



## Research Paper

# Cytokine inflammation state in non-alcoholic steatohepatitis surpasses that of chronic hepatitis C and alcoholic liver disease

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## ABSTRACT

Increased serum levels of cytokines were reported in persistent inflammatory conditions such as non-alcoholic steatohepatitis (NASH), chronic hepatitis C (CHC) and alcoholic liver disease (ALD). The aim of this study was to compare cytokines IL-6, TNF- $\alpha$ , VEGF, EG-VEGF, BB-PDGF and ICAM-1 levels in these patients. Ninety patients seen in two Mexican outpatient clinics (Liver Unit, UANL and HIPAM and UNAM) were included: NASH (30), CHC (30) and ALD (30). Serum cytokines IL-6, TNF- $\alpha$ , VEGF, EG-VEGF, BB-PDGF and ICAM-1 were measured by ELISA. A statistically significant difference was found in 5/6 mediators studied in NASH patients vs. CHC and ALD. Regarding ICAM-1 (5.482 $\pm$ 613 vs. 2.145 $\pm$ 1011 vs. 1.830 $\pm$ 1224 pg/mL;  $P$ <0.05; respectively), IL-6 (2.430 $\pm$ 1506 vs. 726 $\pm$ 735 vs. 516 $\pm$ 603 pg/mL;  $P$ <0.05, respectively), TNF- $\alpha$  (3686 $\pm$ 1409 vs. 677 $\pm$ 747 vs. 437 $\pm$ 70 pg/mL;  $P$ <0.05; respectively), VEGF (2.267 $\pm$ 486 vs. 421 $\pm$ 557 vs. 554 $\pm$ 619 pg/mL;  $P$ <0.05; respectively) and EG-VEGF (2.146 $\pm$ 1914 vs. 1.225 $\pm$ 1388 vs. 799 $\pm$ 1046 pg/mL;  $P$ <0.05; respectively). VEGF positively correlated with TNF- $\alpha$  ( $r$ +0.51 and  $P$ =0.004) in NASH and negatively in CHC ( $r$ -0.44 and  $P$ =0.01). The only positive correlation for BB-PDGF was with EG-VEGF levels ( $r$ +0.41 and  $P$ =0.02). IL-6 exhibited a positive correlation vs. ICAM-1 in ALD ( $r$ +0.42 and  $P$ =0.02). We demonstrated a significant increase in pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, VEGF and EG-VEGF) and ICAM-1 in patients with NASH. Correlations showed differential cytokine and adhesion molecule patterns on the basis of the liver disease etiology. These abnormalities in cytokine profile can influence the pathophysiology of liver injury.

Cordero-Pérez P.<sup>1</sup>, Martínez-Macías R. M.<sup>1</sup>, Cura-Esquivel I. A.<sup>1</sup>, Gutiérrez-Reyes G.<sup>2</sup>, Gutiérrez-Ruiz M. C.<sup>3</sup>, Torres-González L.<sup>1</sup> and Muñoz-Espinosa L. E.<sup>1\*</sup>

<sup>1</sup>Liver Unit, Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México.

<sup>2</sup>Liver, Pancreas and Motility Laboratory (HIPAM), Department of Experimental Medicine, Faculty of Medicine, Universidad Nacional Autónoma de México-UNAM.

<sup>3</sup>Laboratorio de Fisiología Celular, Universidad Autónoma Metropolitana, México DF.

\*Corresponding author. E-mail: linda\_uanl@hotmail.com  
Tel: (+52) 818 329 4205  
Fax: (+52) 818 989 4088.

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## INTRODUCTION

Hepatitis is the outcome of a complex interaction of hepatic cells where inflammatory mediators orchestrate interactions and regulate intrahepatic inflammatory pathways. The hepatic micro-environment is tightly regulated to maintain a balance between a state of local refractation/tolerance and immunity. Any disruption in this balance due to an infection or deposition of toxic substances can lead to hepatitis, which, if left uncontrolled, could render progressive liver damage, cirrhosis, cancer and ultimately liver failure.

