

# Hypertriglyceridemia during infectious mononucleosis

Emilio Manuel Páez-Guillán (✉ [emiliompg@hotmail.com](mailto:emiliompg@hotmail.com))

Complejo Hospitalario Universitario de Santiago de Compostela <https://orcid.org/0000-0002-3544-6083>

Joaquín Campos-Franco

Complejo Hospitalario Universitario de Santiago de Compostela: Complejo Hospitalario Universitario de Santiago de Compostela

M<sup>a</sup> del Rosario Alende-Sixto

Complejo Hospitalario Universitario de Santiago de Compostela: Complejo Hospitalario Universitario de Santiago de Compostela

Yago Garitaonaindía-Díaz

Complejo Hospitalario Universitario de Santiago de Compostela: Complejo Hospitalario Universitario de Santiago de Compostela

Arturo González-Quintela

Complejo Hospitalario Universitario de Santiago de Compostela: Complejo Hospitalario Universitario de Santiago de Compostela

---

## Research

**Keywords:** Epstein-Barr virus, Infectious mononucleosis, Dyslipidemia, Hypertriglyceridemia

**Posted Date:** September 20th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-915947/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

## Background

Hypertriglyceridemia can be observed in lymphoproliferative disorders. Epstein-Barr virus-induced infectious mononucleosis can be considered a self-limiting lymphoproliferative disorder. The aim of this study is to investigate serum triglyceride concentrations, associated factors, and time-course changes in patients with infectious mononucleosis.

## Methods

We report on an adult patient with extreme hypertriglyceridemia (triglycerides > 1000 mg/dL) during infectious mononucleosis. We then reviewed the clinical records of 360 patients admitted to the hospital due to infectious mononucleosis (median age 19 years, range 15–87 years; 51.4% male). Serum triglyceride concentrations were compared with those of a control sample from the general population, aged 18–30 years (n = 75). A second measurement of serum triglyceride concentrations, obtained during convalescence (median of 30 days after the initial determination), was available for 160 patients.

## Results

Triglyceride concentrations in the acute phase (median 156 mg/dL; range, 27–452 mg/dL) were significantly higher than those of controls ( $P < 0.001$ ). A total of 194 patients (53.9%) showed hypertriglyceridemia (triglycerides > 150 mg/dL), which was more common in the older patients. A significant correlation was observed between serum triglycerides and white blood cell counts, total cholesterol levels, and markers of liver damage. Serum triglyceride concentrations tended to decrease during convalescence ( $P < 0.001$ ) and were lower than the initial measurement in 83.7% of the cases. Conversely, total serum cholesterol concentrations during the acute phase were lower than those of the controls and increased during convalescence ( $P < 0.001$ ).

## Conclusions

Patients with severe (in-hospital) infectious mononucleosis frequently show mild, transient hypertriglyceridemia. Further studies are needed to elucidate the mechanisms underlying these findings.

## Introduction

Infectious mononucleosis produced by Epstein-Barr virus (EBV) primary infection is characterized by fever, pharyngotonsillitis, lymphadenopathy, blood lymphocytosis, and a variety of potential systemic complications [1–4]. EBV infects B lymphocytes, in which it induces polyclonal proliferation that is usually controlled by the cellular natural killer and T cytotoxic response [5]. Infectious mononucleosis is

