

Evaluation of the level of high-density lipoproteins as a predictor of severity in abdominal sepsis

Evaluación del nivel de lipoproteínas de altas densidad como predictor de gravedad en la sepsis abdominal

Ansony R. Godínez-Vidal^{1*}, Carlos E. López-Betancourt¹, Gabriela E. Gutiérrez-Uvalle²,
Mariel González-Calatayud², Julio C. Zavala-Castillo², and Noé I. Gracida-Mancilla²

¹Department of General Surgery; ²Department of Abdominal Sepsis Clinic, General Surgery, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico

Abstract

Background: Alterations in the lipid profile are part of the acute phase response; this corresponds to the so-called lipemia of sepsis. **Objective:** The objective of the study was to determine if the serum level of high-density lipoprotein (HDL) is related to severity and mortality. **Methods:** Retrospective, descriptive, and cross-sectional study of patients diagnosed with abdominal sepsis during the period from April 2016 to February 2017. The severity was determined by Acute Physiology and Chronic Health Evaluation II, Sepsis-related Organ Failure Assessment (SOFA), Mannheim, CONUT, the presence of organic faults and mortality. **Results:** We included 154 cases, 59 female and 95 male; the main organ causing abdominal sepsis was the appendix 41.6%. The overall mortality was 14.3%. The presence of organic faults was 35.1%. The mean HDL level was 37.64 mg/dl (standard deviation $\pm$ 16.16). The findings, subjected to statistical verification by Student's t-test, showed significance among the cases with SOFA > 4 ($p = 0.01$) and Mannheim > 26 ($p = 0.001$), CONUT > 6 ($p = 0.001$), the presence of organic failures ($p = 0.001$), and mortality ($p = 0.003$). **Conclusions:** HDL levels are related to severity, with the development of organic failures and mortality in sepsis.

Key words: Severity. High-density lipoprotein. Mortality. Sepsis.

Resumen

Antecedentes: Las alteraciones en el perfil de lípidos son parte de la respuesta de fase aguda, lo que corresponde a la denominada lipemia de la sepsis. **Objetivo:** Determinar si la concentración sérica de lipoproteínas de alta densidad (HDL) se relaciona con la gravedad y la mortalidad. **Método:** Estudio retrospectivo, descriptivo, transversal, de pacientes con diagnóstico de sepsis abdominal, durante el periodo de abril de 2016 a febrero de 2017. Se determinó la gravedad mediante APACHE II, SOFA, Mannheim, CONUT, la presencia de fallas orgánicas y la mortalidad. **Resultados:** Se incluyeron 154 casos, 59 mujeres y 95 hombres. El principal órgano causante de sepsis abdominal fue el apéndice (41.6%). La mortalidad global fue del 14.3%. La presencia de fallas orgánicas fue del 35.1%. El valor medio de HDL se situó en 37.64 mg/dl (desviación estándar: $\pm$ 16.16). Los hallazgos, sometidos a verificación estadística mediante la prueba t de Student, mostraron significancia entre los casos con SOFA > 4 ($p = 0.01$) y Mannheim > 26 ($p = 0.001$), CONUT > 6 ($p = 0.001$), presencia de

Correspondence:

*Ansony R. González-Vidal

Dr. Balmis, 148, Col. Doctores, Del. Cuauhtémoc

C.P. 06726, Ciudad de México, México

E-mail: ansony.rgv@gmail.com

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fallas orgánicas ($p = 0.001$) y mortalidad ($p = 0.003$). **Conclusión:** Los valores de HDL se relacionan con la gravedad, con el desarrollo de fallas orgánicas y con la mortalidad en la sepsis.

Palabras clave: Gravedad. Lipoproteínas de alta densidad. Mortalidad. Sepsis.

