COVID-19, dyslipidemia and familial hypercholesterolemia: an up-date

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Abstract
COVID-19 (coronavirus disease 2019) is an infection caused by the SARS-CoV-2 coronavirus, which can evolve into a severe respiratory condition, affecting the world population in a pandemic manner. In this study, we aimed to update the findings of the mechanisms that associate dyslipidemia with COVID-19 infection, the evolution of severe form and the influence of lipid-lowering treatment on outcomes. The search was performed in the PubMed and Embase databases and the selection was based on dyslipidemia and COVID-19 studies, which resulted in 31 articles. In results, the evidence in changes in cholesterol metabolism was found in SARS-CoV-2 virus infection with variations in high-density lipoprotein (HDL) levels. In addition, it provided an increase in triglycerides (TG) and very-low-density lipoprotein cholesterol (VLDLc). Patients with familial hypercholesterolemia (FH) with COVID-19 representing a group of individuals who develop early atherosclerotic disease with a higher risk of cardiovascular event, which should intensify the lipid-lowering treatment due to the potential risk of coronary endothelial dysfunction caused by viral infection. Cholesterol modifying drugs have a potential to change the life cycle of the virus, resulting in a range of pleiotropic effect on infectivity, immunity and inflammation, such as statins, fibrates, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors (iPCSK9), omega-3 fatty acids, bile acids sequestrants and nicotinic acid. As dyslipidemia is one of the main risk factors for the severe form of COVID-19, causing endothelial dysfunction previously installed in dyslipidemic patients, the use of lipid-lowering drugs can reduce the risk factors for the unfavorable outcome in these patients.
Keywords: Dyslipidemia; Familial Hypercholesterolemia; COVID-19; SARS-CoV-2; Hypolipidemic.

Resumo
A COVID-19 (doença do coronavírus 2019) é uma infecção causada pelo coronavírus SARS-CoV-2, que pode evoluir para um quadro respiratório grave, afetando a população mundial de forma pandêmica. Neste estudo, objetivamos atualizar os achados dos mecanismos que associam a dislipidemia à infecção por COVID-19, a evolução da forma grave e a influência do tratamento hipolipemiante nos desfechos. A busca foi realizada nas bases PubMed e Embase, e a seleção foi baseada em estudos de dislipidemia e COVID-19, que resultaram em 31 artigos. Os resultados evidenciaram que alterações no metabolismo do colesterol foram encontradas na infecção pelo vírus SARS-CoV-2 com variações nos níveis de lipoproteína de alta densidade (HDL). Além disso, a infecção proporcionou aumento de triglicerídeos (TG) e colesterol da lipoproteína de muito baixa densidade (VLDLc). Pacientes com hipercolesterolemia familiar (HF) com COVID-19 representam um grupo de indivíduos que desenvolvem doença aterosclerótica precoce com maior risco de evento cardiovascular, o que deve intensificar o tratamento hipolipemiante devido ao risco potencial de disfunção endotelial coronariana causada por infecção viral. Os medicamentos modificadores do colesterol têm potencial para alterar o ciclo do vírus, resultando em uma série de efeitos

pleiotrópicos na infectividade, imunidade e inflamação, como estatinas, fibratos, ezetimiba, inibidores da pró-proteína convertase-subtilisina/kexina tipo 9 (iPCSK9), ácidos graxos ômega 3, sequestrantes de ácidos biliares e ácido nicotínico. Como a dislipidemia é um dos principais fatores de risco para a forma grave de COVID-19, causando a disfunção endotelial previamente instalada em pacientes dislipidêmicos, o uso de hipolipemiantes pode reduzir o risco de fatores para o desfecho desfavorável nesses pacientes.
Palavras-chave: Dislipidemia; Hipercolesterolemia Familiar; COVID-19; SARS-CoV-2; Hipolipemiante.