an acute, self-limiting lymphoproliferative disorder [3]. Furthermore, EBV infection underlies certain malignant lymphoproliferative disorders, particularly in immunocompromised hosts [6, 7]. Alterations of the lipid profile in malignant lymphoproliferative disorders are well-known. In patients with lymphoid leukemia (both acute and chronic) and non-Hodgkin's lymphoma, the characteristic pattern includes hypertriglyceridemia, elevated very low-density lipoproteins (VLDL) and low levels of high-density lipoproteins (HDL) [8–13]. This pattern is very similar to that observed in patients with a deficiency of lipoprotein-lipase, which hydrolyzes triglycerides in chylomicrons and VLDL into free fatty acids and monoacylglycerol [12]. Lipid abnormalities can precede the diagnosis of certain lymphoproliferative syndromes (chronic lymphoid leukemia) for which they could be a risk marker [14]. Plasma lipids could serve as a biomarker for the diagnosis and therapeutic management of malignant lymphoproliferative disorders [15]. Hypertriglyceridemia is also common in the hemophagocytic syndrome [16] and it is a diagnostic criterion for the syndrome and a marker for follow-up [17]. The so-called “lipid paradox”, which includes a contrast between a very low serum total cholesterol and/or HDL, and a paradoxical concomitant hypertriglyceridemia, has also been observed in certain forms of virus-induced hemophagocytic syndrome [18]. Low levels of cholesterol might be related to cholesterol receptor dysregulation due to proinflammatory cytokines, while hypertriglyceridemia could be associated with excessive hepatic secretion of VLDL and lower lipoprotein-lipase activity [18]. The lipid paradox is not limited to lymphoproliferative and hemophagocytic syndromes but is also observed in other immune-based disorders [19, 20].

Few studies have investigated lipid alterations during infectious mononucleosis. Rivera et al., observed hypertriglyceridemia in relation to hepatitis in 6 cases of infectious mononucleosis [21]. More recently, Apostolou et al. found atherogenic lipid changes in 29 patients with infectious mononucleosis; an increase in serum triglyceride concentrations was associated with an increase in the concentrations of apolipoprotein C-III, which is an inhibitor of lipoprotein lipase [22]. Likewise, Sayyahfar et al. reported transient hypertriglyceridemia in 36 children with infectious mononucleosis [23]. In this article, we report on an adult patient with extreme hypertriglyceridemia during infectious mononucleosis. We subsequently studied serum triglyceride concentrations, associated factors, and time-course changes in a larger sample of patients with severe infectious mononucleosis.

## Methods

*Case report.* A 60-year-old man was admitted to the hospital in 2003 due to fever (39°C) and jaundice. His symptoms had started 12 days earlier with general malaise, myalgia, mild cough, and slightly sore throat. His general practitioner had treated him with clarithromycin (500 mg bid) and paracetamol. The physical examination revealed only the jaundice, the presence of some small cervical lymphadenopathies and a palpable hepatic margin 2 cm below the costal margin. The main findings from the complementary examinations (Table 1) were the presence of lymphocytosis in peripheral blood with abundant (> 10%) atypical forms (activated lymphocytes), and hyperbilirubinemia. The patient also presented marked dyslipidemia with serum triglyceride concentration > 1000 mg/dL and total cholesterol > 600 mg/dL, with increased LDL and VLDL fractions (Table 1). The abdominal ultrasound highlighted only liver

hyperechogenicity. The additional investigations revealed the following: weakly positive antinuclear antibodies in serum (1/80); immunoglobulin-G (IgG), 1580 mg/dL; IgA, 314 mg/dL; and IgM, 411 mg/dL. The serological tests for human immunodeficiency virus, hepatitis B, and hepatitis C were negative. The tests for hepatitis A virus, herpes simplex virus, varicella-zoster virus, and cytomegalovirus revealed only a past infection (presence of positive IgG with negative IgM). The serum heterophile antibody test was negative; however, the IgM against the viral capsid antigen (VCA) of EBV was positive. The patient underwent only symptomatic treatment. In the following weeks, the patient developed successively IgG antibodies against VCA, followed by antibodies against EBV nuclear antigen (EBNA), with a progressive disappearance of IgM against VCA, thereby confirming the EBV primary infection. In parallel, the lymphocytosis progressively disappeared, the bilirubin and transaminase levels normalized, and the serum lipid concentrations decreased (Table 1). In the following 17 years, with no specific treatment, his serum triglyceride levels remained between 110 and 190 mg/dL, and the total cholesterol remained between 220 and 250 mg/dL.