Introduction

The most important at initial stages of inflammatory response to infection is diagnosis, quantifying its severity; therefore, identifying signs and symptoms suggesting that the suspicion of sepsis is a priority^{1,2}. Inflammation markers diagnostic value lies in that they might differentiate infectious processes from those that are not and predict the severity of a pathological process or disease, thus allowing the implementation of an adequate therapeutic plan and measuring its response³⁻⁶. Alterations in the lipid profile are part of the body's acute phase response, and in the case of infectious processes they correspond to the so-called "lipemia of sepsis"⁷. The reduction of cholesterol levels in septic processes is attributed to bacterial endotoxins, tumor necrosis factor, interleukin 2, and interferon alpha⁸. In addition, both high-density (high-density lipoprotein [HDL]) (by 60%) and low-density lipoprotein (by 40%) participate in Gram-negative bacteria lipopolysaccharides and Gram-positive bacteria lipoteichoic acid elimination. Gram-negative bacteria lipopolysaccharide lipid is a strong host inflammatory response-inducer⁹. The causes whereby there is a decrease in HDL during a septic process are unknown, but there are various hypotheses, such as HDL particles consumption, liver synthesis decrease (mainly in case of liver failure), and redistribution toward extravascular space¹⁰. HDL has been observed to modulate macrophage response: (a) it promotes the flow of free cholesterol from macrophages, which results in lipopolysaccharide-induced inflammatory response suppression; and (b) HDLs are agonists of transcriptional regulator activating transcription factor 3, which downregulates inflammatory molecules expression, thus resulting in inflammatory response suppression in sepsis. HDL molecules have also been shown to act on endothelial cells as follows: (a) inhibiting adhesion molecules stimulated by tumor necrosis factor, interleukin 1 and thrombin; (b) activating nitric oxide synthase (nitric oxide generated by this enzyme in small vessels promotes vascular flow and prevents thrombosis); and (c) avoiding endothelial thrombosis

activation promoted by the production of prostacyclin and cyclooxygenase 2, and suppressing tissue factor and adhesion molecules expression¹¹.

Abdominal sepsis is a serious, life-threatening condition and, therefore, it requires immediate implementation of therapeutic measures. These measures depend on the severity of the condition, which is determined in different ways: through clinical scales, determining its biomarkers, or assessing complications, such as secondary organ failure and mortality. Among the different described biomarkers, many of them are only available in research centers or are too expensive. Serum HDL level has been described as an indicator of severity in various diseases, including some infectious conditions, but its usefulness as a severity marker in abdominal sepsis has not been studied. Measurement of serum HDL concentrations is a laboratory test that can be carried out easily and is inexpensive and quick to obtain. If the measurement of HDL values could be corroborated to be a test that is as sensitive and specific as the use of clinical physiological tests to determine the severity of abdominal sepsis, the time for diagnosis and health-care institutions resources could be optimized.

The purpose of the present investigation is to determine the usefulness of serum HDL concentration as a predictor of severity and mortality in patients with abdominal sepsis.

Methods

A retrospective, descriptive, and cross-sectional study of patients diagnosed with abdominal sepsis due to secondary peritonitis, treated during the period from April 2016 to February 2017, was carried out. In all cases, sepsis severity was determined using two physiological scales: Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sepsis-related Organ Failure Assessment (SOFA), as well as a surgical index (Mannheim peritonitis index), a nutritional index (CONtrolling NUTritional status, CONUT), and the development of organ failure and mortality. In all cases, serum HDL concentration was measured. The sample was divided in two groups: low, with HDL < 29 mg, and

Table 1. Classification in mild and severe cases

Severity indicator	Severe	Mild
APACHE II	> 15	< 14
SOFA	> 4	< 3
Mannheim	> 26	< 25
CONUT	> 6	< 5
Organ failure	With failure	Without failure
Outcome	Deceased	Alive

Table 2. High-density lipoprotein versus severity scales, presence of organ failure, and mortality

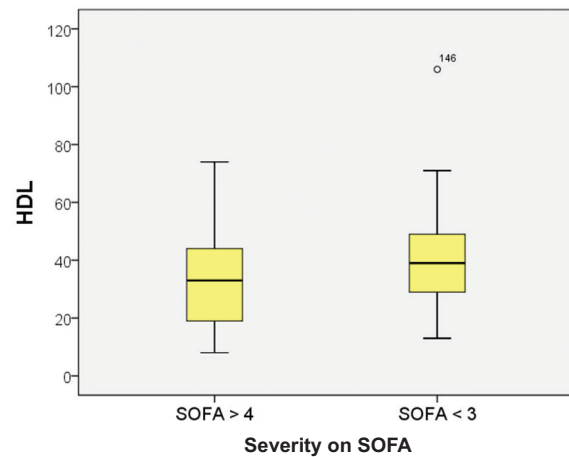
Variable	Severity by HDL		p	OR
	Severe HDL < 29 mg/dL Mean (SD)	Mild HDL > 30 mg/dL Mean (SD)		
APACHE II	12.6 (7.3)	9.4 (6.0)	0.079	-
SOFA	4.1 (2.3)	3.3 (1.7)	0.001	0.4
MPI	22.2 (8.1)	16.9 (8.4)	0.001	0.25
CONUT	8.5 (2.7)	3.8 (2.8)	0.001	0.06
Mortality	11/49 (22.4%)	14/114 (12.3%)	0.003	0.33
Organ failure	25/50 (50%)	29/104 (27.9%)	0.001	2.5