Resumen
El COVID-19 (enfermedad por coronavirus 2019) ES una infección causada por el coronavírus SARS-CoV-2, que puede evolucionar a una afección respiratória grave, afectando a la población mundial en una pandemia. En este estudio, nuestro objetivo fue actualizar los hallazgos de los mecanismos que asocian la dislipidemia con la infección por COVID-19, la evolución de la forma grave y la influencia del tratamiento hipolipemiante en los resultados. La búsqueda se realizó en las bases de datos PubMed y Embase y la selección se basó en estúdios de dislipidemia y COVID-19, resultando en 31 artículos. En resultados, la evidencia de cambios en el metabolismo del colesterol en la infección por el vírus SARS-CoV-2 con variaciones en los niveles de lipoproteínas de alta densidad (HDL). Además, proporciono un aumento de los triglicéridos (TG) y del colesterol de lipoproteínas de muy baja densidad (VLDLc). Los pacientes con hipercolesterolemia familiar (HF) con COVID-19 representan un grupo de individuos que desarrollan enfermedad aterosclerótica temprana con mayor riesgo potencial de disfunción endotelial coronaria causada por la infección viral. Los medicamentos modificadores del colesterol tienen el potencial de alterar el ciclo del vírus, lo que resulta en una serie de efectos pleiotrópicos sobre la infectividad, la inmunidad y la inflamación, como las estatinas, los fibratos, la ezetimiba, los inibidores de la proproteína convertasa-subtilisina/kexina tipo 9 (iPCSK9), ácidos grasos Omega 3, secuestrantes de ácidos biliares y ácido nicotínico. Como la dislipidemia es uno de los principales factores de riesgo para la forma grave de COVID-19, causando disfunción endotelial previamente instalada en pacientes dislipidêmicos, el uso de hipolipemiantes puede reducir el riesgo de factores para el desenlace desfavorable en estos pacientes.
Palabras clave: Dislipidemia; Hipercolesterolemia Familiar; COVID-19; SARS-CoV-2; Hipolipemiante.

1. Introduction

COVID-19 pandemic, an infection by novel coronavirus, the Sars-CoV-2, that causes severe acute respiratory syndrome, has already caused 4,6 million deaths worldwide (WHO, 2021). Since March 2020, when the World Health Organization (WHO) announced the beginning of a global pandemic (Morens et al., 2020), several countries have taken different decisions to contain the spread of virus, and the scientific world's attention has turned to COVID-19's research in an incessant development of vaccines, and in parallel, to seek pharmacological therapies capable of treating the severe form caused by the virus (Casari et al., 2021). For this, it would be necessary to recognize the physiopathological mechanisms of COVID-19, and then be able to develop a specific and effective treatment.

In this context, the role played by lipids in the development of infection has been investigated, due to their importance in cell membrane components, intercellular communication and energy storage. We already know how lipids are crucial for the virus to penetrate in the host cell membrane and replicate, causing an alteration in the host cell metabolism (Abu-Farha et al., 2020). In critically ill patients of COVID-19 altered levels of lipids were found and some studies have identified lipid metabolism biomarkers associated with COVID-19 (Abu-Farha et al., 2020; Hu et al., 2020; Casari et al., 2021). Thus, intervention in membrane sphingolipids and interference in lipid metabolism caused by the virus may represent a way forward in the development of therapies for COVID-19 (Casari et al., 2021).

About 30 to 60 % of the general population is affected by dyslipidemia, which makes it one of the most prevalent public health conditions (Garcez et. al, 2014; Opoku et al., 2019). Thus, dyslipidemia has become a potential comorbidity associated with the severity of COVID-19 (Choi et al, 2020). This study aimed to update the findings that associate dyslipidemia with COVID-19 infection, the evolution to severe disease and the influence of treatment with lipid-lowering drugs on the development of COVID-19.

2. Methodology

The acronym PO – participants and outcome, was applied to structure the search strategies. Therefore, the acronym was composed of: P = patients diagnosed with dyslipidemia; O = COVID-19 infection. Articles were searched in PubMed and Embase, using the keywords: Dyslipidemia, Hypercholesterolemia, COVID-19 and SARS-CoV-2 in May 2021. The search included the Medical Subject Headings (MeSH) terms and their respective entry terms using the Boolean operator tools according to the high-sensitivity search strategy, developed by the Cochrane Collaboration (Lefebvre et al. 2021). All potential eligible studies were considered, such as randomized clinical trials and observational studies - case-control, case report, regardless of the language and date of publication. Narrative or systematic reviews were not included, but a manual search in their references was applied. Two researchers (JPPS and JAGT) first evaluated the titles and abstracts of all primary studies and after the full text was read. A third researcher (KBG) resolved the resolution of possible disagreements in both steps. The manual search was also applied in the reference lists of the studies and duplicates were excluded. Searches in electronic databases and manual searches identified 470 studies published from 2020 to 2022. After removing duplicates (61), we evaluated titles and abstracts of 409 studies. After, 378 articles were excluded because they did not meet the inclusion criteria. Thirty-one articles were selected at the end – 14 about drug management and clinical outcome, 17 about pre-COVID-19 lipid profile (Figure 1). The main conclusions obtained from them are described in the next subsections.