*Study population and design.* The clinical records of adult (15-year old) patients with infectious mononucleosis who were admitted to the Department of Internal Medicine of the Santiago de Compostela (Spain) University Hospital between 1995 and 2018 were reviewed. The hospital is a reference center for an area of approximately 400,000 inhabitants. A definite diagnosis of infectious mononucleosis was considered when the usual clinical syndrome was accompanied by positive IgM antibodies against the viral capsid antigen of EBV and/or a positive heterophil antibody test (*Lennon & Crotty, 2015*). The main reasons for hospital admission were severe signs of systemic inflammatory response, difficulty with oral intake, and the presence of complications. A total of 401 patients met the diagnostic criteria; baseline (acute phase) serum triglyceride measurements (after 12 h of fasting) were not available for 41 cases. The case reported in this study was not included in the analysis. The study therefore included 360 patients (51.4% male patients; median age, 19 years; range, 15–87 years). Four patients had a previous history of dyslipidemia. For 160 patients, a second triglyceride measurement was available during the convalescence period (after a median of 30 days from the acute-phase determination; range, 14–177 days). A random subsample (n = 75) of the general adult population in the area [24], aged 18–30 years (median age, 23 years) was used for the comparison of serum triglyceride concentrations. The study was reviewed and approved by the Galician Ethics Committee.

*Statistical analyses.* The Mann-Whitney test was used to compare numerical data between groups. The Wilcoxon test was used to compare paired samples of numerical values. The Spearman's rank test was used to assess the correlations, and the chi-squared test was used to compare proportions.

## Results

The median serum triglyceride concentration during acute infectious mononucleosis was 156 mg/dL (range, 33–452 mg/dL). A total of 194 patients (53.9%) presented hypertriglyceridemia (serum triglyceride concentrations > 150 mg/dL). Eighteen patients (5.0%) presented triglyceride concentrations > 300 mg/dL. No patient presented complications that could be attributed to hypertriglyceridemia, such as

hemolysis and pancreatitis. The serum triglyceride concentrations in the patients with infectious mononucleosis were significantly higher than those of the healthy individuals from the general adult population (Fig. 1).

Table 2 shows the correlation between serum triglyceride concentrations and hematologic parameters, liver tests, and serum cholesterol levels. A statistically significant positive correlation was observed between triglyceride concentrations and total leukocyte counts, lymphocyte counts, serum total cholesterol, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and, particularly, gamma-glutamyl transpeptidase levels (Table 2). A positive correlation between serum triglyceride concentrations and age was also observed ( $\rho$ , 0.120;  $P$  = 0.023). Hypertriglyceridemia ( $> 150$  mg/dL) was observed in 33 of 42 patients (78.6%) older than 30 years and in 162 of 318 patients (50.6%) aged 30 years or younger ( $P < 0.001$ ).

Serum triglyceride concentrations significantly decreased during the convalescence phase (Fig. 1). Overall, triglyceride concentrations decreased in 134 of 160 patients (83.7%). Triglyceride concentrations normalized in the vast majority of patients in whom it was previously elevated (the second determination was normal [ $\leq 150$  mg/dL] in 78.8% of 160 studied patients).

Total serum cholesterol concentrations followed an inverse progression to that of triglycerides. In the acute phase of infectious mononucleosis, cholesterol levels were lower than those of the individuals in the general population. Serum cholesterol concentrations increased significantly in the convalescent phase (Fig. 1).

## Discussion

This study shows that more than half of patients admitted to the hospital with infectious mononucleosis present hypertriglyceridemia. The median serum triglyceride concentration in the patients with infectious mononucleosis was approximately twice than that of the individuals of a similar age range from the general adult population. Hypertriglyceridemia was more often observed in adults older than 30 years. Hypertriglyceridemia was mild in most cases, although 5% of the patients with acute infectious mononucleosis showed serum triglyceride concentrations  $\geq 300$  mg/dL. Extreme hypertriglyceridemia (triglycerides  $> 1000$  mg/dL) was observed in only one index case. Triglyceride concentrations were correlated with leukocytosis, lymphocytosis, liver damage markers, and total serum cholesterol levels. Serum triglyceride concentrations significantly decreased in the convalescence phase after infectious mononucleosis. Normalization was not uniform, thereby suggesting that infectious mononucleosis could aggravate preexisting dyslipidemia in certain cases. Total serum cholesterol levels followed an inverse course to that of serum triglycerides, with low levels during acute illness and a tendency to increase in convalescence from infectious mononucleosis. The lipid pattern observed in acute infectious mononucleosis (a self-limiting, benign lymphoproliferative disorder) is similar to that observed in malignant lymphoproliferative disorders [8–13]