Alcoholic liver disease (ALD) is a major cause of morbidity and mortality worldwide. Chronic alcohol consumption leads to hepatocellular injury, fat accumulation and liver inflammation which in turn leads to cirrhosis and hepatocellular carcinoma. Chronic alcohol consumption leads to injury of the hepatocytes by TNF- $\alpha$ , with consequent apoptosis and phagocytosis by the Kupffer cells. The Kupffer cells are activated by phagocytosing the apoptotic cells and their inflammatory cytokine production is increased (Canbay et al., 2003;

McClain et al., 2004). Various cytokines are associated with ALD, including hepatoprotective cytokines, such as Interleukin-6 (IL-6) and anti-inflammatory cytokines, such as IL-10 (Tilg and Diehl, 2000; Gao, 2005).

Chronic hepatitis C (CHC) is one of the most common causes of cirrhosis comprising 40% of chronic liver disease and representing a major health problem worldwide (Webster, 2015). Recently, the scientific research focused on several cytokines which may be associated with the persistence of virus C infection and the development of fibrosis, such a cytokine transforms growth factor (TGF)- $\beta$ 1 (Massague, 1990; Gorham, 2005). Thus, in one recent study by Par et al. (2013) sustained virological response (SVR) was associated with a baseline increased production of TNF- $\alpha$  and IL-6 by TLR-4 activated monocytes and decreased production of IL-4 and IL-10 by PMA activated lymphocytes. However, it was also reported that low IL-6 serum concentration may be associated with SVR, which is contrary to other studies (Pavón-Castillero et al., 2013).

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, and the spectrum of this disease includes simple liver steatosis, non-alcoholic steatohepatitis (NASH), liver fibrosis and liver cirrhosis. The risk factors that contribute to the progression from simple steatosis to NASH include chronic liver inflammation, lipotoxicity, insulin resistance (IR) and oxidative stress (Sanyal et al., 2001; Kojima et al., 2007). Among these factors, persistent hepatic inflammation (for example, pro-inflammatory cytokines and recruitment of inflammatory cells) is considered a major factor causing NASH progression which predicts poor clinical outcome in patients (Sun and Karin, 2012).

Although inflammation is a key component and contributor to hepatic wound healing and fibrogenic responses, inflammatory signaling pathways have received relatively little attention as targets for chronic liver disease.

The aim of this research was to characterize different patterns of serum markers of inflammation in patients with NASH, CHC and ALD.

## MATERIALS AND METHODS

An observational, cross-sectional study at the Liver Unit of "Dr. José Eleuterio González" University Hospital, UANL, located in Monterrey, Mexico and at the Liver, Pancreas and Motility Laboratory (HIPAM) medical school, UNAM located in Mexico, City was conducted. Ninety patients receiving ongoing medical attention on both cities from August, 2012 to December, 2013 were invited to participate. Sixty patients were recruited at UANL's Liver Unit, the main northeast Mexican tertiary care center for the study of patients with liver diseases and 30 patients were diagnosed with NAFLD and 30 with CHC. The remaining 30 patients with ALD were recruited at the

General Hospital of Mexico, the main tertiary care hospital at central Mexico for patients who do not have social security benefits and come from different regions of the country including rural areas. Inclusion criteria were:  $\geq$ 18 years old, diagnosis of CHC by hepatitic C virus (HCV) and HCV genotype (GT); confirmed diagnosis of ALD and NASH through liver biopsy or non/invasive studies.

Exclusion criteria were: co-existent malignant neoplasia, hepatitis B, HIV, autoimmune hepatitis, drug-induced liver disease and/or the concurrence of either CHC, NASH and/or ALD in the same patient. All subjects gave written informed consent and the study was approved by UANL's School of Medicine, IRB. The study was conducted in compliance with Helsinki declaration.

## Clinical and laboratory assessment

All patients underwent medical and laboratory evaluations including, whenever possible, liver ultrasound scans, liver biopsy and/or FibroMax. Table 1 shows the recorded baseline variables. Liver enzyme levels were expressed in IU/L. Patients with CHC, HCV genotype (GT) and viral load (VL) (IU/mL) were also recorded. Variables values were recorded concurrently to the date of the medical visit when the patient agreed to participate in the study.