SD: standard deviation; HDL: high-density lipoprotein; MI: Mannheim peritonitis index;
OR: odds ratio

high, with HDL > 30 mg, with this value being used as a discrimination point. For the scales and severity indices, the cases were divided into mild (APACHE II < 14, SOFA < 3, Mannheim < 25 points, and CONUT < 5) and severe (APACHE II > 15, SOFA > 4, Mannheim > 26, and CONUT > 6) (Table 1). The groups were compared using 2 × 2 tables, and frequencies were assessed using the Chi-square test. To determine the association between HDL figures and severity scales, organ failure development and mortality, Student's t-test was used for hypothesis statistical testing, with $p < 0.05$ being established as significant.

Results

One-hundred and fifty-four cases (59 women and 95 men), with a mean age of 46.9 years (standard deviation [SD]: ± 18.8) were included in the study. The organs causing abdominal sepsis were the appendix (64 cases; 41.6%), the small intestine (32 cases;

**Figure 1.** Relationship between high-density lipoprotein (HDL) figures and the SOFA scale. It can be appreciated that the lower the HDL value, the higher the SOFA score.

20.8%), the colon (24 cases; 15.6%), the stomach (10 cases; 6.5%), bile ducts (9 cases; 5.8%), the uterus (4 cases; 2.6%), the kidney (4 cases; 2.6%), the pancreas (3 cases; 1.9%), and other organs (4 cases; 2.6%). Organ failure occurred in 54 patients (35.1%). Twenty-two patients died (14.3%) and 132 (85.7%) survived. Regarding the evaluated severity scales, an average APACHE II score of 10.4 (SD: ± 6.6) was found, ranging from 1 to 37; for the SOFA scale, there was a mean of 3.5 (SD: ± 2), with a range from 1 to 13; for the Mannheim severity scale, a mean of 18.7 points (SD: ± 6.59) was found, with a range of 4 to 43; and for CONUT, the mean was 5.3 (SD: ± 3.5), ranging from 0 to 12. HDL had a mean value of 37.6 mg/dL (SD: ± 16.1). HDL figures were then compared against the severity scales (Table 2). The findings, subjected to statistical verification using Student's t-test, showed statistical significance between cases with HDL < 29 mg/dL and SOFA scores > 4 ($p = 0.001$) (Fig. 1), Mannheim > 26 ($p = 0.001$) (Fig. 2), and CONUT > 6 ($p = 0.001$) (Fig. 3), but not with APACHE ($p = 0.079$) (Fig. 4).

When HDL figures were compared against the presence of organ failure and mortality (Table 2), statistical significance was demonstrated with HDL < 29 mg/dL and the presence of organ failure ($p = 0.001$) (Fig. 5) and with mortality ($p = 0.003$) (Fig. 6).

Discussion

In this study, serum HDL concentration was compared in patients with abdominal sepsis, contrasting

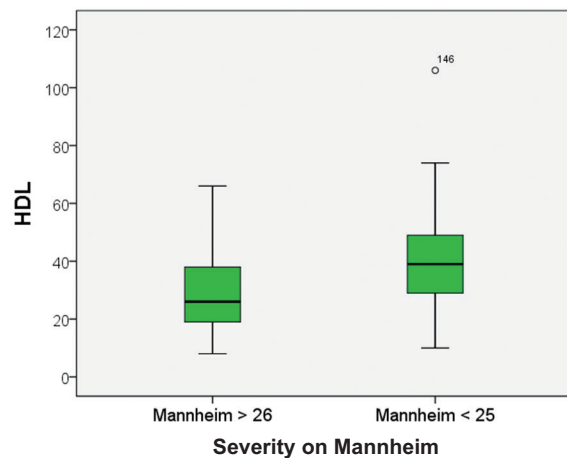


Figure 2. Relationship between high-density lipoprotein (HDL) figures and the Mannheim scale. It can be appreciated that the lower the HDL value, the higher the Mannheim score.

