The clinical value of high-density lipoprotein in the evaluation of new coronavirus pneumonia

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\textbf{A} – research concept and design; \textbf{B} – collection and/or assembly of data; \textbf{C} – data analysis and interpretation; \textbf{D} – writing the article; \textbf{E} – critical revision of the article; \textbf{F} – final approval of the article

\textbf{Abstract}


\textbf{Objectives.} To investigate the changes of high-density lipoprotein (HDL) level in patients with COVID-19 and assess its value in the evaluation and prognosis of this disease.

\textbf{Material and methods.} This paper is a cross-sectional retrospective study. Eighty-six severe COVID-19 patients, 132 non-severe COVID-19 patients and 76 healthy individuals (control group) were recruited to measure triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) using enzyme-coupled colorimetry.

\textbf{Results.} The serum HDL-C level in COVID-19 group was 1.02 ± 0.28 mmol/L which was significantly lower than in control group (1.52 ± 0.55 mmol/L) (\(p < 0.05\)). In addition, the serum HDL-C level in severe COVID-19 group was 0.83 ± 1.67 mmol/L, which was significantly lower than that in non-severe COVID-19 group (1.15 ± 0.27 mmol/L) (\(p < 0.05\)).

\textbf{Conclusions.} Changes in HDL levels in patients with COVID-19 can reflect the severity of the disease and have a clinical significance in establishing the prognosis.

\textbf{Key words:} blood lipids, critical illness, new coronavirus pneumonia, high-density lipoprotein cholesterol
Introduction

The new coronavirus pneumonia (NCP, COVID-19) outbreak began in Wuhan in December 2019.1 It can cause multiple organ damage, mainly to lung tissue, and induce inflammation in the body.1,2 In recent years, more and more studies have shown that plasma high-density lipoprotein (HDL) not only participates in reverse transport of cholesterol, but also widely affects the inflammatory response of the body.3

Objectives

The purpose of this study was to analyze the changes of HDL levels in patients with COVID-19 and the clinical value of this measurement in the evaluation and prognosis of this disease.

Patients and methods

General information

Cross-sectional retrospective analysis was performed in the present study. All cases were divided into 3 groups: severe COVID-19 group, non-severe COVID-19 group and healthy control group. The severe group included 86 patients with severe/critical COVID-19, of an average age of 54.36 ±12.61 years, while the non-severe group consisted of 132 mild COVID-19 patients, of an average age of 44.02 ±17.13 years. Seventy-six healthy individuals with an average age of 47.73 ±8.68 years, receiving medical examinations, served as the healthy control group. The exclusion criteria were as follows: malignant tumors, severe head trauma and other diseases. This study was approved by the ethics committee of our hospital and all participants signed the informed consent prior to the study.

Diagnostic criteria and classification criteria

All COVID-19 patients enrolled met the diagnostic criteria of the New Coronavirus Pneumonia Diagnosis and Treatment Program (trial version 7) issued by the National Health Commission of China on March 4, 2020.4 All cases were confirmed using the new coronavirus nucleic acid test through real-time fluorescent reverse-transcription polymerase chain reaction (RT-PCR). Patients were classified according to the new version of the diagnosis and treatment plan into the following categories: 1) light or mild clinical symptoms, no pneumonia manifestations in the imaging; 2) common type of the disease, with symptoms of fever, respiratory tract, etc. (pneumonia visible in the imaging); 3) severe disease, meeting any of the following criteria: shortness of breath, breathing frequency ≥30 times/min; blood oxygen saturation (SO2) ≤93%; arterial blood oxygen partial pressure (PaO2)/oxygen absorption concentration (FiO2) ≤300 mm Hg at rest; 4) critical form of the disease, meeting any of the following criteria: respiratory failure, mechanical ventilation required; shock (or combined with other organ failure), requiring intensive care unit (ICU) treatment.

Research methods

Cases that met the diagnostic criteria for new coronavirus pneumonia were classified according to the New Coronavirus Pneumonia Diagnosis and Treatment Program (trial version 7), and patients from categories 1 and 2 were included into the non-severe group, while patients from categories 3 and 4 were included into the severe group. Venous blood was collected from all enrolled subjects on the 1st day of admission to measure triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels using enzyme-coupled colorimetric method.