## Operative definitions

All patients who had a liver biopsy whereby NASH diagnosis was confirmed was according to international guidelines (Canbay et al., 2003). The diagnosis of chronic HCV infection was done by the presence of anti-HCV antibodies by a third-generation enzyme immunoassay (ELISA) and HCV-RNA in serum.

All patients included in the ALD group had alcohol dependence according to DSM-IV criteria. Patients with ALD and diagnosis of alcoholism were according to the World Health Organization (ethanol consumption  $\geq$  70 g/day in men and ethanol consumption  $\geq$  50 g/day in women in the last 5 years). ALD diagnosis was ultimately confirmed either by non-invasive markers and clinical and laboratory criteria.

Confirmation of cirrhosis was sought on the patient's medical record and defined either as METAVIR F4, whenever a liver biopsy was available or as F4 by non-invasive methods (FibroTest  $\geq$ 0.75, FibroScan  $\geq$ 12.5, APRI  $\geq$ 2 and thrombocytopenia  $\leq$ 100, 00/mm) and/or clinical criteria (gastroesophageal varices and and/or hepatic decompensation) (Table 1).

## Cytokine and adhesion molecules assays

Measurement of inflammatory mediators and serum concentrations following inflammatory mediators were

**Table 1:** Baseline features of the patients.

Baseline features	NAFLD (N=30)	CHC (N=30)	ALD (N=30)	P*
Age (year)	40.40±14.0	46.40±21.0	49.80±9.6	0.092
Female/Male gender	12/18 (40/60%)	17/13 (57/43%)	4/26 (13/87%)	<0.001
Weight (kg)	83.30±17.0	62.70±29.7	71.90±13.0	0.002
Size (m)	1.70±0.1	1.40±0.5	1.59±0.1	0.008
BMI (kg/m <sup>2</sup> )	30.30±4.0	24.90±13.0	28.30±4.6	0.052
Glucose (mg/dL)	97.20±33.0	82.70±36.3	93.60±15.0	0.147
BUN (mg/dL)	10.60±6.0	13.00±8.4	17.00±14.0	0.058
Creatinine (mg/dL)	0.70±0.3	0.80±0.4	1.50±3.0	0.262
Total bilirubin (mg/dL)	1.90±4.6	0.70±0.6	2.50±2.8	0.094
Albumin (g/dL)	4.30±4.3	3.40±1.5	3.10±1	<0.001
AST (IU/L)	60.40±54.0	84.30±79.6	51.80±30.0	0.088
ALT (IU/L)	83.20±106.0	80.20±73.1	40.70±27.1	0.059
AST/ALT	1.00±0.8	0.90±0.5	1.40±0.6	0.008
ALKP (IU/L)	127.50±89.0	102.10±86.7	157.00±84.8	0.046
GGT (IU/L)	141.90±194.0	85.60±134.8	115.80±125.7	0.377
Cholesterol (mg/dL)	185.20±47.0	137.00±63.9	120.80±125.5	0.015
Triglycerides (mg/dL)	164.50±73.0	81.80±60.7	89.50±91.9	<0.001
Cirrhosis	6 (21%) †	8 (27%) ‡	26 (87%) §	<0.001

\* Differences among the distribution of the baseline features were tested through ANOVA (if continuous) or Chi-squared (categorical) †, ‡, §. Cirrhosis was defined through liver biopsy (n=6, n=1 and, n=5) and non-invasive studies (FibroScan, FibroTest and APRI), (n=0, n=2 and n=5) through clinical features (n=0, n=4 and n=16), respectively. PAC: Pattern of alcohol consumption and AIR: Alcoholic intoxication risk.

assayed by commercial enzyme-linked immunosorbent assay kits: ICAM-1, IL-6 and TNF- $\alpha$  (Chemicon International Inc., Temecula, CA, USA) and VEGF, EG-VEGF and BB-PDGF (Chemicon International Inc., Temecula, CA, USA).

### Statistical analysis

Descriptive statistics were used (mean and standard deviation). The chi-square, Fisher exact test, student's T-test or ANOVA tests were used to detect differences. Statistical significance was defined as  $P < 0.05$  by using SPSS v.22 (SPSS Inc. Software, Chicago, Illinois, USA). Three separated Spearman correlation tests were run to explore correlations between all baseline features and each etiology. Only statistically significant and clinically relevant correlations were described.

