HFE, TGF-BETA1 AND SQUAMOUS CELL CARCINOMA ANTIGEN-1 POLYMORPHISMS AND LIVER DISEASE STAGE IN CHRONIC HCV INFECTION

C. Turato, M.G. Ruvoletto, A. Biasiolo, S. Quarta, N. Tono, L. Cavalletto, L. Chemello, C. Merkel, A. Gatta, P. Pontisso

Clinica Medica 5, Department of Clinical and Experimental Medicine, Padova, Italy

Background and aim. Recent advances in genomics have increased the interest of host genetic profiles on liver disease progression. The ov-serpin squamous cell carcinoma antigen (SCCA) has been recently found over-expressed in HCC and a novel SCCA1 variant (SCCA-PD), presenting a G_{351} to A mutation in the reactive loop of the protein, has been identified. Aim of the present study was to explore SCCA-PD versus HFE and TGF-beta1 polymorphisms in HCV infected patients with different extent of liver disease.
Methods. Eighty-three patients with chronic HCV infection (30 chronic hepatitis, 26 cirrhosis, 27 HCC) and 50 controls were studied. SCCA-PD polymorphism was assessed by PCR amplification and digestion with BsmI. C282Y and H63D mutations of HFE gene were determined after PCR amplification and enzymatic digestion with SnabI and MboI, respectively. TGF-beta1(codon 25) genotype (+915 G/C) was evaluated by ARMS-PCR using sequence-specific primers. Serum levels of SCCA-IgM were determined using an ELISA kit (Hepa-IC, Xeptagen).
Results. The C282Y ± genotype was significantly higher in patients with cirrhosis (OR = 20.20, $p = 0.01$), and HCC (OR = 14.43, $p = 0.04$), while for the H63D ± genotype, similar distribution was observed in HCV infected patients and in controls. The distribution of the TGF-beta1 gene polymorphism was not statistically different in patients and controls, although the frequency of the Arg/Pro genotype was lower in cirrhotic patients compared to controls (3.8% versus 14%, $p = 0.25$). SCCA-PD was detected with higher frequency (49.9%) in patients with cirrhosis (Odds ratio = 3.17, $p = 0.03$) than in chronic hepatitis (16.7%) or HCC (25.9%), where figures were comparable with those of the controls (24%). SCCA-IgM reactivity in serum was usually lower in patients with SCCA-PD compared to wild type patients, with a significant difference in patients with cirrhosis (mean ± S.D.: 132.44 ± 73.13 U/ml versus 229.93 ± 220.00 U/ml, $p = 0.018$). These results were supported by the negative association of SCCA-PD polymorphism with HCC found by stepwise logistic regression analysis.
Conclusions. Genetic mutations at the HFE gene were associated with advanced stage of liver disease and HCC, while TGF-beta1 polymorphism was not clinically useful to discriminate disease stage. The newly identified SCCA-PD polymorphism was significantly associated with liver cirrhosis, while apparent protection from hepatocellular carcinoma was observed in cirrhotic patients carrying the mutation.

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EFFECTS OF UDCA ON THE FOETUS-MATERNAL CIRCULATION OF BILIRUBIN IN CHOLESTASIS OF PREGNANCY

F. Azzaroli[a], E. Baglivo[a], V. Feletti[a], M. Locatelli[b], N. Rizzo[c], D. De Aloysio[c], G. Pelusi[c], M. Montagnani[a], F. Lodato[a], D. Festi[a], A. Colecchia[a], A. Roda[b], E. Roda[a], G. Mazzella[a]

[a] *Department of Digestive Diseases and Internal Medicine, University of Bologna, Italy*
[b] *Department of Pharmaceutical Sciences, University of Bologna, Italy*
[c] *Department of Obstetrics and Gynaecology, University of Bologna, Italy*

Background and aim. Prematurity is frequent in intrahepatic cholestasis of pregnancy (ICP) and represent a risk factor for bilirubin neurotoxicity in the newborn. Aim of our study was to investigate the foetus-maternal circulation of bilirubin which is still undefined.
Methods. Thirty patients with ICP (14 treated with 25 mg/kg/day, 16 untreated) and 11 controls were enrolled in the study. Bilirubin was determined in serum (standard automated colorimetric method) collected at delivery both from maternal and cord blood. First meconium evacuated by the neonate was also collected for bilirubin determination by a quadrupole mass spectrometer (Micromass, UK) equipped with ESI source. Mann–Whitney and ANOVA tests were used as appropriate for the statistical analysis.
Results. Total bilirubin was significantly decreased by UDCA administration in maternal serum compared to ICP patients (0.25 ± 0.16 versus 0.59 ± 0.47, $p = 0.034$); the evaluation of total bilirubin differential concentrations in cord blood artery and vein highlighted a physiological outflow from the foetal compartment preserved in cholestasis longer than 3 weeks. The outflow was significantly enhanced by UDCA administration compared to ICP and CTRL (Δ0.176 versus 0.023, $p = 0.042$). Bilirubin in meconium was significantly higher in samples from the treated group compared to those from controls and untreated ICP patients (43.36 ± 3.62 versus 17.77 ± 7.004 and 10.84 ± 4.32 ng/mg dry weight, $p < 0.02$).
Conclusions. UDCA administration reduces maternal total bilirubin concentration, improves conjugated bilirubin outflow from the fetal compartment and may stimulate bilirubin accumulation into meconium.