Statistical processing

The statistical analysis was carried out using SPSS v. 20.0 software (IBM Corp., Armonk, USA). The countable data was expressed as a percentage and assessed with a χ2 test. The measurement data was displayed as mean ± standard deviation (SD) and evaluated with the Student’s t-test. A value of p < 0.05 indicated statistically significant difference.

Results

The serum HDL-C levels in the COVID-19 group and healthy control group were 1.02 ±0.28 mmol/L and 1.52 ±0.55 mmol/L, respectively. After data was analyzed using the Student’s t-test, the serum HDL-C levels in the COVID-19 group turned out to be significantly lower than those in the healthy control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>COVID-19 group</th>
<th>Healthy control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>48.19±16.33</td>
<td>47.73±8.68</td>
</tr>
<tr>
<td>White blood cells [×10⁹/L]</td>
<td>6.77±3.59</td>
<td>6.14±2.05</td>
</tr>
<tr>
<td>Absolute value of lymphocytes [×10⁶/L]</td>
<td>1.09±0.81</td>
<td>1.92±0.74</td>
</tr>
<tr>
<td>Absolute value of neutrophils [×10⁹/L]</td>
<td>5.21±3.59</td>
<td>3.56±1.33</td>
</tr>
<tr>
<td>Total cholesterol [mmol/L]</td>
<td>3.81±0.82</td>
<td>4.64±1.00</td>
</tr>
<tr>
<td>Triglyceride [mmol/L]</td>
<td>1.42±1.38</td>
<td>1.64±1.12</td>
</tr>
<tr>
<td>High-density lipoprotein [mmol/L]</td>
<td>1.02±0.28</td>
<td>1.52±0.55</td>
</tr>
<tr>
<td>Low-density lipoprotein [mmol/L]</td>
<td>2.46±0.77</td>
<td>2.55±0.75</td>
</tr>
</tbody>
</table>
lower than those in the healthy control group (p < 0.05) (Table 1). The HDL-C levels in severe COVID-19 group and non-severe COVID-19 group were 0.83 ± 1.67 mmol/L and 1.15 ± 0.27 mmol/L, respectively. The HDL-C level in the non-severe group was significantly higher than in the severe group, and the statistical results were significantly different (p < 0.05) (Table 2).

**Discussion**

The COVID-19 is caused by a new coronavirus (2019-nCoV) infection and the disease progresses rapidly. At the same time, general population susceptibility and significant infectivity can be observed.8 A number of studies have shown that 2019-nCoV can induce a cytokine storm after invading the body and aggravating the inflammatory response. Interleukin 2 (IL-2), granulocyte colony stimulating factor (G-SCF) and macrophage inflammatory protein (MIP-1a) as well as tumor necrosis factor α (TNF-α) and other inflammatory factors have increased to varying degree in patients’ plasma.8,9 The COVID-19 is mainly caused by lung tissue lesions and patients present abnormally increased inflammatory factors, leading to overactivation of immune cells, which accumulate and activate in the lung tissue, resulting in diffuse damage to pulmonary capillary endothelial cells and alveolar epithelial cells. Pulmonary damage produces in turn a large amount of inflammatory exudate that eventually blocks the bronchial tubes at all levels, causing continuing deterioration of lung function, leading to acute respiratory distress syndrome (ARDS) and respiratory failure.7,8 The results of our study showed that the level of HDL-C in the COVID-19 patients was significantly lower than in the healthy control group (p < 0.05). At the same time, the level of HDL-C in the severe COVID-19 group was significantly lower than in the non-severe COVID-19 (p < 0.05). This shows that blood lipid levels, especially HDL-C levels, vary in patients with COVID-19. The severity of this disease can affect the fluctuation of HDL-C levels. Severe COVID-19 patients have significantly lower HDL-C levels than non-severe patients. Therefore, the changes of HDL-C level can be used as a predictor of the severity of COVID-19.