Figure 1 – Flowchart with the description of the search in literature.
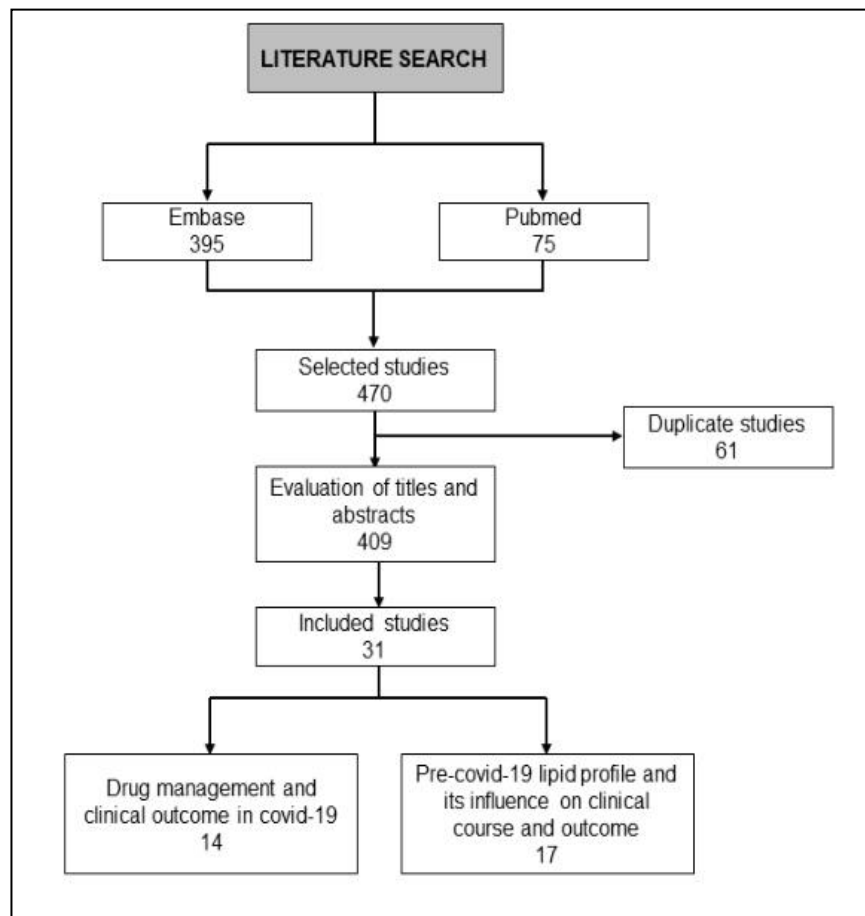
Source: Authors.

3. Results and Discussion

3.1 Changes in cholesterol metabolism with COVID-19 infection

In COVID-19 infection, the presence of high concentrations of pro- inflammatory cytokines (cytokine storm) is associated with severe disease outcomes (Soi et al., 2020). However, high-density lipoprotein cholesterol (HDLc) counter-regulates this action, as it is involved in the innate immune response regulation through its interaction with the adenosine triphosphate A1 (ABCA1) or adenosine triphosphate G1 (ABCG1) transporter, which negatively regulate the activation of T lymphocytes and the expression of inflammatory mediators in macrophages and dendritic cells (Kaji, 2013). Acute phase HDLc is related to COVID-19 activity and is inversely associated with C-reactive protein (CRP) levels in the disease (Kaji, 2013). A low amount of HDLc contributes to a dysregulation of the innate immune response, which would be the first line of defense against SARS-CoV-2 (McKechnie & Blish, 2020). In addition, persistent inflammation culminates in a modulation of apolipoproteins linked to HDLc, characterized by a decrease in apolipoproteins A1 (ApoA1), apolipoprotein E (ApoE) and an increase in amyloid protein A, affecting the anti-inflammatory, antioxidant and immunomodulatory function of HDLc (Mehta et al., 2020).

The unbalance of the antioxidant system observed commonly in infectious processes culminates in the formation of oxidized and modified lipoproteins that activate chemotaxis by macrophages, increasing the release of pro-inflammatory cytokines such as interleukin 6 (IL6), interleukin 1 (IL1) and tumor necrosis factor (TNF) (Mehta et al., 2020). Excessive production of oxidized lipoproteins also alters their entire transport system, worsening reverse cholesterol transport.