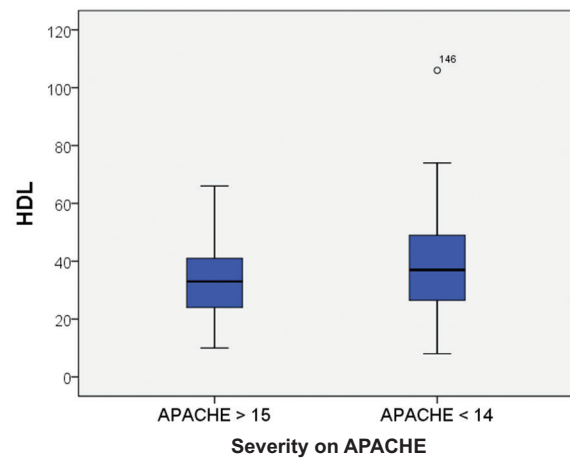


Figure 4. Relationship between high-density lipoprotein (HDL) figures and APACHE. It can be appreciated that the lower the HDL value, the higher the APACHE score, but without statistical significance.

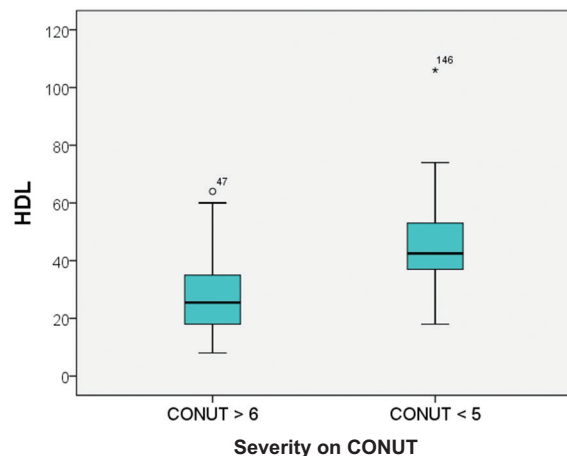


Figure 3. Relationship between high-density lipoprotein (HDL) figures and the CONUT scale. It can be appreciated that the lower the HDL value, the higher the CONUT score.

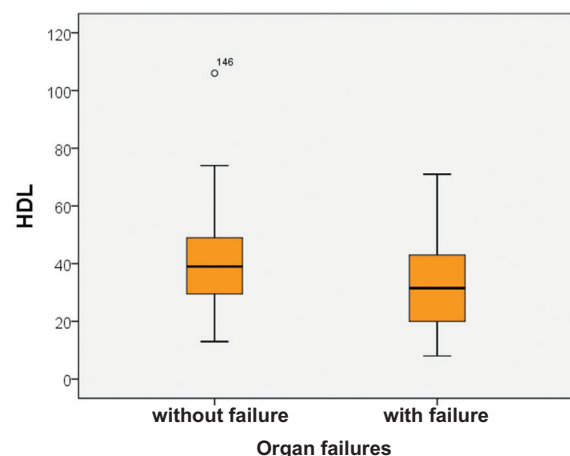


Figure 5. Relationship between high-density lipoprotein (HDL) figures and the presence of organ failure. It can be appreciated that the lower the HDL value, the higher the presence of organ failure.

it against the severity scores obtained on the SOFA, APACHE II, Mannheim and CONUT severity scales, and with the presence of organ failure and mortality.