### RESULTS

Table 1 shows the baseline features of the patients studied. Four variables were etiology-specific: VL (1, 347, 793  $\pm$  1, 709, 726 IU/mL) and GT1 infection 19/8 (63/27%) in patients with CHC; mean insulin level (20  $\pm$  18 IU/mL) recorded only for patients with NASH and alcoholism criteria and ALD 22/8 (73/27%) alongside alcoholic

intoxication risk  $\geq 38$  g/day 25/5 (83/17%) regarding ALD group.

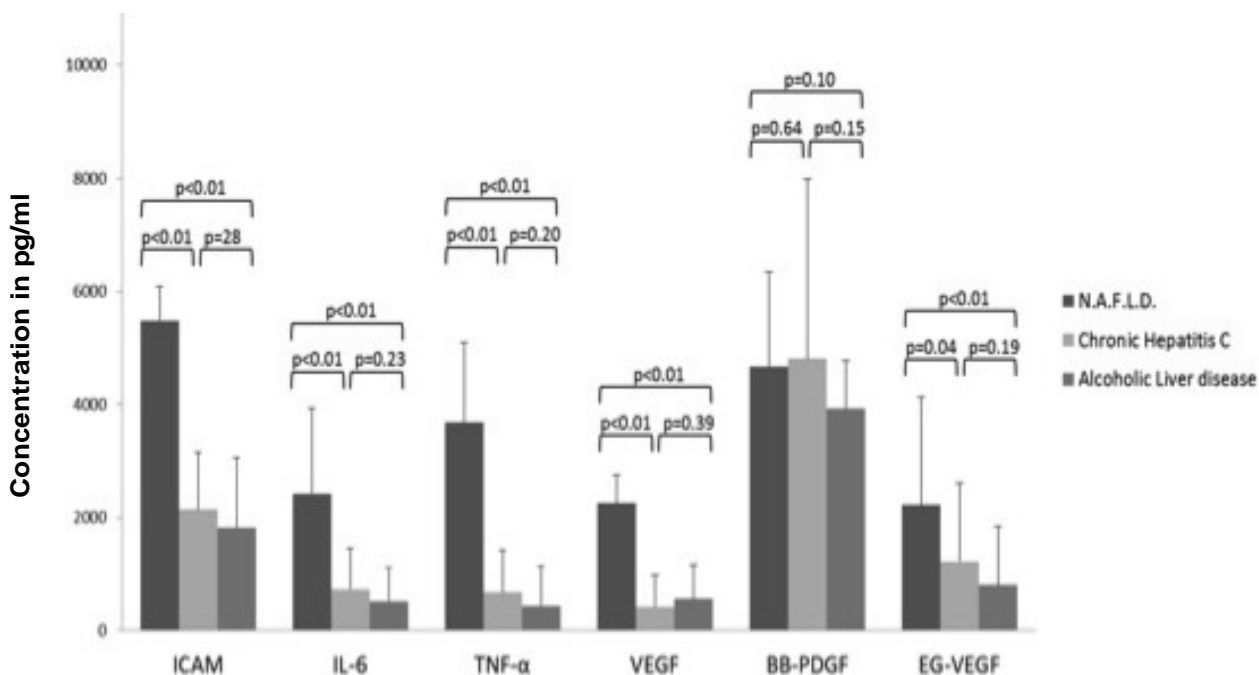
Similar baseline distributions ( $P > 0.05$ ) were rendered for age (year), BMI (kg/m<sup>2</sup>), glucose (mg/dL), BUN (mg/dL), creatinine (mg/dL), total bilirubin (mg/dL), AST (IU/L), ALT (IU/L) and GGT (IU/L) (Table 1). The remaining features showed that female patients prevailed over males in the CHC group as opposed to sex distribution among the NAFLD and ALD-diseased patients (57% vs. 40% vs. 13% and  $P < 0.001$ , respectively). Patients with NASH showed the highest mean levels of cholesterol and triglycerides vs. CHC and ALD (185.2  $\pm$  47, 137  $\pm$  63.9 and 120.80  $\pm$  125.5, mg/dL  $P = 0.015$  and 164.5  $\pm$  73, 81.80  $\pm$  60.7 and 89.50  $\pm$  91.9 mg/dL and  $P < 0.001$ ; respectively). Both the AST/ALT index and the ALKP measurements were the highest among patients with ALD when compared with those with NAFLD and CHC (1.40  $\pm$  0.6 vs. 0.9  $\pm$  0.5 vs. 1  $\pm$  0.8,  $P = 0.008$  and 157  $\pm$  84.8 vs. 127.5  $\pm$  89 vs. 102.1  $\pm$  86.7 IU/L,  $P = 0.046$ , respectively), whereas when their albumin levels were compared ALD showed the lowest level (3.1  $\pm$  1 vs. 4.3  $\pm$  4.3 vs. 3.4  $\pm$  1.5 g/dL,  $P < 0.001$ ) (Table 1).