This effect is characterized by the insufficient interaction of Apo A1 with the ABCA1 of macrophages and decreased esterification of cholesterol esters by lecithin acyl transferase (LCAT). Thus, there is a reduction in the return of cholesterol esters to the liver, and uptake by liver LDL receptors (LDLR). Low levels of Apo E and apolipoprotein CIII (Apo CIII) in HDLc also result in low lipoprotein lipase (LPL) activity, leading to accumulation of triglycerides (TG) and very-low-density lipoprotein cholesterol (VLDLc) (Sorokin et al., 2020).

In a study conducted by Alcántara-Alonso *et al*. (2021), patients with COVID-19 infection showed increase in the TG/HDLc ratio, which was associated with a reduction in insulin sensitivity (Baez-Duarte et al., 2017) and adverse cardiovasculars events (Yang et al., 2017), which emphasizes the importance of using HDLc levels as a marker of disease progression (Ding et al., 2020). In addition, it is suggested the TG/HDLc ratio as a new biochemical marker of severe prognosis and requirement for mechanical ventilation in patients with COVID-19 (Alcantara-Alonso et al, 2021).

The level of cellular cholesterol is an essential contributor to SARSCoV-2 viral infection. SARS-CoV-2 reaches the cell surface by binding to the receptor angiotensinogen converting enzyme 2 (ACE2). In the next step, the virus can enter through a cell surface mechanism or through clathrin-mediated endocytosis, a cholesterol dependent pathway that involves monosialotetrahexosylganglioside1 (GM1) containing lipid clusters (Jeon & Lee, 2018; Wang et al., 2020). TMPRSS2 is a protease that facilitates the entry of SARS-CoV-2 by binding to the Spike protein (S protein) of the virus. With low cellular cholesterol concentration, the ACE2 receptor is cut by TMPRSS2, facilitating the virus surface entry. In high cellular cholesterol concentration, the ACE2 receptor translocates to the GM1 and the virus enters via endocytic pathway. Therefore, when cellular cholesterol levels increase, ACE2 receptor shifts to the GM1 entry, which is presumably a more efficient mechanism of cellular virus entrance (Wang et al., 2020).

3.2 Dyslipidemias and COVID-19

Dyslipidemias are blood lipid abnormalities, generally characterized by hypercholesterolemia with LDLc elevation, HDLc reduction and hypertriglyceridemia, which promote atherosclerosis (Jornayvaz et al., 2010). In inflammatory situations, there is a reduction of HDLc and ApoA1 and an increase of TG, observed in COVID-19 infection, showing an association with

the disease progression and symptom severity, based on a meta-analysis study (Hariyanto & Kurniawan, 2020), dyslipidemia seems to be associated with the severe form of COVID-19, and there are some hypotheses to justify this relationship. First, in dyslipidemic patients who have an increase in LDLc, interaction with macrophages in atheromatous plaques may occur, leading to increased expression of pro-inflammatory cytokines such as interleukin 1β (IL-1β) and interleukin 18 (IL-18), as which are already high in infection (Tall & Yvan-Charvet, 2015; Casari et al., 2021). Furthermore, the increase in LDLc and TG can cause endothelial dysfunction (Froldi & Dorigo, 2020), which may be accentuated in COVID-19 infection due to the ACE2 receptor, which is also expressed by endothelial cells (Kim et al., 2012; Froldi & Dorigo, 2020). The endothelium actively participates in the immune response, playing a fundamental role in the infection, as it releases soluble substances, the chemokines, which attract leukocytes to the infection site and produce cytokines that activate the inflammatory response. The endothelium is also responsible for regulating the tone and maintaining vascular homeostasis, and in COVID-19 the recruitment of immune cells, either by the direct aggression of the virus on the endothelium or by immunomediation, can result in generalized endothelial dysfunction, associated with apoptosis (Godoi et al., 2020;Bermejo-Martin et al., 2020). ACE2 receptors have their expression reduced in COVID-19 infection, causing an imbalance in the rates of angiotensin-2, establishing a microvascular vasoconstriction with decreased tissue nutrition, and compromising the function of organs such as the brain, heart and kidney (Varga et al., 2020). All these combinations can lead to the development of cardiovascular complications, which can cause serious outcomes in patients with COVID-19 (Hariyanto & Kurniawan, 2020).

Another systematic review and meta-analysis (Atmosudigdo et al., 2021), which aimed to assess the association of dyslipidemia as a factor in mortality and severity of COVID-19, in addition to assessing whether other comorbidities influence this association, concluded that older age, male gender and hypertension are independent risk factors for disease severity (Atmosudigdo et al., 2021).