Some of the pioneers in HDL value investigation were Chien et al.¹², who studied 63 patients with sepsis of pulmonary origin and found that values > 25 mg/dL had 100% survival. Contreras et al.⁷ report that HDL-cholesterol levels < 20 mg/dL are an independent predictive criterion of 30-day mortality, even exceeding the predictive value of APACHE II assessment; moreover, they comment that low apolipoprotein A-I values constitute an independent marker of 90-day mortality with a relative risk that exceeds SOFA and Model for End-stage Liver Disease clinical scores,

which indicate the severity of chronic liver disease. Roveran et al.¹³ found that patients with sepsis and low HDL values (< 33.06 mg/dL) were at higher risk of developing stage 2 or 3 Kidney Disease: Improving Global Outcomes acute kidney failure related to septic process. This is consistent with the present investigation, where a HDL value < 30 mg/dL was correlated with the presence of organ failure ($p = 0.001$). Cirstea et al.¹⁴ conducted a study in 200 patients with sepsis where they found that HDL low values (< 25 mg/dL) were an independent factor associated with multiple organ failure and 28-day mortality increase. We found a mortality increase with HDL < 30 mg/dL ($p = 0.003$);

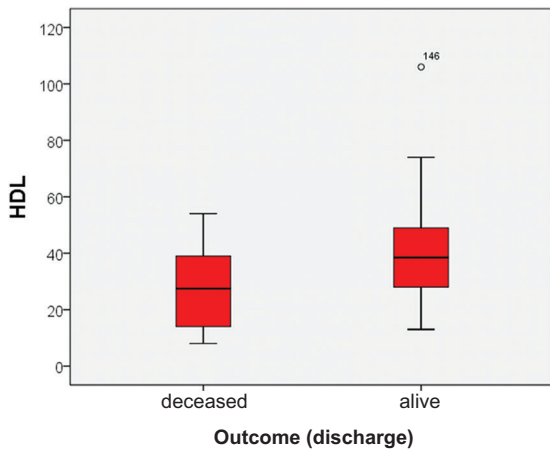


Figure 6. Relationship between high-density lipoprotein (HDL) figures and mortality. It can be appreciated that the lower the HDL value, the higher the mortality.

therefore, new therapies should be designed, and resources redirected for this at-risk population. Tanaka et al.¹⁰ studied 75 patients admitted to the intensive care unit and found that disease severity in septic patients, calculated with the SOFA scale, was inversely associated with HDL figures; furthermore, they observed a mortality increase in patients with figures < 7.72 mg/dL compared to a SOFA score > 6 within the first 3 days. Moreover, in our study, there was a correlation with the SOFA scale, but its cutoff point was 4, with a statistically significant result. We do not consider intensive care unit days of stay as a variable, which ultimately translates into higher costs and increased morbidity and mortality, and this is currently important, when medicine is sought to be cost-effective, which is why there are phase 2 and 3 investigations intended to promote HDL and apolipoprotein A1 concentration increase.

It should be noted that our study only focused on patients with abdominal sepsis, while in most reviewed studies, no selective categorization was found for an abdominal septic process; this, together with the sample heterogeneity, makes for the values to differ from those published, with various cutoff points for HDL levels. Our research is the first to correlate HDL figures with morbidity prognostic scales, such as CONUT and Mannheim. In the first scale, patients at risk for undernourishment are expected to have an increase in morbidity and mortality given that one of the measured parameters is total cholesterol, which, as previously described, has implications in the septic process and, due liver mobilization,

it will be decreased; furthermore, in patients with organ failure, the liver will not be able to adequately perform this function, and increased catabolism and prolonged fasting also directly affect the patient and his/her prognosis and thus, early nutrition, either enteral or parenteral, plays an important role in sepsis current treatment. The second scale, the Mannheim peritonitis index, evaluates the need for patient reoperation and by means of it we found that there is an inverse correlation with an HDL figure < 29.9 mg/dL ($p = 0.001$), which translates into a more serious septic process that requires more surgical interventions, thus increasing the catabolic state and, therefore, increasing morbidity and mortality. We found that low HDL values increase patient mortality. We reported a mortality of 14.3%. When analyzing the data, blood HDL concentrations are inversely proportional to the presence of organ failure and mortality. HDL values were significantly correlated with Mannheim, SOFA, and CONUT scores to determine severity, but there was no statistical significance with APACHE II scores.

Conclusion

HDL values are negatively associated with patient morbidity with a cutoff point of 30 mg/dL in comparison with the SOFA, Mannheim, and CONUT severity scales, with an impact on patient mortality. Furthermore, with HDL < 30 mg/dL there is an increased risk for the development of organ failure, with the implications this entails in patient survival. Thus, HDL determination is useful for predicting severity and mortality in patients with abdominal sepsis.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical disclosure

Protection of people and animals. The authors declare that no experiments on humans or animals were performed for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This

document is in the possession of the corresponding author.

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