Remarkably, cirrhosis was more commonly seen among ALD group (87%). Furthermore, the aforementioned baseline distributions rendered additional statistical significant differences after a Student's t-test sub analysis regarding AST when comparing CHC vs. ALD patients; ALT regarding NAFLD vs. ALD and CHC vs. ALD-diseased patients and ALKP regarding CHC vs. ALD patients (Table

**Table 2:** Differences among the mean levels of cytokines and adhesion molecules between NAFLD, CHC, ALD.

Parameter	ICAM-1 (pg/mL)	IL-6 (pg/mL)	TNF- $\alpha$ (pg/mL)	VEGF (pg/mL)	BB-PDGF (pg/mL)	EG-VEGF (pg/mL)
NAFLD	5.482 $\pm$ 613*	2.430 $\pm$ 1506*	3.686 $\pm$ 1409*	2.267 $\pm$ 486*	4.508 $\pm$ 1677	2.146 $\pm$ 1914*
CHC	2.145 $\pm$ 1011	726 $\pm$ 735	677 $\pm$ 747	421 $\pm$ 557	4.814 $\pm$ 3161	1.225 $\pm$ 1388
ALD	1.830 $\pm$ 1224†	516 $\pm$ 603†	437 $\pm$ 70†	554 $\pm$ 619†	3.922 $\pm$ 855	799 $\pm$ 1046†

\*  $P < 0.05$ , NAFLD vs. CHC; †  $P < 0.05$ , NAFLD vs. ALD. ICAM-1: Intercellular adhesion molecule; IL-6, Interleukin 6; TNF- $\alpha$ : Tumor necrosis factor  $\alpha$ ; VEGF: Vascular endothelial growth factor; BB-PDGF: Homodimeric platelet derived growth factor; EG-VEGF: Endothelial growth-vascular endothelial growth factor; NAFLD: Non-alcoholic fatty liver disease; CHC: chronic hepatitis C; ALD: Alcoholic liver disease.

**Figure 1:** Levels of the cytokines and adhesion molecules in patients with N.A.F.L.D., chronic hepatitis C and alcoholic liver disease.

1).

### Cytokines and adhesion molecules levels in patients with NASH, CHC and ALD

Table 2 and Figure 1 shows the mean levels of the cytokines and adhesion molecules measured in this study. NASH cytokines and adhesion molecules mean levels surpassed those measured among CHC and ALD patients, regarding ICAM-1 (5.482 $\pm$ 613 vs. 2.145 $\pm$ 1011 vs. 1.830 $\pm$ 1224 pg/mL;  $P < 0.05$ ; respectively), IL-6 (2.430 $\pm$ 1506 vs. 726 $\pm$ 735 vs. 516 $\pm$ 603 pg/mL;  $P < 0.05$ , respectively), TNF- $\alpha$  (3686 $\pm$ 1409 vs. 677 $\pm$ 747 vs. 437 $\pm$ 70 pg/mL;  $P < 0.05$ ; respectively), VEGF (2.267 $\pm$ 486 vs. 421 $\pm$ 557 vs. 554 $\pm$ 619 pg/mL;  $P < 0.05$ ; respectively) and EG-VEGF (2.146 $\pm$ 1914 vs. 1.225 $\pm$ 1388 vs. 799 $\pm$ 1046 pg/mL;  $P < 0.05$ ; respectively) (Figure 1 and Table 2). Furthermore, BB-PDGF mean levels were comparable

among these the three etiologies (Table 2).