The lipid profile measured during hospitalization in patients with a severe course of COVID-19, who had low HDLc and increased TG levels prior to infection, showed that a worse outcome was associated with the continuation of this dyslipidemia during infection, in addition to being positively correlated with levels of D-Dimer and ferritin, showing that they are strong predictors of a severe course of the disease (Masana et al., 2021). The presence of atherogenic dyslipidemia during infection was strongly associated with a worse prognosis of COVID-19, suggesting that the lipid profile should be considered a sensitive marker of inflammation and should be measured in patients with COVID-19 (Masana et al., 2021).

However, another study analyzing the association of hyperlipidemia with overall mortality within 28 days of COVID-19 in hospitalized patients did not show evidence that an unbalanced lipid profile would be significantly associated with all-cause mortality, even in patients with cardiovascular diseases (CVDs) and previous diabetes mellitus. Therefore, hyperlipidemia would not be the main risk factor for the severity of COVID-19, but a contributing factor for worse outcomes (Wu et al., 2021).

3.3 COVID-19 in patients with familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a disease of autosomal dominant genetic inheritance with an estimated prevalence of 1 in 250 individuals in the heterozigotic form (HeFH), characterized by an elevation of 2-3 times the plasma concentration of LDLc. In untreated individuals, it induces premature cardiovascular disease, markedly by risk of coronary event in middle-aged patients. This epidemiological data suggests that patients with FH are at increased risk of cardiac complications, particularly if the underlying genetic disease has remained undetected. This scenario justifies the high proportion of critically ill patients with COVID-19 below the age of 50 years (Vuorio et al., 2020).

The other condition in FH patients is the association of high levels of lipoprotein(a) [Lp(a)] compared to the general population (Vuorio et al., 2020; Vuorio et al., 2020) and with a consequent increased risk of atherothrombotic event

concomitant with COVID-19, even after recovery (Vuorio et al., 2020). The potential synergism between viral infection and hypercoagulability resulting from high levels of Lp(a) in these patients deserves furthers investigation (Vuorio et al., 2020). Charakida *et al.* (2009) also observed high concentrations of Lp(a) in FH, in addition to transporting cholesterol to atherosclerotic lesions, has direct pro-inflammatory and atherothrombotic characteristics, which is associated with endothelial dysfunction and severity in COVID-19 infection (Vuorio, 2020).

Homozygous familial hypercholesterolemia (HoFH), which is the most severe form of this disease, affecting approximately 1 in every 300,000 to 1 million individuals worldwide, is characterized by an increase in LDLc up 4 to 6 times the normal range since birth and develop severe premature cardiovascular disease with onset in childhood and adolescence. Despite the existence of multiple lipid-lowering therapies including lipid apheresis, these patients remain at high cardiovascular risk for all life (Cuchel et al., 2014). In these patients,the risk and severity of infection with COVID-19 significantly increases, since the entry of SARS-CoV-2 into the host cell through ACE2 receptors may be accelerated in the presence of high cholesterol levels (Jeon & Lee, 2018; Wang et al., 2020). There are currently no epidemiological data about the severity of COVID-19, as well as the prevalence of acute cardiac events in individuals with HoFH during the COVID-19 pandemic, perhaps because protective measures were more intense and effective for this population (Kayikcioglu et al., 2020). Therefore, it is necessary to confirm whether the risk and severity of COVID-19 is actually increased in these individuals (Vuorio et al., 2021). In any case, it is suggested to intensify the lipid-lowering treatment of FH patients with COVID-19 due to the potential risk of coronary endothelial dysfunction caused by the viral infection (Peretz et al., 2019).

3.4 Treatments for dyslipidemias at COVID-19 (Table 1)

Cholesterol is essential for SARS-CoV-2 infectivity and replication, and cholesterol-modifying drugs have the potential to alter the virus life cycle by blocking the production of multiple sterols, oxysterols and isoprenoids, resulting in a range of pleiotropic effects in infectivity, immunity and inflammation, deserving additional consideration in the treatment of COVID-19 (Sturley et al., 2020; Schmidt et al., 2020).

As SARS-CoV-2 infection and progression to the severe disease of COVID-19 are related to older age, atherosclerotic disease, diabetes mellitus, hypertension and obesity (Iqbal et al., 2020), a large proportion of individuals with these conditions are treated with lipid-lowering medications, making it necessary to verify issues related to the safety of the continuity of these drugs in patients infected with COVID-19 (Iqbal et al., 2020). Among the medications are statins, fibrates, ezetimibe, PCSK9 inhibitors, omega 3 fatty acids, bile acid sequestrants and nicotinic acid (Iqbal et al., 2020; Vargas et al., 2020).

