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Liver dysfunction associated with artificial nutrition in critically ill patients

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Abstract

Introduction Liver dysfunction associated with artificial nutrition in critically ill patients is a complication that seems to be frequent, but it has not been assessed previously in a large cohort of critically ill patients.

Methods We conducted a prospective cohort study of incidence in 40 intensive care units. Different liver dysfunction patterns were defined: (a) cholestasis: alkaline phosphatase of more than 280 IU/l, gamma-glutamyl-transferase of more than 50 IU/l, or bilirubin of more than 1.2 mg/dl; (b) liver necrosis: aspartate aminotransferase of more than 40 IU/l or alanine aminotransferase of more than 42 IU/l, plus bilirubin of more than 1.2 mg/dl or international normalized ratio of more than 1.4; and (c) mixed pattern: alkaline phosphatase of more than 280 IU/l or gamma-glutamyl-transferase of more than 50 IU/l, plus aspartate aminotransferase of more than 40 IU/l or alanine aminotransferase of more than 42 IU/l.

Results Seven hundred and twenty-five of 3,409 patients received artificial nutrition: 303 received total parenteral nutrition (TPN) and 422 received enteral nutrition (EN). Twenty-three percent of patients developed liver dysfunction: 30% in the TPN group and 18% in the EN group. The univariate analysis showed an association between liver dysfunction and TPN ($p < 0.001$), Multiple Organ Dysfunction Score on admission ($p < 0.001$), sepsis ($p < 0.001$), early use of artificial nutrition ($p < 0.03$), and malnutrition ($p < 0.01$). In the multivariate analysis, liver dysfunction was associated with TPN ($p < 0.001$), sepsis ($p < 0.02$), early use of artificial nutrition ($p < 0.03$), and calculated energy requirements of more than 25 kcal/kg per day ($p < 0.05$).

Conclusion TPN, sepsis, and excessive calculated energy requirements appear as risk factors for developing liver dysfunction. Septic critically ill patients should not be fed with excessive caloric amounts, particularly when TPN is employed. Administering artificial nutrition in the first 24 hours after admission seems to have a protective effect.

APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; EN = enteral nutrition; ICU = intensive care unit; INR = international normalized ratio; IQ = interquartile; LCT = long-chain triglyceride; LD = liver dysfunction; MCT = medium-chain triglyceride; MODS = Multiple Organ Dysfunction Score; OR = odds ratio; TPN = total parenteral nutrition.

Table 7

Logistic regression analysis for liver dysfunction

	OR	95% CI	*p*
TPN	1.97	1.3–3	0.002
MODS	1.1	1.04–1.2	0.003
Early artificial nutrition (first day)	0.6	0.4–0.9	0.01
Energy requirements < 25 kcal/kg per day	0.62	0.41–0.94	0.03
Sepsis	1.76	1.08–2.9	0.05
Mechanical ventilation	0.5	0.3–1.07	0.05
Medical patient	0.6	0.3–1.02	0.06
MCT on TPN	1.4	0.9–2.2	0.09
APACHE II score	0.98	0.94–1.01	0.2
Surgical patient	0.6	0.3–1.2	0.2
Severe malnutrition	0.8	0.39–1.7	0.6
Septic shock	1.2	0.6–2.2	0.6
Gender (women)	0.98	0.65–1.48	0.9
Age	0.99	0.98–1.01	0.9

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; MCT, medium-chain triglyceride; MODS, Multiple Organ Dysfunction Score; OR, odds ratio; TPN, total parenteral nutrition.

Key messages

- Critically ill patients on artificial nutrition who developed LD have a characteristic profile: they had a higher MODS score on admission, they were septic, and they were treated with TPN and nutrition was started later.
- Sepsis and the use of TPN are the most important conditions that increase the incidence of liver failure.
- Cholestasis and the mixed pattern are the most frequent patterns of LD.
- Acalculous cholecystitis is an uncommon finding in our patients.

coordinator of the Spanish Working Group on Metabolism and Nutrition (section of the Spanish Society of Critical Care). The other authors declare that they have no competing interests.

Authors' contributions

TG and ABo conceived the study, participated in its design and coordination, and helped to draft the manuscript. TG performed the statistical analysis. MR and DM were involved in drafting the manuscript or revising it critically for important intellectual content. ABl, MF, JAA, and JCM participated in the design of the study and they coordinated the meetings with the participants. AG and AM have given final approval of the version to be published. All authors read and approved the final manuscript.