Infection and inflammation lead to multiple alterations of the lipid and lipoprotein metabolism [25]. Sepsis can induce a decrease in total and HDL-cholesterol levels [26, 27]. Hypertriglyceridemia is usually less prominent in infectious or inflammatory disease. Plasma triglyceride levels can increase from increased VLDL secretion as a result of adipose tissue lipolysis, increased de novo hepatic fatty acid synthesis, and decreased lipoprotein lipase activity [25, 28]. In our study, hypertriglyceridemia in patients with infectious mononucleosis was similar to that observed by Apostolou et al. in a detailed study of 29 patients of a similar age [22] in which the increased triglyceride levels at diagnosis were positively associated with inflammatory markers such as serum C-reactive protein and interleukin-1b concentrations. The authors also found a significant decrease in apolipoprotein C-III levels, a powerful inhibitor of lipoprotein-lipase levels, at baseline compared with controls and a subsequent increase after 4 months of follow-up in the convalescence phase [22]

The present study has the strengths of a large sample size and follow-up (retrospective cohort design). As weaknesses, the study is retrospective and descriptive. Regarding the external validity, it should be taken into account that all patients were admitted to the hospital, so the findings can only be applied to patients with infectious mononucleosis of similar severity. Further studies are needed to determine the mechanisms of dyslipidemia during mononucleosis and its potential analogy with that occurring in lymphoproliferative disorders.

## Declarations

Ethics approval and consent to participate: as stated above, the study was reviewed and approved by Galician Ethics Committee

Consent for publication: not applicable

Availability of data and materials: the dataset analysed during the current study were collected by consulting the medical records belonging to the Santiago de Compostela University Hospital, but restrictions apply to the availability of these data, which were used under license of the current study, and so are not publicly available.

Competing interests: the authors declare that they have no competing interests

Funding: none to declare

Authors' contributions: AG and JC designed and directed the project. EP, RA and IG gathered the data. EP, YG and AG analysed the data. EP and AG wrote the manuscript. All authors read and approved the manuscript.

Acknowledgements: not applicable

## References

1. Cohen JI. Epstein-Barr virus infection. *N Engl J Med*. 2000;343:481–92.
2. Godshall SE, Kirchner JT. Infectious mononucleosis. Complexities of a common syndrome. *Postgrad Med*. 2000;107:175–9, 183–4, 186.
3. Straus SE, Cohen JI, Tosato G, Meier J. NIH conference. Epstein-Barr virus infections: biology, pathogenesis, and management. *Ann Intern Med*. 1993;118:45–58.
4. Lennon P, Crotty M, Fenton JE. Infectious mononucleosis. *BMJ*. 2015;350:h1825.
5. Ohga S, Nomura A, Takada H, Hara T. Immunological aspects of Epstein-Barr virus infection. *Crit Rev Oncol Hematol*. 2002;44:203–15.
6. Dierickx D, Habermann TM. Post-Transplantation Lymphoproliferative Disorders in Adults. *N Engl J Med*. 2018;378:549–62.
7. Shannon-Lowe C, Rickinson AB, Bell AI. Epstein-Barr virus-associated lymphomas. *Philos Trans R Soc Lond, B, Biol Sci*. 2017;372.
8. Blackett PR, Koren E, Blackstock R, Downs D, Wang CS. Hyperlipidemia in acute lymphoblastic leukemia. *Ann Clin Lab Sci*. 1984;14:123–9.
9. Blackman JD, Cabana VG, Mazzone T. The acute-phase response and associated lipoprotein abnormalities accompanying lymphoma. *J Intern Med*. 1993;233:201–4.
10. Juliusson G, Vitols S, Liliemark J. Disease-related hypocholesterolemia in patients with hairy cell leukemia. Positive correlation with spleen size but not with tumor cell burden or low density lipoprotein receptor activity. *Cancer*. 1995;76:423–8.
11. Marini A, Carulli G, Azzarà A, Grassi B, Ambrogi F. Serum cholesterol and triglycerides in hematological malignancies. *Acta Haematol*. 1989;81:75–9.
12. Spiegel RJ, Schaefer EJ, Magrath IT, Edwards BK. Plasma lipid alterations in leukemia and lymphoma. *Am J Med*. 1982;72:775–82.
13. Wijeratne S, Wray R, Collinson PO, Wierzbicki AS. Hypertriglyceridaemia and malignancy. *Int J Clin Pract*. 2005;59:253–5.
14. Mozessohn L, Earle C, Spaner D, Cheng SY, Kumar M, Buckstein R. The Association of Dyslipidemia With Chronic Lymphocytic Leukemia: A Population-Based Study. *J Natl Cancer Inst*. 2017;109.
15. Usman H, Rashid R, Ameer F, Iqbal A, Zaid M, Hasnain S, et al. Revisiting the dyslipidemia associated with acute leukemia. *Clin Chim Acta*. 2015;444:43–9.
16. Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. *Am J Med*. 2014;127:1118–25.
17. Okamoto M, Yamaguchi H, Isobe Y, Yokose N, Mizuki T, Tajika K, et al. Analysis of triglyceride value in the diagnosis and treatment response of secondary hemophagocytic syndrome. *Intern Med*. 2009;48:775–81.
18. Clement J, Colson P, Saegeman V, Lagrou K, Van Ranst M. “Bedside assessment” of acute hantavirus infections and their possible classification into the spectrum of haemophagocytic syndromes. *Eur J Clin Microbiol Infect Dis*. 2016;35:1101–6.