Correlations showed differential cytokine and adhesion molecule patterns on the basis of the liver disease etiology. VEGF positively correlated with TNF- $\alpha$  ( $r = +0.51$  and  $P = 0.004$ ) in NASH and negatively in CHC ( $r = -0.44$  and  $P = 0.01$ ). The only positive correlation for BB-PDGF was with EG-VEGF levels ( $r = +0.41$  and  $P = 0.02$ ). IL-6 exhibited a positive correlation vs. ICAM-1 in ALD ( $r = +0.42$  and  $P = 0.02$ ).

### DISCUSSION

The major pro-inflammatory cytokines studied in the pathogenesis of NASH include TNF- $\alpha$ , IL-6, IL-1 $\alpha$ , IL-1 $\beta$  and IL-18. Genetic predisposition to NASH has lately been a matter of great interest. TNF- $\alpha$  polymorphism in certain populations was associated with susceptibility for NAFLD. A balance between pro-inflammatory and anti-

inflammatory cytokines seems to have a major role in systemic, local metabolic and inflammatory processes involved in the development of NAFLD and IR.

In this study, we demonstrated a significant increase in pro-inflammatory cytokines in patients with NASH, being most predominant elevations of TNF- $\alpha$ , IL-6, VEGF, EG-VEGF. TNF- $\alpha$  is the pro-inflammatory cytokine characterized by various biological effects including metabolic, inflammatory, proliferative but also necrotic with enhanced expression in liver and adipose tissue, thus, making it an optimal causative agent for NAFLD. This was confirmed in numerous studies in which increased expression of TNF- $\alpha$  was found in adipose tissue of diverse animal models of obesity, IR and T2DM suggesting TNF- $\alpha$  is a key link in obesity-induced IR (Stojsavljević et al., 2014). Indeed our patients with NASH also had more overweight and had more commonly dyslipidemia.

Endotoxemia in obesity resulting from small intestinal bacterial overgrowth stimulates macrophages through TLR receptors to produce TNF- $\alpha$  that possibly up-regulates IL-6 production from adipocytes and macrophages infiltrated in adipose tissue. Hence, adipose tissue in obese subjects has an important role in enhancing low-grade chronic inflammation leading to IR and lipid accumulation in liver (Stojsavljević et al., 2014).

TNF- $\alpha$  is associated with the progression from NAFLD to NASH. Plasma and intrahepatic TNF- $\alpha$  correlate with increased inflammation, steatosis and histological evidence of liver damage in patients with NASH (Negash and Gale, 2015).

Obesity and its attendant metabolic abnormalities might induce maladaptive expression of VEGF that in turn exacerbates lipotoxicity and consequent tissue dysfunction (Muioio, 2010). Increases of VEGF were also related with resolution of fibrosis and revascularization of fibrotic tissue (Kantari-Mimoun et al., 2015) whereas, when VEGF levels decrease, fibrosis may augment. VEGF was also applied in the development of portal hypertension and hepatocellular carcinoma (Fallowfield, 2015). VEGF and EG-VEGF were most increased in NASH patients, however, in the group reported here there was a low prevalence of cirrhotics (21%).

Platelets may be a source of growth factors such as PDGF and contribute to activation of profibrotic coagulation cascades. However, several studies described anti-fibrotic effects of platelets. As such, thrombocytopenic mice developed exacerbated liver fibrosis, while platelets suppressed collagen expression of cocultured HSCs in a Met-dependent manner (Seki and Shwabe, 2015). However, in our study, PDGF-BB was not different among the studied groups.

## Conclusions

We demonstrated a significant increase in pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, VEGF and VEGF-EG)

and ICAM-1 in patients with NASH. Correlations showed differential cytokine and adhesion molecules patterns on the basis of the liver disease etiology. These abnormalities in cytokine profile can influence pathophysiology of liver injury.

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