Gastroenterol Hepatol. 2017;40(6):388–394

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Serum cytokeratin-18 fragment levels as noninvasive marker of nonalcoholic steatohepatitis in the Chilean population☆

Juan Pablo Arab[a], Cristián Hernández-Rocha[a], Carolina Morales[b], José Ignacio Vargas[a], Nancy Solís[a], Margarita Pizarro[a], Camila Robles[b], Daniela Sandoval[b], Simon Ponthus[a], Carlos Benítez[a], Francisco Barrera[a], Alejandro Soza[a], Arnoldo Riquelme[a], Marco Arrese[a,*]

[a] *Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*
[b] *Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*

Received 21 October 2016; accepted 10 February 2017
Available online 3 June 2017

KEYWORDS
Steatosis;
Fatty liver;
Cytokeratin-18;
Steatohepatitis;
Non-invasive

Abstract Nonalcoholic steatohepatitis (NASH) is the most aggressive form of nonalcoholic fatty liver disease (NAFLD) and involves the risk of progression to more advanced stages of liver disease. Non-invasive methods are needed to identify patients with NASH.
Objective: To evaluate the diagnostic performance of the determination of serum levels of cytokeratin-18 (CK-18) as a non-invasive marker of NASH in the Chilean population.
Methods: Serum CK-18 levels were determined in a group of 41 patients with biopsy-proven NAFLD. NASH diagnosis was based on Brunt's criteria (histological parameters and ballooning), and the NAFLD activity score (NAS) and the presence of fibrosis were determined. The correlation between the NAFLD activity score (NAS) and CK-18 was evaluated with Spearman's rank correlation coefficient. A ROC curve was produced to assess the diagnostic value of CK-18 for NASH. The NAFLD fibrosis score (NFS) (to predict fibrosis and NASH) was compared to CK-18 with simple linear regression. Data were expressed in median [25–75th percentile] and evaluated with the Wilcoxon rank test.
Results: The mean age of the study group (23% male) was 50.4 ± 11.1 years. 34.2% were diagnosed with NASH (NAS ≥ 5). CK-18 levels were significantly higher in patients with NASH versus those without NASH (183.6 IU/l [97.4–734.4] vs. 117.2 IU/l [83.8–954.8], $p = 0.016$). CK-18 levels were a good predictor of NASH on biopsy with an area under the curve (AUC) of 0.732 (95%

☆ Please cite this article as: Arab JP, Hernández-Rocha C, Morales C, Vargas JI, Solís N, Pizarro M, et al. Fragmento sérico de citoqueratina-18 como marcador no invasivo de esteatohepatitis no alcohólica en población chilena. Gastroenterol Hepatol. 2017;40:388–394.

* Corresponding author.
E-mail address: marrese@med.puc.cl (M. Arrese).

CI, 0.572–0.897). A CK-18 cut-off of 130.5 IU/l had a sensitivity of 92.9%, specificity of 63%, positive predictive value of 56.5% and negative predictive value of 94.4%, and was able to correctly classify 73.2% of patients with NASH. NFS identified advanced liver fibrosis (AUC 0.739, 95% CI, 0.56–0.91), but was of limited value to identify NASH (AUC 0.413, 95% CI, 0.21–0.61).
Conclusion: CK-18 is a good non-invasive marker for NASH. Although NFS was found to be an accurate marker of advanced liver fibrosis, it was not of value to identify NASH. In patients with NAFLD, CK-18 and NFS could be useful in predicting NASH and liver fibrosis, respectively.

PALABRAS CLAVE
Esteatosis;
Hígado graso;
Citoqueratina-18;
Esteatohepatitis;
No invasivo

Fragmento sérico de citoqueratina-18 como marcador no invasivo de esteatohepatitis no alcohólica en población chilena

Resumen La esteatohepatitis no alcohólica (EHNA) es la forma más agresiva de hígado graso no alcohólico (HGNA) e involucra el riesgo de progresión a etapas más avanzadas de enfermedad hepática. Se requieren métodos no invasivos para identificar a pacientes con EHNA.
Objetivo: Evaluar el rendimiento diagnóstico de la determinación de los niveles séricos de citoqueratina-18 como marcador no invasivo de EHNA en población chilena.
Métodos: Se determinaron los niveles séricos de CK-18 en un grupo de 41 pacientes con HGNA-probado por biopsia. El diagnóstico de EHNA se basó en los criterios histológicos recomendados (presencia de balonamiento) y se calculó el puntaje de actividad del HGNA (PAH) y grado de fibrosis. Mediante correlación de Spearman se evaluó la asociación entre CK-18 y PAH. Se confeccionó una curva ROC para evaluar la capacidad de CK-18 como test diagnóstico para EHNA. Además, se evaluó el rendimiento del puntaje de fibrosis en hígado graso no alcohólico (NFS) para pesquisa de fibrosis y EHNA y se lo comparó con CK-18 por regresión lineal simple. Los datos son expresados en medianas [percentil 25-75] y evaluados con test de rangos de Wilcoxon.
Resultados: La edad promedio del grupo estudiado (23% hombres) fue de 50,4 ± 11,1 años. Un 34,2% fue diagnosticado con EHNA (PAH≥5). Los niveles de CK-18 fueron mayores en los pacientes con EHNA versus los sin EHNA (183,6 UI/l [97,4-734,4] vs. 117,2 UI/l [83,8-954,8], p = 0,016). Los niveles de CK-18 fueron buenos predictores de la presencia de EHNA en la biopsia con un área bajo la curva (AUC) de 0,732 (IC95% 0,572-0,897). Un punto de corte de 130,5 UI/l de CK-18 exhibió una sensibilidad de 92,9% y una especificidad de 63%, con un VPP de 56,5% y un VPN 94,4%, y clasificó correctamente al 73,2% de los pacientes con EHNA. El NFS tuvo un buen rendimiento para diagnóstico de fibrosis avanzada (AUC 0,739, IC95% 0,56–0,91), pero limitado para identificar EHNA (AUC 0,413, IC95% 0,21-0,61).
Conclusión: La determinación de CK-18 es un buen marcador no invasivo de EHNA. Si bien, NFS tiene un buen rendimiento en la identificación de pacientes con fibrosis avanzada, no fue de utilidad para diagnosticar EHNA. En pacientes con HGNA, la determinación de CK-18 y NFS es útil en la pesquisa de EHNA y fibrosis hepática respectivamente.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinical and pathological entity characterised by steatosis in at least 5% of hepatocytes. It may or may not be associated with inflammatory changes and fibrosis.[1] Histological elements of inflammation and ballooning of hepatocytes with or without fibrosis identify so-called non-alcoholic steatohepatitis (NASH), which is considered a more aggressive form of the disease and the significance of which lies in its potential progression to hepatic cirrhosis or hepatocellular carcinoma.[2]

The overall prevalence of NAFLD has been estimated at 25.24% (95% CI: 22.10–28.65) of the population.[3–5] In Chile, a study with abdominal ultrasound reported a prevalence of NAFLD of 23% in the population studied.[6]

Serum aminotransferase levels have traditionally been used as indicators of disease seriousness. However, it should be borne in mind that these levels may fluctuate over time and that they are seen to be elevated in only 50% of patients with NASH. This means that there may be significant liver disease even with normal aminotransferase levels.[7] For this reason, liver biopsy remains the gold standard for diagnosing NAFLD and for distinguishing isolated steatosis from NASH and more advanced forms of liver damage.[8] This procedure has a significant cost and a clinical risk that render its rational use advisable.[9] Currently, non-invasive