Among various lipoproteins in the body, HDL has the smallest volume and the highest density. It mainly reverses cholesterol from the peripheral tissues to the liver for further recycling or excretion in the form of cholic acid.9 However, in recent years, the role of HDL in inflammatory infection has been gradually better understood. Some studies have shown that HDL can prevent the activation of peripheral blood monocytes and macrophages lipopolysaccharides (LPS) and lipid wall phosphates (LTA), thereby reducing TNF-α and interleukin 1β (IL-1β) synthesis and secretion.10 When the body is infected, LPS, which constitute the main component of endotoxin, are released from the outer cell membrane to form a complex with HDL, thereby achieving the effect of neutralizing toxicity and reducing inflammation; HDL levels also decrease.11 The HDL and LPS are combined and consumed in the body. Once exhausted, the patient’s inflammatory response is difficult to be effectively controlled, eventually leading to multiple organ dysfunction or even death.

Many studies have shown that HDL can inhibit the combination of various types of viruses and host cells, including enveloped and non-enveloped DNA and RNA viruses, such as Japanese encephalitis virus, rubella virus, Epstein–Barr virus, herpes simplex virus, human immunodeficiency virus (HIV), coxsackievirus, , poliovirus, and other viruses. In the early stage of viral infection, HDL exerted antiviral activity, mainly inhibiting the penetration of the virus into the cells after it was adsorbed.12 Another study showed that the function of HDL isolated from mice infected with influenza A is impaired and its anti-inflammatory and antioxidant properties are reduced13; further injection of D-4F ApoAI mimic peptide into infected mice can reduce the inflammation in the lungs and inhibit the production of IL-6 and prevent macrophages from entering the arteries.14 The D-4F ApoAI mimic peptide also has antiviral activity and can reduce influenza virus titer by 50%.15 The above research provides new ideas for inhibiting 2019-nCoV. Perhaps exogenous HDL can be used as a kind of antiviral treatment. It also proves that the level of HDL in patients with COVID-19 can reflect the disease severity.

The HDL synthesis occurs mainly through the liver and small intestine, and most of the severe COVID-19 patients have impaired liver function and small intestinal mucosal ischemia, so HDL synthesis is also reduced; at the same time, intake of large amounts of carbohydrate compounds can accelerate the decomposition of proteins in HDL.16 Therefore, treatment of severe COVID-19 patients should include maintaining liver and intestinal mucosal function, and appropriately reducing carbohydrate intake, so as to ensure the synthesis of HDL and improve the prognosis.

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**Table 2. Comparison of blood lipid results in severe group, non-severe group and healthy control group**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>TC [mmol/L]</th>
<th>TG [mmol/L]</th>
<th>HDL-C [mmol/L]</th>
<th>LDL-C [mmol/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>86</td>
<td>3.65 ±0.75</td>
<td>1.91 ±1.87</td>
<td>0.83 ±1.67</td>
<td>2.32 ±0.71</td>
</tr>
<tr>
<td>Non-severe</td>
<td>132</td>
<td>3.93 ±0.84</td>
<td>1.1 ±0.79</td>
<td>1.15 ±0.27*</td>
<td>2.56 ±0.81</td>
</tr>
<tr>
<td>Healthy control</td>
<td>76</td>
<td>4.64 ±1.01</td>
<td>1.64 ±1.12</td>
<td>1.52 ±0.55**</td>
<td>2.55 ±0.75</td>
</tr>
</tbody>
</table>

* compared with the severe group (p < 0.05); ** compared with the non-severe group (p < 0.05).
Conclusions

The HDL, as part of the natural immunity of the body, has antiviral and anti-inflammatory properties. The results of this study show that changes in HDL levels in patients with COVID-19 can reflect the disease severity and have clinical significance in assessing the prognosis. The lower HDL-C levels, the worse the prognosis. At the same time, HDL-C has certain application prospects in the treatment of COVID-19, providing an important reference for the clinical diagnosis and treatment. However, other potential biomarkers need to be further investigated to enable a comprehensive understanding of COVID-19.

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