.[25]

In Table 1, it was found that 50.8% of the total patients were also suffered from hypertension. In addition, as much as 87.9% of the total study sample suffered from dyslipidemia (n = 327). T2DM and hypertension are found together more frequently, where the incidence ranges from 60-65%. In addition, it is known that hypertension occurs two to three times more frequently in patients with diabetes.[40] Factors involved in this association include: (1) the frequency of both diseases increases with age; (2) have the same predisposing factors; (3) hypertension secondary to complications of diabetes, usually nephropathy in type 1 diabetes; (4) hypertension in type 2 diabetics may precede or may be associated with, diabetic nephropathy.[40] Diabetes and hypertension have interrelated pathways such as oxidative stress, the renin-angiotensin-aldosterone system (RAAS), insulin resistance, the sympathetic nervous system (SNS), PPAR, and adipokines. These pathways are interconnected and interact with one another and can even result in a vicious circle. The development of proteinuria in diabetic patients leads to hyperlipidemia which increases the likelihood of CVD in these patients.[30]

Based on the severity of COVID-19, it was found that 176 people had severe illness (47.3%) and as many as 62 people had a critical illness (16.3%). For patient outcomes, as many as 124 people died (33.3%). According to data from countries affected early in the pandemic, 40% of cases experienced mild illness, 40% experienced moderate illness including pneumonia, 15% of cases experienced severe illness, and 5% of cases experienced critical condition.[3,41] In China, a national study reported a higher prevalence of diabetes among patients with severe COVID-19 compared to moderate patients (16.2% vs 5.7%).[42,43]

Individuals with diabetes are commonly affected by low-level chronic inflammation, which can facilitate a cytokine storm, contributing to the severe outcome of COVID-19 and eventual death.[40] Patients with diabetes are known to have an increased risk of infection, which is partly attributed to hyperglycemia leading to immune dysfunction, among other effects.[42] On the other hand, severe and ensuing hyperinflammatory SARS-CoV-2 infection contributes to hyperglycemia through indirect negative effects on insulin target tissues and potential direct negative effects on pancreatic β-cells.[42,44]

Altered in lipid profiles have been reported since the early stages of the COVID-19 pandemic; especially a decrease in cholesterol levels.[13,14] A study by Roccaforte et al found that infection with the SARS-CoV-

2 virus and the resulting pro-inflammatory state may have a major impact on lipid metabolism, resulting in reductions in LDL cholesterol, total cholesterol, and HDL cholesterol levels.[7] Dyslipidemia in COVID-19 is considered to be the result of complex biological and pathological processes triggered by SARS-CoV-2.[11,12] A recent study found that SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) in cholangiocytes, causing cholangiocyte dysfunction and inducing a systemic inflammatory response leading to hepatic impairment.[45,46] Impairment of liver function due to SARS-CoV-2 infection can interfere with LDL uptake and reduce LDL biosynthesis; however, serum liver function tests, including alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), usually show moderate elevations in less than 50% of patients.[18,19,47]

In this study, 31 people had mild liver impairments (8.3%) and 24 people (6.5%) had moderate liver impairments. Similar results were observed by Cai, where out of 417 patients with COVID-19 in Shenzhen, it was found that most of the patients had abnormal liver test results within 1–2 x upper range of normal values, and only a few (< 4%) patients had liver test results in abnormal higher than 2x upper normal value.[46] Another study by Xie et al. reported a retrospective study of 79 COVID patients in non-ICU wards in China, in which 31.6% of patients had elevated ALT and 35.4% of patients had elevated AST.[48]

In this study, if we assess the data in Table 4., it was found that COVID-19 patients with moderate liver impairment had a higher average LDL value compared to COVID-19 patients with mild liver impairment (102.13 mg/L vs 93. 29 mg/L). This is in contrast to several previous studies which stated that liver function damage due to SARS-CoV-2 infection could interfere with LDL uptake and result in a decrease in serum LDL levels. Therefore, changes in liver function are most likely not the main contributor to dyslipidemia in T2DM patients with COVID-19 in this study.