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References

1. ASPEN Board of Directors and the Clinical Guidelines Task Force: **Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients.** *JPEN J Parenter Enteral Nutr* 2002, **26(1 Suppl):**1SA-138SA.
2. Cerra FB: **Hypermetabolism, organ failure and metabolic support.** *Surgery* 1987, **101:**1-14.
3. Shattuck KE, Klein GL: **Hepatobiliary complications of parenteral nutrition.** In *Enteral and Tube Feeding* 3rd edition. Edited by: Rombeau JL, Rolandelli RH. Philadelphia: WB Saunders; 1997:141-156.
4. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ: **Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome.** *Crit Care Med* 1995, **23:**1638-1652.
5. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system.** *Crit Care Med* 1985, **13:**818-829.
6. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: **Definitions for sepsis and multiple organ failure and guidelines for the use of innovative therapies in sepsis.** *Crit Care Med* 1992, **20:**864-874.
7. Buzby GP, Knox LS, Crosby LO, Eisenberg JM, Haakenson CM, McNeal GE, Page CP, Peterson OL, Reinhardt GF, Williford WO: **Study protocol: a randomized clinical trial of total parenteral nutrition in malnourished surgical patients.** *Am J Clin Nutr* 1988, **47(2 suppl):**366-381.
8. American Society for Parenteral and Enteral Nutrition: *Clinical Pathways and Algorithms for Delivery of Parenteral and Enteral Nutrition Support in Adults* Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 1998.
9. Montejo JC: **Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units.** *Crit Care Med* 1999, **27:**1447-1453.
10. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, Langer B, Jeejeebhoy KN: **Nutritional assessment: a comparison of clinical judgement and objective measurements.** *N Engl J Med* 1982, **306:**969-972.
11. Bonet A, Sánchez Alvarez C, Núñez Ruiz R: **Protocolo de nutrición parenteral.** In *Guias de Practica Clínica en Medicina Intensiva. [Total parenteral nutrition protocol. Clinical Practice Guidelines in Critical Care]* Edited by: Latorre FJ, Ibáñez J. Madrid: Meditex; 1996:1-7.
12. Quigley EM, Marsh MN, Shaffer JL, Markin RS: **Hepatobiliary complications of total parenteral nutrition.** *Gastroenterology* 1993, **104:**286-301.
13. Briones ER, Iber FL: **Liver and biliary tract changes and injury associated with total parenteral nutrition: pathogenesis and prevention.** *J Am Coll Nutr* 1995, **14:**219-228.
14. Meadows N: **Monitoring and complications of parenteral nutrition.** *Nutrition* 1998, **14:**806-808.
15. Clarke PJ, Ball MJ, Kettlewell MGW: **Liver function tests in patients receiving parenteral nutrition.** *JPEN J Parenter Enteral Nutr* 1991, **15:**54-59.
16. Braxton C, Lowry SF: **Parenteral nutrition and liver dysfunction – new insight?** *JPEN J Parenter Enteral Nutr* 1995, **19:**3-4.
17. de Pablo MA, Angeles Puertollano M, Álvarez de Cienfuegos G: **Immune cell functions, lipids and host natural resistance.** *FEMS Immunol Med Microbiol* 2000, **29:**323-328.
18. Richardson TR, Sgoutas D: **Essential fatty acid deficiency in four adult patients during total parenteral nutrition.** *Am J Clin Nutr* 1975, **28:**258-263.
19. Keim NL: **Nutritional effectors of hepatic steatosis induced by parenteral nutrition in the rat.** *JPEN J Parenter Enteral Nutr* 1987, **11:**18-22.
20. Sheldon GF, Petersen SR, Sanders R: **Hepatic dysfunction during hyperalimentation.** *Arch Surg* 1978, **113:**504-508.
21. Buzby G, Mullen JL, Stein TP, Rosato EF: **Manipulation of TPN caloric substrate and fatty infiltration of the liver.** *J Surg Res* 1981, **31:**46-54.
22. Burke JF, Wolfe RR, Mullany CJ, Mathews DE, Bier DM: **Glucose requirements following burn injury. Parameters of optimal glucose infusion and possible hepatic and respiratory abnormalities following excessive glucose intake.** *Ann Surg* 1979, **190:**274-285.