Statins are inhibitors of hydroxyl-methylglutaryl-coenzyme A (HMG-CoA) reductase, inhibiting the synthesis of intracellular cholesterol. They are considered one of the most effective therapeutic in the treatment of hyperlipidemias and prevention of atherosclerotic cardiovascular diseases, in particular acute coronary syndromes (ACS) (Law et al., 2003). However, statins are not only endogenous cholesterol-lowering drugs, but also have pleiotropic effects including restoration of endothelial dysfunction, stabilization of atheromatous plaques, regulation of angiogenesis, antifibrotic and antithrombotic effects, making them as a potential therapeutic in patients with COVID-19, particularly for its properties in thrombotic manifestations that can occur, in severe stages of COVID-19 infection (Ferrara & Vitiello, 2021). The direct antiviral effects of statins were also recognized, making these drugs a possible candidate to interfere in the fusion of the virus with the host cell due to the blockade in the production and reduction in the intracellular availability of cholesterol (Ferrara & Vitiello, 2021).

Many studies have been carried out to identify the correlation of dyslipidemia in patients with severe infection by COVID-19 and use of statins, evaluating several clinical outcomes. In a study conducted by Tan *et al.* (2020), 717 hospitalized patients were included, of which 156 had dyslipidemia, with 97% of these using statins. Logistic treatment models have shown

a lower chance of admission to the intensive care unit (ICU) for statin users when compared to non-users, supporting the continued prescribing of statins in patients with COVID-19 (Tan et al., 2020). Saeed *et al.* (2020) also emphasized that the administration of statins was associated with a reduction in hospital mortality from COVID-19 in patients with diabetes mellitus.

In contrast, the findings of Mitacchione *et al.* (2021) in a study including 842 patients, 179 (21%) of which were treated with statins before hospital admission, showed that statins did not affect hospital mortality in patients with COVID-19, which should be considered as an adjuvant and independent therapy, being part of a standard therapy in the care of patients with comorbities infected by COVID-19 (Mitacchione et al., 2021).

In a meta-analysis study, aiming to analyze the association between the use of statins and hospital outcomes related to COVID-19, nine studies were selected including a total of 3,449 patients. Based on the available data, the use of statins did not improve the results the severity and mortality of COVID-19 infection (Hariyanto & Kurniawan, 2020). Several reasons were attributed, among them the signaling of a compensatory immune response (supported by a retrospective analysis of a multicenter clinical trial study about the efficacy of rosuvastatin against infection-induced acute respiratory distress syndrome, which presented a higher level of IL-18 and mortality in patients treated with statins) (Rogers et al., 2019); myotoxicity with kidney injury by concomitant administration of antiretroviral drugs that use the same pathway of metabolism by cytochrome P450, increasing the chances of adverse effects of statins; and finally, that the anti-inflammatory effects of statins are relatively low compared to corticosteroids, making statins a low-performance drug in combating the COVID-19 cytokine storm. Therefore, the hospital outcome of COVID-19 was not changed with the administration of these drugs (Hariyanto & Kurniawan, 2020).

Fibrates are agonists of peroxisomes activating alpha receptors (PPARα) and are mainly used in the treatment of hypertriglyceridemia (Schofield et al., 2013). Increased TG levels are associated with inflammation and are used as part of H-score that determines the presence of secondary hemophagocyticlymphohistiocytosis, which corresponds to a syndrome of hypercytonemia that can occur in COVID-19 infection (Machowicz et al., 2016; Mehta et al., 2020). Fibrates, like statins, also have recognized anti-inflammatory properties and have been suggested to be a potential antiviral agent (Fedson, 2013). However, despite this evidence, no studies have been conducted to verify the effects of fibrates on viral respiratory infections in humans (Iqbal et al., 2020). Another effect attributed to fibrates, especially Fenofibrate, would be the increased levels of sulphatides, which in large quantities can reduce the capacity for infection or the severity of the coronavirus disease, and should be investigated for a beneficial effect against infections by these types of virus (Buschard, 2020).

Ezetimibe is a Niemann-Pick C1-Like (NPC1L1) protein blocker, inhibiting the intestinal absorption of dietary cholesterol and consequent LDLc reduction (Phan et al., 2012). It is known as a safe drug in relation to the interaction with other medications used in the treatment of COVID-19 and with few adverse effects, but no studies reporting the use of ezetimibe in viral or bacterial pneumonia have been conducted (Iqbal et al., 2020).