Another factor that causes changes in lipid profiles in COVID-19 patients is the interaction between SARS-CoV-2 infection and lipids, which is based on several previous studies. Many studies have reported that lipid rafts may have a fundamental role in the life cycle of the coronavirus. Lipid rafts are eukaryotic membrane microdomains that contain glycosphingolipids, high concentrations of cholesterol, and transport and adhesion proteins.[7,13]

Viral infection relies on interactions between components of the host cell's plasma membrane and the viral envelope. The presence of cholesterol on the surface of target cells is essential for allowing coronavirus infection. In the early stages of SARS-CoV infection, for example, cholesterol rafters and lipid membranes may be important determinants of viral entry into cells, as shown in other viral infections [7,9], where the virus attacks these surface molecules on host cells in areas specific plasma membrane characterized by lipid rafts.[7,10] Several cholesterol-rich microdomains facilitate interactions between spike glycoproteins in SARS-CoV-2 and ACE2, which are localized in lipid rafts.[7] In addition, cholesterol has recently been shown to be involved in binding to and changing the oligomer state of the N-terminal fusion peptide of SARS-CoV, which is essential for viral entry into host cells.[49] The impact of cholesterol on coronavirus infectivity was further supported by examining the cholesterol-lowering effect on SARS-CoV infection, which resulted in a significant decrease in viral mRNA.[50]

Roccaforte et al in their study found that baseline lipid levels, especially total cholesterol, HDL cholesterol, and LDL cholesterol levels in patients with SARS-CoV-2 infection were significantly lower than in a healthy control population ($P<0.001$), while triglyceride levels were found to be higher.[7] A cross-sectional analysis of 1411 inpatients with confirmed COVID-19 in Spain showed that low HDL-C levels and high TG before infection and on admission were strong predictors of disease severity and correlated with higher D-dimer and ferritin levels.[13,17]

A comprehensive study of serum lipids at the cellular level reported changes in cholesterol metabolism due to COVID-19 as the cause of decreased blood cholesterol levels.[7,51] They implied that infection with SARS-COV-2 reduced Apo-A1 and HDL-C levels, both of which are associated with disease severity. In addition, two prospective studies to assess lipid changes in COVID-19 found that HDL-C and Apo-A1 were inversely associated with measures of disease severity such as mortality, and inflammatory markers such as

CRP and IL-6.[7,52,53] They also reported significantly increased TG levels and lower TC and LDL-C levels in severe patients compared to milder cases. Many similar studies have shown an inverse relationship between LDL and HDL with C-reactive protein (CRP) as a marker of inflammation severity.[7,54,55]

In this study, total cholesterol, triglyceride, and LDL values were found to be lower in patients with critical COVID-19 degrees when compared to moderate and severe COVID-19 degrees (Table 2). In addition, based on Table 3., it was found that COVID-19 patients who died had lower total cholesterol, triglyceride, and LDL levels compared to COVID-19 patients who were PBJ or moved to non-isolation care. This is in line with previous studies, where low cholesterol levels in patients with COVID-19 can be a strong predictor of disease severity and can be associated with increased mortality.

The role of cholesterol in immunity is increasingly recognized in several observational studies. Lower LDL levels are associated with a higher prevalence of death and a poorer prognosis in patients with severe infections.[56–58] It has also been suggested that low cholesterol levels may be considered a marker of poorer prognosis in septic patients. Various studies have shown that heterozygous hypolipidemia is associated with a decreased inflammatory response to infection and a higher risk for severe infection and sepsis.[56,59]

CONCLUSION

Based on the results of the data obtained, the conclusions of this study are as follows: (1) The majority of patients are male with an average age of 57.5 years, BMI 18.5-24.9 kg/m2, (2) the majority also had hypertension and the majority suffered from dyslipidemia, (3) based on the severity of COVID-19, it was found that most patients had severe illness, (4) as many as 31 people suffered from mild liver impairments and 24 people had moderate liver impairments, where the patients who suffered from moderate liver impairments had a higher average of LDL compared to the ones with mild liver impairments (102.13 mg/L vs 93.29 mg/L), (5) total cholesterol, triglycerides, and LDL values were lower in T2DM patients with critical illness of COVID-19 and in T2DM patients with COVID-19 who died.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and H. Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This research has received no external funding.

COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

Not applicable.

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