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IS ADIPONECTIN A POTENTIAL PROTECTIVE FACTOR AGAINST ATHEROSCLEROSIS IN PRIMARY BILIARY CIRRHOSIS (PBC)?

A. Variola[a], M. Durazzo[b], G. Niro[c], A. Premoli[b], V. Baldo[d], R. Gambino[b], G. Musso[b], M. Cassader[b], S. Bo[b], F. Ferrara[a], A. Bressan[a], E.R. Rizzotto[a], A. Floreani[a]

[a] *Department of Surgical and Gastroenterological Sciences, University of Padova, Italy*
[b] *Department of Internal Medicine, University of Turin, Italy*
[c] *Gastroenterology, S. Giovanni Rotondo, Italy*
[d] *Department of Environmetal and Public Health, University of Padova, Italy*

Hypercholesterolemia is a common finding in PBC, but the risk of cardiovascular events in these patients is not increased in respect to the general population. High serum adiponectin levels appear to play protective role in development of either metabolic syndrome and cardiovascular disease.
Aim. To search potential factors that may protect PBC against atherosclerosis.
Methods. Circulating levels of adiponectin, resistin, leptin, TNFα were assessed in 137 consecutive PBC patients (124 F, 13 M, mean age 61 ± 12 years), and in 31 patients with NASH associated to metabolic syndrome. Reference values were obtained from 54 healthy control subjects with HOMA < 2. Body mass index (BMI) was comparable in the three groups, whereas total cholesterol was significantly higher in PBC compared to either NASH and controls (219 ± 53 in PBC versus 186 ± 40 in NASH versus 199 ± 35 in controls, $p < 0.02$).
Results. Are expressed as mean + S.D.

Pts	Adiponectin (ng/ml)	Resistin (ng/ml)	Leptin (ng/ml)	TNFα (pg/ml)
PBC	14.338 ± 12.220*	7.28 ± 4.70*	17.296 ± 17.921*	3.0 ± 6.86
NASH	6.109 ± 3.900	4.64 ± 2.21	7.794 ± 4.179	1.08 ± 0.59
Controls	8.617 ± 5.919§	3.58 ± 1.24§	7.421 ± 10.323	1.28 ± 0.75

*PBC vs. NASH/controls = $p < 0.005$; §NASH vs. controls = $p < 0.05$.

Among PBC group only adiponectin was positively correlated to the advancing histological progression ($r^2 = 0.91$, $p = 0.04$), and negatively correlated with BMI ($r^2 = 0.045$, $p < 0.01$). Subjects with hypercholesterolemia (>210 mg/dl) had significantly higher levels of adiponectin ($p < 0.04$) compared to subjects with normal serum cholesterol. Logistic linear regression analysis revealed that adiponectin was independently correlated to: histological stage ($p < 0.01$), Mayo score ($p < 0.04$), and age ($p < 0.01$).

Conclusions. The high concentrations of adiponectin in PBC patients should be regarded as possible protective factor against atherogenesis even in advanced histological stage; search of further factors should be encouraged.

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A NON-INVASIVE DIAGNOSTIC ALGORITHM FOR THE DIAGNOSIS OF CHRONIC LIVER DISEASE: THE ROLE OF ECHOGRAPHY AND APRI TEST

M. Persico, F.S. Moschella, B. Palmentieri, V. La Mura, G. Serafino, R. Torella, I. De Sio

Department of Internal Medicine and Hepatology, Second University of Naples, Italy

Background. Diagnosis and staging of chronic liver disease is mainly based on liver biopsy (LB). Many attempts were made in order to replace LB with non-invasive markers of disease activity. Our study focuses on the role of ultrasound examination (US) associated to AST/platelets ratio index (APRI test) on the differential diagnosis between chronic active hepatitis (CAH) and liver cirrhosis (LC).
Methods. Three hundred and twenty one consecutive indoor patients with no clinical signs of liver cirrhosis who underwent to LB in our clinic were evaluated for hepatic surface to US and for APRI test. Patients were divided into two groups according to regular or irregular surface to US and APRI test was performed both in all patients and in patients with irregular liver surface. ROC curve analyses was used when appropriate. Statistical analyses were aimed to compare results of US and US plus APRI to histological score. The histological score was assessed according to Ishak's classification.
Results. The sensitivity, specificity, predictive positive value (PPV) and predictive negative value (NPV) to diagnose cirrhosis was 79%, 64%, 35%, 92% for APRI > 0.5 and 16%, 97%, 62%, 83% for APRI > 2; the sensitivity, specificity, PPV and NPV of hepatic irregular surface to diagnose cirrhosis was respectively 76%, 92%, 71%, 94%. In patients with hepatic irregular surface a cut-off of APRI > 2 enabled to diagnose cirrhosis with a specificity of 100% and PPV of 100%.
Conclusions. A stepwise combination algorithm may be suggested to stage chronic liver disease (i.e. LC versus CAH) with a non invasive method. In particular, patients with regular liver surface at US may be considered non-cirrhotic patients whereas among patients with irregular liver surface, those with APRI > 2 may be diagnosed as having LC. LB needs to be considered only for patients with irregular liver surface and APRI < 2.

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