23. Thompson SW: **Hepatic toxicity of intravenous fat emulsions.** In *Fat Emulsions in Parenteral Nutrition* Edited by: Meng HC, Willmore DW. Chicago: American Medical Association; 1976:90-95.
24. Preisig R, Rennert O: **Biliary transport and cholestatic effects of amino acids.** *Gastroenterology* 1977, **73:**1240-1248.
25. Burt ME, Hanin I, Brennan MF: **Choline deficiency associated with total parenteral nutrition.** *Lancet* 1980, **2:**638-639.
26. Fouin-Fontunet H, Le Quernec L, Erlinger S, Lerebours E, Colin R: **Hepatic alterations during total parenteral nutrition in patients with inflammatory bowel disease: a possible consequence of lithocholate toxicity.** *Gastroenterology* 1982, **82:**932-937.
27. Penn D, Schmidt-Sommerfeld E, Pascu F: **Decreased tissue carnitine concentrations in newborn infants receiving total parenteral nutrition.** *J Pediat* 1981, **98:**976-978.
28. Zamir O, Nussbaum MS, Bhadra S, Subbiah MT, Rafferty JF, Fischer JE: **Effect of enteral feeding on hepatic steatosis induced by total parenteral nutrition.** *JPEN J Parenter Enteral Nutr* 1994, **18:**20-25.
29. Pallarés R, Sitges-Serra A, Fuentes J: **Cholestasis associated with total parenteral nutrition.** *Lancet* 1983, **1:**758-762.
30. Pacelli F, Bossola M, Papa V, Malerba M, Modesti C, Sgadari A, Bellantone R, Doglietto GB, Modesti C, EN-TPN Study Group: **Enteral vs parenteral nutrition after major abdominal surgery: an even match.** *Arch Surg* 2001, **136:**933-936.
31. Woodcock NP, Zeigler D, Palmer DM, Buckley P, Mitchell CJ, MacFie J: **Enteral versus parenteral nutrition: a pragmatic study.** *Nutrition* 2001, **17:**1-12.
32. Borum ML, Lynn J, Zhong Z, Roth K, Connors AF Jr, Desbiens NA, Phillips RS, Dawson NV: **The effect of nutritional supplementation on survival in seriously ill hospitalized adults: an evaluation of the SUPPORT data. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments.** *J Am Geriatr Soc* 2000, **48(5 suppl):**S33-S38.
33. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V: **Early post-operative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition.** *Crit Care Med* 2001, **29:**242-248.
34. Marik PE, Pinsky M: **Death by parenteral nutrition.** *Intensive Care Med* 2003, **29(6):**867-869.
35. Heyland DK, MacDonald S, Keefe L, Drover JW: **Total parenteral nutrition in the critically ill patient: a meta-analysis.** *JAMA* 1998, **280:**2013-2019.
36. Hirata K, Ikeda S, Honma T, Mitaka T, Furuhata T, Katsuramaki T, Hata F, Mukaiya M: **Sepsis and cholestasis: basic findings in the sinusoid and bile canaliculus.** *J Hepatobiliary Pancreat Surg* 2001, **8:**20-26.
37. Pallarés R, Sitges-Serra A, Fuentes J, Jaurrieta E, Guardia J, Fernández-Nogués F, Sitges-Creus A: **Factores etiopatogénicos posiblemente implicados en la disfunción hepática asociada a la nutrición parenteral: estudio prospectivo de 104 pacientes adultos. [Etiopathogenic factors possibly implicated in hepatic dysfunction associated with parenteral nutrition: prospective study of 104 adult patients].** *Med Clin (Barc)* 1984, **83:**832-836.
38. Buchman A: **Total parenteral nutrition-associated liver disease.** *JPEN J Parenter Enteral Nutr* 2002, **26:**S43-S48.
39. Sandhu IS, Jarvis C, Everson GT: **Total parenteral nutrition and cholestasis.** *Clin Liver Dis* 1999, **3:**489-508.
40. Cavicchi M, Beau P, Crenn P, Degott C, Messing B: **Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure.** *Ann Intern Med* 2000, **132:**525-532.
41. Spiliotis JD, Kalfarentzos F: **Total parenteral nutrition-associated liver dysfunction.** *Nutrition* 1994, **10:**255-260.
42. Angelico M, Della Guardia P: **Review article: hepatobiliary complications associated with total parenteral nutrition.** *Aliment Pharmacol Ther* 2000, **14(suppl 2):**54-57.
43. Morán Penco JM, Salas Martinez J, Maciá Botejara E: **¿Qué sucede en el hígado durante la alimentación artificial? [What**