19. Ivanišević J, Kotur-Stevuljević J, Stefanović A, Jelić-Ivanović Z, Spasić S, Videnović-Ivanov J, et al. Dyslipidemia and oxidative stress in sarcoidosis patients. *Clin Biochem*. 2012;45:677–82.
20. Chen X, Zhao Z-W, Li L, Chen X-J, Xu H, Lou J-T, et al. Hypercoagulation and elevation of blood triglycerides are characteristics of Kawasaki disease. *Lipids Health Dis*. 2015;14:166.
21. Rivera JM, Jiménez-Alonso J, Pérez-Jiménez F, Laín JM, Hens M, Nuño E, et al. [Hypertriglyceridemia in infectious mononucleosis]. *Rev Clin Esp*. 1984;172:135–6.
22. Apostolou F, Gazi IF, Lagos K, Tellis CC, Tselepis AD, Liberopoulos EN, et al. Acute infection with Epstein-Barr virus is associated with atherogenic lipid changes. *Atherosclerosis*. 2010;212:607–13.
23. Sayyahfar S, Lavasani A, Nateghian A, Karimi A. Evaluation of Lipid Profile Changes in Pediatric Patients with Acute Mononucleosis. *Infect Chemother*. 2017;49:44–50.
24. González-Quintela A, Gude F, Boquete O, Rey J, Meijide LM, Suarez F, et al. Association of alcohol consumption with total serum immunoglobulin E levels and allergic sensitization in an adult population-based survey. *Clin Exp Allergy*. 2003;33:199–205.
25. Khovidhunkit W, Kim M-S, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res*. 2004;45:1169–96.
26. van Leeuwen HJ, Heezius ECJM, Dallinga GM, van Strijp JAG, Verhoef J, van Kessel KPM. Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med*. 2003;31:1359–66.
27. Fraunberger P, Hahn J, Holler E, Walli AK, Seidel D. Serum cholesterol levels in neutropenic patients with fever. *Clin Chem Lab Med*. 2002;40:304–7.
28. Feingold KR, Hardardóttir I, Grunfeld C. Beneficial effects of cytokine induced hyperlipidemia. *Z Ernährungswiss*. 1998;37(Suppl 1):66–74.

## Tables

Tables 1 and 2 are not available with this version

## Figures

Image not available with this version

## Figure 1

Upper panel: serum concentrations of triglycerides and total cholesterol in patients with acute infectious mononucleosis and general population controls. Lower panel: comparison of serum concentrations of triglycerides and total cholesterol in patients with infectious mononucleosis in the acute phase and the convalescence phase (n=160).