Monoclonal antibodies anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) are new drugs that reduce significantly LDLc levels, consequently reducing cardiovasculars events, being well tolerated and safe (Iqbal et al., 2020). PCSK9 inhibitors is often associated with beneficial effects against inflammation in atherosclerotic processes (Paciullo, 2017), suggesting that the use of PCSK9 inhibitory antibodies could modulate the deregulated immune response during COVID-19 infection, but its usefulness in attenuating inflammation and the benefits during sepsis are still a debated issue (Momtazi et al, 2017). One of the adverse effects of PCSK9 inhibitors would be the flu-like syndrome reported by users of these drugs (Hansel et al., 2010), but it is not clear whether the condition would increase the susceptibility to respiratory viruses such as COVID-19 (Iqbal et al., 2020).

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), omega-3 components, reduce TG levels (Leslie et al., 2015) and have been associated with favorable effects on several cardiovascular risk markers such as high blood pressure and platelet aggregation (Miller et al., 2014). It has been attributed to omega-3 fatty acids, specifically EPA and DHA, an anti-inflammatory effect; however, controversially, the formation of potentially toxic oxidation products may occur with omega-3 supplementation in patients with COVID-19. Consequently, it is not recommended until randomized and controlled trials are performed (Rogero et al., 2020). However, to date, there is no evidence available on the use of omega-3 fatty acids in acute infection or illness, despite representing safety and not having significant drug interactions with the medications studied in trials for the treatment of COVID-19 (Iqbal et al., 2020).

Bile acid sequestrants are positively charged molecules that interact with negatively charged bile acids, preventing cholesterol absorption from the intestine (Soran et al., 2018). Although they do not interfere with other agents, they can inhibit the absorption of a series of drugs administered orally, and studies are needed to assess this interaction with drugs used in the treatment of COVID-19 (Feingold et al., 2020).

Finally, nicotinic acid acts to reduce lipoproteins containing apolipoprotein B (ApoB) and increase Apo A1, translating into LDLc reduction and HDLc increase (Yadav et al., 2015). Niacin has been shown to attenuate endotoxemic lung inflammation in animal models (Kwon et al., 2011), but data on viral infections in humans are lacking (Iqbal et al., 2020).

Table 1 – Studies related treatment in COVID-19 and dyslipidemic conditions.

Authors/Publication data	Country	Participants	Clinical diagnosis	Treatment	Outcomes
Scicali et al, 2020 [74]	Italy	-	Familial hypercholesterolemia	Statins and iPCSK9	Reduce severe disease
Banach et al,2020 [73]	Poland	-	Familial hypercholesterolemia	Lipid-lowering agents	Recommendation
Vargas et al,2020 [45]	Spain	-	Dyslipidemic patients	Lipid-lowering agents	Recommendation
Hariyanto et al,2020 [53]	Indonesia	3,449	Dyslipidemic patients	Statin	Statin use did not improve severity outcomes and mortality from COVID-19 infection
Iqbal et al,2020 [44]	UK	-	Dyslipidemic patients	Lipid-lowering agents	Recommendation
Buschard,2020 [59]	Denmark	-	Hypertension and Metabolic syndrome	Fibrates (Fenofibrate)	Reduce severe disease and infection
Saeed et al,2020 [51]	USA	4,252	Patients with/without diabetes mellitus receveing/not statins	With diabetes: Atorvastatin(76%) Rosuvastatin(1%) Pravastatin(5%) Simvastatin(18%) Without diabetes: Atorvastatin(73%) Rosuvastatin(1%) Pravastatin(6%) Simvastatin(20%)	Observational analysis, statin in diabetes mellitus reduced risk of in-hospital mortality during COVID-19
Tan et al,2020 [50]	Singapore	717	Dyslipidemic (21.8%) Associated hypertension, diabetes and CVD (24-59%) Older - 62.5 years (55-68)	Statin (96.7%) Fibrates (7.7%) Ezetimibe (6.4%)	Lower chance of ICU admission of statin users when compared to non-statin users
Mitacchione et al, 2021 [52]	Italy	842	Patients hospitalized for COVID-19	Statins Atorvastatin(49%) Simvastatin (30%) Rosuvastatin(16%) Other statins (5%)	Not affected in-hospital mortality
Vuorio et al,2021 [35]	Finland	-	Familial hypercholesterolemia	Lipid-lowering agents (statin, iPCSK9, Ezetimibe)	Recommendation
Ferrara et Vitiello,2021 [49]	Italy	-	Dyslipidemic patients	Lipid-lowering agents - Statin	Recommendation

Source: Authors.

3.5 Management in the treatment of familial hypercholesterolemia (FH) in COVID 19

Patients with FH have premature cardiovascular disease and when an infection with COVID-19 occurs, they become more vulnerable to severe and earlier cardiovascular events due to vascular endothelial dysfunction, and higher levels of Lp(a) with atherothrombotic risk during illness, even after recovery (Vuorio et al., 2020; Banach et al., 2020). Lipid-lowering treatment should not be suspended during infection (Scicali et al., 2020) and even intensified after recovery. It is recommended high-intensity statins, fixed combinations of statins with ezetimibe and/or triple therapy besides PCSK9 inhibitors for stabilization of atheromatous plaques and prevention of new events (Mach et al., 2020).

The use of PCSK9 inhibitors in patients with COVID-19 and severe hypercholesterolemia should be considered, mainly due to the high risk of an acute cardiovascular event, as in patients with FH. A single injection can be administered and drug therapy should be continued (Leggio et al., 2021).

3.6 Post-COVID Complications and Monitoring

COVID-19 pandemic brought functional impairment in multiple organs including lungs, heart, kidney, liver, brain and vascular system (Cao et al., 2020). Patients with conditions of prior morbidity associated with metabolic disorders such as hypertension, obesity and diabetes mellitus are more susceptible to major post-COVID-19 complications (Cao et al., 2020).

Complications related to endothelial dysfunction after the critical stage of the disease are related to several causes. Coagulation disorders in COVID-19 suggest that vasculopathy appears to be an independent risk factor that promotes higher mortality in affected patients (Cao et al., 2020). Pre-existing lipid profile disorders often accompany endothelial cell dysfunction, making endothelial cells more vulnerable to attack by SARS-CoV-2 (Cao et al., 2020). A high virulence of SARS-CoV-2 infecting endothelial cells can cause acute and local damage to blood vessels, triggering coagulopathies as significant clinical sequelae (Maiolino et al., 2013). In a second scenario, the accumulation of LDLc in the subendothelium during disease, where oxidative modifications of LDLc occur, corresponds to an initial step in atherogenesis (Williams & Tabas, 1995). Finally, SARS-CoV-2 infection induces endothelial inflammation, referred to as endothelial direct viral invasion and host apoptosis and pyroptosis, causing vasculitis and aggravating post-COVID-19 complications (Varga et al., 2020).

In the long term, COVID-19, as well as other Sars-CoV infections, can cause dyslipidemia, dysglicemia, kidney and liver disease in survivors (Wu et al., 2020; Ogeng'o et al., 2020). In a follow-up study of patients recovered from COVID-19 after 3-6 months, LDLc and HDLc levels were found to be significantly increased in severe cases (Li et al., 2021). Mild or moderate liver damage caused by viral infection may be an important contributing factor to dyslipidemia in patients with COVID-19 (Wei et al., 2020). Regarding coagulation parameters, they did not show correlation between these and LDLc and HDLc levels, suggesting that the recovery from dyslipidemia and the improvement of coagulation disorders probably involve different pathways (Li et al., 2021).

As patients with FH are more likely to trigger endothelial microcirculation dysfunction with activation of the coagulation cascade, it is recommended to use statins that reduce serum D-Dimer levels by around 15% (Schol-Gelok et al., 2018), or inhibitors of PCSK9 that decrease the level of atherothrombogenic Lp(a) by about 30% (Raal et al., 2015; Kastelein et al., 2015).

4. Conclusion

Reducing the impacts of COVID-19 consists of diagnosing and predicting disease severity at an early stage. Therefore, that infection can be effectively monitored and managed, reducing the financial burden on the health system (Kimhofer et al., 2020). Dyslipidemias are one of the main risk factors for the severe form of COVID-19 due to the influence of lipids on infection and viral replication, causing endothelial dysfunction already installed in previously dyslipidemic patients. In FH patients, in addition to increased LDLc levels, high levels of Lp(a) point to atherothrombotic complications in these patients, justifying the intensification of lipid-lowering treatment. Monitoring of the lipid profile, as well as control with lipid-lowering drugs, which can influence the infectivity and inflammatory response caused by viral infection, we could reduce risk factors in as attempt to change these outcomes.

This up-date opens new perspectives to further studies in order to better comprehend the mechanism related to COVID-19 and dyslipidemia status, as well as personalized treatment to increase the response and quality of life after the infection.

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